Incidence of dementia : secular trends and associated factors

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Incidence de la démence
Tendances évolutives au cours du temps et déterminants

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Secular trends and associated factors

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Incidence de la démence
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La démence entraine des conséquences non seulement pour le patient, mais également pour sa famille et pour la société elle-même et représente une priorité de santé publique. La connaissance et la compréhension des tendances temporelles de cette maladie est un sujet de recherche majeur, essentiel pour le futur. Cette thèse avait pour but d'analyser les tendances séculaires de l'incidence de la démence, ainsi que de certains de ses composants et conséquences et d'en comprendre les déterminants. Dans la première partie de ce travail, nous avons apporté un argument supplémentaire de la tendance à la baisse de l'incidence de la démence, retrouvé chez les femmes entre les années 90 et les années 2000. Ensuite, nous avons rapporté une amélioration globale des performances cognitives pour les générations plus récentes de personnes âgées, qui semble être due à une amélioration acquise relativement précocement au cours de la vie plutôt qu'à un déclin moins important des performances au cours du vieillissement. Enfin, nous avons mis en évidence une diminution de la mortalité sans démence et de la mortalité des femmes démentes, ainsi qu'une augmentation de l'espérance de vie en bonne santé et de la durée de vie en démence. Ces résultats sont en accord avec une amélioration de l'état de santé des personnes âgées au cours des deux dernières décennies, ce qui est prometteur pour le futur. D'autres travaux afin de mieux comprendre ces tendances et leurs déterminants sont cependant nécessaires ; ils permettront de mieux préciser les stratégies de prévention devant être mis en place pour diminuer ou retarder la démence.

Mots clés : Tendances séculaires, Démence, Performances cognitives, Espérances de vie

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Incidence of dementia
Secular trends and associated factors

Consequences of dementia are impacting not only patients, but also their family and even society; it has thus been highlighted as an important public health priority. Understanding temporal trends of this disease thus became a major research topic, critical for the future. This thesis aimed at investigating secular trends of dementia incidence as well as some of its components and consequences, trying to understand their determinants. In the first part of this work, we have brought further evidence toward a decreasing trend of dementia incidence, only found for women between the 90's and the 2000's in our study. Then, we have reported a global improvement of cognitive performance for younger elderly generations, potentially due to improvement early in life rather than to a slower decline across aging. Finally, we have evidenced a decrease in mortality without dementia and for demented women, as well as an increase of healthy life expectancy and survival with dementia. These results are in line with an improvement of health of older people during the last two decades, which is promising for the future. Further research to better understand these secular trends are yet needed; it will help precise prevention strategies needed to reduce or delay dementia.

Keywords: Secular trends, Dementia, Cognitive performance, Life expectancy

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Scientific Production

Articles

- Thesis publications

Grasset L, Brayne C, Joly P, Jacqmin-Gadda H, Peres K, Foubert-Samier A, et al. Trends in dementia incidence: Evolution over a 10-year period in France. *Alzheimers Dement*. 2016;12(3):272-80.

Grasset L, Jacqmin-Gadda H, Proust-Lima C, Pérès K, Amieva H, Dartigues JF, Helmer C. Time trends of cognition and cognitive decline: Results from the PAQUID study. *(In revision)*

Grasset L, Matthews FE, Pérès K, Foubert-Samier A, Helmer C, Dartigues JF, Brayne C. Evolution of dementia diagnosis over time (1988 – 2013): Evidence from French and English cohorts. Implication for secular trends analyses. *(Under writing process)*

Grasset L, Pérès K, Joly P, Foubert-Samier A, Dartigues JF, Helmer C. Secular trends of mortality and life expectancy over a 10-year period according to dementia. *(Under writing process)*

- Publications related to the field

Grasset L, Joly P, Jacqmin-Gadda H, Letenneur L, Wittwer J, Amieva H, et al. Real benefit of a protective factor against dementia: Importance of controlling for death. Example of sport practice. *PloS one*. 2017;12(4):e0174950.

Tabue-Teguo M, **Grasset L**, Avila-Funes JA, Genuer R, Proust-Lima C, Peres K, et al. Prevalence and Co-Occurrence of Geriatric Syndromes in People Aged 75 Years and Older in France: Results From the Bordeaux Three-city Study. *J Gerontol A Biol Sci Med Sci*. 2017 (Epub Ehead of Print).

Pérès K, Brayne C, Matharan F, **Grasset L**, Helmer C, Letenneur L, et al. Trends in the prevalence of dementia in French farmers from two epidemiological cohorts. *J Am Geriatr Soc*. 2017;65(2):415-20.

Oral communications

Grasset L, Helmer C, Matthews F, Dartigues JF, Brayne C. Evolution of dementia diagnosis over time (1988 – 2013): Evidence from French and English cohorts. Implication for secular trends analyses. AAIC conference 2017.

Grasset L, Jacqmin-Gadda H, Proust-Lima C, Pérès K, Amieva H, Dartigues JF, Helmer C. Time trends in level and decline of cognition and function of elderly people 10 years apart: the Paquid study. ADPD conference 2017.

Grasset L, Brayne C, Joly P, Jacqmin-Gadda H, Peres K, Foubert-Samier A, et al. Trends in dementia incidence: Evolution over a 10-year period in France. *Alzheimer's & Dementia*. 2015;11(7, Supplement):P219-P20. Conference Paper AAIC 2015.

Résumé substantiel

1. Introduction

En raison de l'allongement de l'espérance de vie, avec pour conséquence le vieillissement de la population dans la plupart des pays industrialisés, les pathologies démentielles (maladie d'Alzheimer et maladies apparentées) représentent actuellement un défi de santé publique. En effet, la proportion de personnes âgées de 60 ans et plus dans le monde pourrait atteindre 16,3% en 2030. L'âge étant le facteur de risque principal de démence, le nombre de personnes atteintes, estimé actuellement à environ 47 millions au niveau mondial, pourrait atteindre plus de 131 millions en 2050 si la prévalence reste inchangée. La démence est une des pathologies contribuant le plus largement à l'incapacité des personnes âgées. La définition même de cette pathologie associe des troubles de la mémoire et un déclin cognitif avec un retentissement sur les activités de la vie quotidienne. Avec l'évolution de la pathologie, ce retentissement sur la vie quotidienne évolue vers une perte progressive d'autonomie nécessitant parfois l'institutionnalisation quand les familles ne peuvent plus gérer la situation à domicile. La démence est ainsi la principale cause d'institutionnalisation et les personnes démentes représentent plus de 70% des résidents d'institution. La survenue d'une démence a donc de nombreuses conséquences sur la vie d'un individu, mais aussi sur la vie de son entourage au niveau physique, psychologique, social et économique. Actuellement, les traitements existant sont uniquement symptomatiques, permettant de limiter l'évolution de la maladie pendant une période donnée. En l'absence de traitement curatif, les approches préventives consistant à limiter les facteurs de risque pour retarder la survenue de la maladie apparaissent particulièrement intéressantes. La démence est une maladie multifactorielle et plusieurs facteurs de risque ont pu être identifiés. Au-delà de l'âge et de l'allèle ε4 de l'apolipoprotéine E, des facteurs modifiables existent avec notamment des facteurs vasculaires tels que l'hypertension artérielle, le diabète, l'hypercholestérolémie, l'obésité ou l'athérosclérose ; leur présence dès "midlife" (i.e. 45-55 ans) semble associée à un risque augmenté de démence. A l'opposé certains facteurs semblent protecteurs comme un niveau d'éducation plus élevé permettant une réserve cognitive plus importante ou encore certains régimes alimentaires, notamment le régime dit méditerranéen, l'activité physique ou les activités sociales. Une diminution de 10% par décennie de la prévalence de 7 facteurs de risque majeurs (bas niveau

d’études, tabagisme, diabète, hypertension, obésité, dépression et inactivité physique) pourrait réduire la prévalence de la maladie d’Alzheimer de 8.3% dans le monde en 2050.

L’étude des tendances séculaires de la démence est importante pour la compréhension de l’évolution de la maladie au cours du temps ainsi que pour identifier de potentiels facteurs permettant de prévenir ou repousser la survenue de démence. Actuellement, les projections de nombre de cas réalisées se basent sur un taux d’incidence de la démence stable, et ne prennent pas en compte une possible évolution de cette incidence qui pourrait conduire à une plus faible augmentation du nombre total de personnes démentes dans le futur. Récemment, des études de prévalence et d’incidence en Europe et aux Etats-Unis ont rapporté des tendances évolutives à la baisse avec notamment une diminution de l’incidence de la démence. En parallèle, une amélioration des performances cognitives et une diminution de la dépendance ont été mises en évidence dans un certain nombre d’études. Même si très peu d’études ont analysé les facteurs impliqués dans ces tendances, ces résultats sont encourageants. En effet, la prévention ainsi qu’une meilleure prise en charge des facteurs de risque au cours des dernières décennies pourrait avoir eu un effet sur le risque de démence et sur le déclin cognitif et fonctionnel. Cependant, l’étude des tendances séculaires de la démence se heurte à certaines difficultés méthodologiques qui doivent être prises en compte afin de produire des résultats non biaisés et robustes. Tout d’abord, la comparaison de populations différentes conduit souvent à un biais de sélection, notamment si le taux de réponse initial ou tout au long du suivi diffère entre les populations comparées. Les individus acceptant de participer sont souvent différents et en meilleure santé que la population générale, ce qui peut conduire à une mauvaise estimation des tendances. Ensuite, le diagnostic de démence est un diagnostic essentiellement clinique où l'appréciation des troubles cognitifs et du retentissement est laissée à l'appréciation du clinicien. Ce diagnostic peut donc varier en fonction du clinicien, de son expérience mais aussi de son "intérêt" à porter un diagnostic. Avec l’évolution actuelle de l'intérêt pour cette maladie, il est probable que le stade auquel le diagnostic est porté ait différé au cours des dernières décennies ce qui complique les comparaisons au cours du temps. Enfin, dans les populations âgées, le risque de démence entre en compétition avec la mortalité, de nombreux facteurs de risque de décès étant en outre des facteurs de risque de démence. L'analyse des tendances évolutives nécessite donc de considérer le risque de démence ainsi que le risque de décès, qui évolue régulièrement avec une augmentation constante de l'espérance de vie depuis plusieurs décennies.

L’objectif principal de cette thèse était donc d’analyser l’évolution de la fréquence des démences au cours du temps ainsi que ses déterminants, tout en prenant en compte les limites méthodologiques inhérentes à ce genre d’études.

2. Méthodes

Ce projet s'appuie sur l'analyse de plusieurs études de cohortes en population. En France, les participants des cohortes PAQUID et 3 Cités (3C) ont été utilisés. PAQUID a recruté 3777 individus de 65 ans et plus vivant à domicile en Gironde et Dordogne en 1988. Les participants ont été revus depuis tous les 2-3 ans afin de collecter des informations essentielles concernant leur état de santé physique, leurs capacités cognitives et fonctionnelles et la survenue d'une éventuelle démence. L'étude des 3 Cités se déroule dans 3 villes en France, Bordeaux, Dijon et Montpellier. Le centre bordelais de l’étude cette étude a recruté 2104 individus de 65 ans et plus vivant à domicile à Bordeaux en 1999. Les participants ont été revus tous les 2-3 ans depuis l’inclusion et des données similaires à celles de PAQUID ont été recueillies à chaque fois. Au Royaume-Uni, les participants des cohortes CFAS I (pour les centres de Cambridge, Newcastle et Nottingham) et II ont été utilisés. CFAS I a inclus plus de 7500 individus entre 1990 et 1993 dont un sous échantillon a reçu une évaluation pour le diagnostic de démence. CFAS II a également inclus plus de 7500 individus entre 2008 et 2011, tous ayant été évalués pour la démence.

Différents types de diagnostic ont été utilisés et comparés dans les travaux de cette thèse. Dans les cohortes françaises, un diagnostic clinique a été établi à chaque visite : les participants bénéficiaient d'abord d'une évaluation complète, notamment cognitive et fonctionnelle, réalisée par la psychologue dans le cadre de sa visite. A l'issue de cette visite, la psychologue sélectionnait les personnes "suspectes" de troubles cognitifs ou de démence. Ces personnes étaient ensuite revues pour un entretien et un examen avec un neurologue ou un gériatre à leur domicile. Le neurologue basait son diagnostic de démence sur les critères cliniques DSM III R dans PAQUID et DSM IV dans 3C. Puis les dossiers étaient revus par un comité de validation composé d’experts. En plus de ce diagnostic clinique, pour prendre en compte l’évolution du diagnostic clinique au cours du temps, un algorithme a été établi pour classifier les individus, basé sur les performances cognitives et le retentissement en termes d’Activités instrumentales de la vie quotidienne (IADL). L’algorithme a été réalisé à partir des scores au MMSE et aux 4 IADL à chaque suivi : un score MMSE inférieur à 24 ET une

atteinte de 2 IADL ou plus ont été utilisés pour classer les déments. D'autres algorithmes utilisant des seuils de score MMSE différents ont aussi été réalisés. Cet algorithme a également été adapté aux données des cohortes anglaises. Au-delà des diagnostics clinique et algorithmique de démence, les capacités cognitives et fonctionnelles ont également été évaluées. En plus du MMSE, différents tests neuropsychologiques comme le Set Test d'Isaacs (IST), le Test de Rétention Visuel de Benton (BVRT) ainsi que le Test de Substitution des Symboles (DSST) ont été évalués lors des visites et utilisés pour ce travail. Des données concernant la dépendance ont aussi été utilisées avec l'échelle des Activités Instrumentales de la Vie Quotidienne (IADL).

Les méthodes statistiques utilisées ont été choisies afin de modéliser les données de la façon la plus adaptée. Dans un premier temps, des modèles multi-états de type « Illness-death » ont été utilisés pour étudier les tendances de la démence. Le modèle illness-death décrit les transitions d'un état initial (vivant ou sain (0)) vers un état absorbant (décès (2)) directement ou par un état intermédiaire (la maladie (1)). Les intensités de transition 01, 02 et 12 sont des fonctions du temps qui peuvent aussi dépendre de covariables. Chaque intensité de transition peut dépendre de variables différentes ce qui permet de prendre en compte des facteurs de risque différents entre les évènements. L'intensité de transition 01 représente l'incidence de la démence à âge spécifique et les intensités de transition 02 et 12 représentent le taux de mortalité à âge spécifique pour des sujets sains et déments respectivement. Ce modèle permet de tenir compte de la censure par intervalle entre l'état initial et l'état intermédiaire ainsi que de la compétitivité des risques de décès. Pour étudier les tendances de la cognition et de la fonction, des modèles linéaires mixtes conjoints ont été utilisés, permettant de modéliser l'évolution des performances aux tests mesurés au cours du suivi tout en prenant en compte l'attrition au cours du suivi.

3. Résultats

a. Tendances séculaires de l'incidence de la démence et déterminants

Cette première étude avait pour objectif d'investiguer une potentielle diminution de l'incidence de la démence au cours des 20 dernières années. Au début de ce travail, un petit nombre d'études avaient rapporté une tendance à la diminution de la prévalence et une seule étude avait montré une tendance non significative vers une incidence plus faible. Il était donc

important de répliquer ces résultats avec des méthodes adaptées. Pour cela, les participants de deux populations à 10 ans d'écart ont été comparés : 1469 individus âgés de 65 ans et plus inclus en 1988-89 dans PAQUID et 2104 individus âgés de 65 ans et plus inclus en 1999-2000 dans 3C-Bordeaux. Deux diagnostics ont été comparés : le diagnostic clinique et le diagnostic algorithmique, stable au cours du temps. L'incidence sur 10 ans de suivi des deux populations a été comparée en utilisant un modèle multi-état Illness-death. Nous avons également cherché à expliquer cette diminution par différents facteurs de risque tels que le niveau d'études, des facteurs vasculaires et la dépression.

La deuxième population (3C-Bordeaux) avait un niveau d'études plus élevé, moins d'antécédents d'AVC, avait moins de fumeurs et était d'avantage traitée contre l'hypertension, l'hypercholestérolémie, et la dépression. En utilisant le diagnostic clinique, une incidence stable entre les deux populations a été retrouvée. Avec le diagnostic algorithmique, une diminution significative de l'incidence de la démence chez les femmes seulement a été mise en évidence. Cette diminution était maintenue après ajustement sur les différents facteurs de risque. Les analyses de sensibilité réalisées confirmaient cette diminution du risque. Cette étude a donc apporté un élément de preuve supplémentaire en faveur du déclin de l'incidence de la démence au cours des 30 dernières années, bien que retrouvé uniquement chez les femmes. Alors qu'une seule étude avait jusque-là été publiée sur des données d'incidence, de façon concomitante à notre publication, trois articles sont parus, sur des données anglaises et américaines. Dans la littérature, les résultats concernant le sexe sont mixtes, certaines études retrouvant une diminution chez les hommes et les femmes, d'autres ne retrouvant la diminution que pour les hommes ou les femmes. Jusqu'à présent, seules peu d'études ont analysé l'effet de facteurs de risque sur la diminution de l'incidence et, comme pour ce travail, les facteurs pris en compte n'ont pas permis d'expliquer totalement la diminution. Malgré la présence de certains problèmes méthodologiques pouvant biaiser les résultats obtenus jusqu'à présent, la tendance à la baisse de l'incidence de la démence est une bonne nouvelle, encourageant à développer la compréhension de cette baisse pour favoriser son maintien.

b. Tendances évolutives de la cognition et de la dépendance

La plupart des études étant en faveur de la diminution de l'incidence et de la prévalence de la démence, il est important d'essayer de mieux comprendre cette évolution. De par sa

définition, la démence est directement liée aux capacités cognitives et fonctionnelles. Etudier plus en détail les composants de la maladie au cours du temps pourrait aider à mieux appréhender les mécanismes impliqués. Il est donc intéressant d'analyser un effet génération de l'évolution des performances cognitives et fonctionnelles, en termes de niveau ou de trajectoire au cours du temps. Pour ce travail, deux générations issues de la cohorte PAQUID ont été utilisées : la première génération G1 a inclus 612 sujets nés entre 1903 et 1912 âgés de 78 à 88 ans au suivi à 3 ans et la deuxième génération G2 a inclus 626 sujets nés entre 1913 et 1922 âgés de 78 à 88 ans au suivi à 13 ans. Les données de suivi sur 12 ans ont été utilisées pour modéliser les trajectoires des performances à différents domaines cognitifs évalués par les tests suivant : MMSE, IST, BVRT et DSST ; et à un score fonctionnel de dépendance (4IADL). Les analyses ont été réalisées à l'aide de modèles linéaires mixtes classiques dans un premier temps puis dans un second temps conjoints au risque de décès et de perdu de vue afin de prendre en compte l'attrition plus faible dans la deuxième génération. Les différents scores ont été transformés afin d'être normalisés.

Les individus de la deuxième génération avaient un niveau d'études plus élevé et prenaient d'avantage d'antihypertenseur et de traitement hypolipémiant. Pour l'ensemble des domaines cognitifs, la seconde génération avait des performances plus élevées à l'inclusion que la première génération. L'évolution des performances sur les 12 ans de suivi était similaire entre les deux générations pour le MMSE et le DSST alors que les participants de la deuxième génération présentaient un déclin plus faible que ceux de la première génération pour l'IST et le BVRT. Après ajustement sur le niveau d'études, les performances à l'inclusion devenaient similaires entre les deux générations pour le MMSE et l'IST, tandis que la deuxième génération maintenait des performances plus élevées pour le BVRT et le DSST. Les résultats concernant le déclin au cours du suivi n'étaient pas modifiés après ajustement sur le niveau d'études. L'ajustement supplémentaire sur les facteurs vasculaires ne modifiait pas réellement les résultats. Concernant la dépendance, une amélioration non significative de la fonction a été retrouvée à l'inclusion, disparaissant totalement après ajustement sur le niveau d'études. La deuxième génération présentait un déclin de la fonction plus faible au cours du suivi que la première génération, même après ajustement sur le niveau d'études. Ce travail a donc confirmé l'amélioration des capacités cognitives pour les générations plus récentes, expliquée par l'amélioration du niveau d'études pour le MMSE et l'IST mais pas pour les autres tests. La littérature concernant l'évolution du déclin en fonction des générations est plus mitigée et pas toujours en faveur des générations plus récentes.

c. Evolution du diagnostic de démence

Comme mentionné précédemment, le diagnostic de démence utilisé dans la majorité des études est influencé par des facteurs subjectifs propres aux cliniciens. En effet, les critères utilisés pour poser un diagnostic ne proposent pas de seuils opérationnels quantifiant le déclin cognitif et les répercutions attendues sur les activités de la vie quotidienne. L'évolution du diagnostic complique donc fortement la comparaison de l'incidence et de la prévalence à différents temps et entre différentes études, pouvant conduire à des estimations biaisées. Une alternative pour l'étude des tendances séculaires est l'utilisation d'algorithme permettant de diagnostiquer les cas de manière stable au cours du suivi et entre études. Cette approche a déjà été utilisée dans les études anglaises CFAS I et II. Le premier objectif de ce travail était donc d'investiguer l'évolution du diagnostic clinique au cours du temps en France. Pour cela, les scores au MMSE des cas incidents à chaque suivi de PAQUID (27 ans de suivi) et du centre bordelais de 3C (14 ans de suivi) ont été analysés à l'aide de modèle linéaire utilisant des splines. Ensuite, le second objectif était d'appliquer l'algorithme déjà utilisé sur les données françaises aux données anglaises. Les prévalences standardisées et pondérées ont été établies à partir des données d'inclusion de CFAS I et II, tout comme les taux d'incidence pondérés à partir de modèles de Poisson.

Pour PAQUID, une augmentation significative du score MMSE au moment du diagnostic a été mise en évidence avant 2001 et une diminution significative après 2001. Un déclin significatif du score MMSE au moment du diagnostic a été retrouvé pour 3C-Bordeaux. Cela confirme le fait que le diagnostic clinique n'a pas toujours été établi aux mêmes stades au cours des 30 dernières années et entre différentes études. Il est probable que cette évolution ne soit pas retrouvée seulement en France. L'utilisation d'un diagnostic stable semble donc nécessaire. Ainsi, quand on appliquait l'algorithme sur les données anglaises, la prévalence de la démence était de 8,8% pour CFAS I et 5,7% pour CFAS II. L'incidence était, elle, de 31,2/1000 PA (95% IC : 28,0-34,8) pour CFAS I et 15,0/1000 PA (13,5-16,7) pour CFAS II. Ces résultats, bien que différents de ceux publiés précédemment basés sur un algorithme différent, l'AGECAT, confirment la diminution de l'incidence et de la prévalence de la démence.

d. Evolution de la mortalité et de l’espérance de vie selon le statut de démence

La diminution de la mortalité a conduit à un allongement de l’espérance de vie, que ce soit à la naissance ou à 65 ans. Cependant, la question se pose de la qualité des années de vie gagnées. En effet, vivre plus longtemps ne signifie pas forcément vivre en meilleure santé et si les années gagnées sont passées en démence, les conséquences peuvent être importantes pour les personnes démentes, leur entourage et la société avec un poids économique. Il semble donc important d’investiguer l’évolution de la mortalité chez des personnes démentes et des personnes non démentes et d'analyser les évolutions d'espérances de vie afin de voir si l’augmentation de l’espérance de vie s’accompagne d’une augmentation de l’espérance de vie sans démence. De plus, au-delà de l'espérance de vie, pour une personne développant une démence l’évolution de la durée de survie en démence est aussi intéressante à analyser. Pour cela, les participants de deux populations à 10 ans d’écart ont été comparés : 1469 individus âgés de 65 ans et plus inclus en 1988-89 dans PAQUID et 2104 individus âgés de 65 ans et plus inclus en 1999-2000 dans 3C, les données sur 10 ans de suivi de ces deux populations ayant été utilisées. Le diagnostic de démence était basé sur l’algorithme défini dans cette thèse et un modèle illness-death a été appliqué aux données pour établir des risques de décès, des espérances de vie et des durées de vie en démence.

Une diminution de la mortalité sans démence a été retrouvée chez les hommes et les femmes alors qu’une diminution de la mortalité des déments n’a été retrouvée que chez les femmes. L’espérance de vie totale ainsi que l’espérance de vie sans démence ont augmenté entre les années 90 et les années 2000 à tout âge et quel que soit le sexe ou le niveau d’études. Globalement, la proportion de vie passée en bonne santé sans démence a eu tendance à légèrement augmenter, avec des différences selon l’âge. Cependant, le pourcentage d’espérance de vie sans démence variait selon le niveau d’études avec une augmentation pour les individus sans diplôme et une stabilisation voir une détérioration pour les individus avec diplôme. Ces résultats semblent en accord avec une compression relative de la morbidité pour les personnes avec un bas niveau d’études. De plus, la survie en démence a augmenté entre les deux générations, principalement pour les femmes. Ce travail montre que bien que l’augmentation de l’espérance de vie soit associée à une augmentation de l’espérance de vie sans démence, elle est aussi suivie d’une augmentation de l’espérance de vie et du temps

passé en démence. Il serait donc intéressant de parvenir à retarder l'apparition de la démence afin d'augmenter encore d'avantage l'espérance de vie en bonne santé.

4. Discussion

La démence conduisant à d'importantes conséquences pour les malades, leur famille et la société, l'étude des tendances séculaires et leur compréhension s'est développé au cours des dernières années. Ce travail de thèse a contribué à confirmer la tendance à la diminution de l'incidence de la démence ainsi que l'amélioration des capacités cognitives pour les générations plus récentes. Cependant, ces progrès ne sont pour l'instant pas encore bien compris. Il est pourtant nécessaire d'identifier les raisons de la diminution du risque de démence. Si l'amélioration du niveau d'éducation, la meilleure prise en charge des maladies vasculaires et l'amélioration globale des conditions de vie peuvent y avoir contribué, les études réalisées n'ont pour l'instant pas réussi à le démontrer. De plus, d'autres facteurs comme l'augmentation de l'obésité ou du diabète ainsi que les inégalités sociales pourraient dans le futur compromettre ces tendances. Avec l'absence de traitements efficaces, la prévention semble une bonne alternative et pourrait encourager le vieillissement réussi. Vivre plus longtemps n'est de nos jours plus suffisant et la qualité des années de vie gagnées importe tout autant. L'objectif principal étant d'augmenter le temps passé en bonne santé tout en diminuant le temps passé en incapacité ; ainsi, retarder les symptômes de démence et particulièrement ceux conduisant à une forte dépendance semble primordial.

Bien que l'ensemble de ces résultats soit encourageant, il est important de noter que l'analyse des tendances séculaires de la démence fait face à certaines difficultés méthodologiques souvent retrouvées dans la littérature. Nous avons donc utilisé des méthodes adaptées afin de prendre en compte le mieux possible la sélection des populations, l'évolution du diagnostic et la compétitivité avec le décès. Cependant, la présence de biais résiduel ne peut être exclue. Les études réalisées dans le futur devront continuer à essayer de produire des résultats les plus corrects et non biaisés possibles.

Les résultats de cette thèse sont en accord avec une amélioration de l'état de santé des personnes âgées au cours des deux dernières décennies. Nos résultats comme les autres études sur le sujet en faveur d'une diminution de la fréquence de la démence sur les dernières décennies, montrent que la prévention peut être efficace face à cette maladie. Il est donc

important de continuer l’investigation des raisons liées à cette amélioration et d'améliorer la compréhension des tendances afin de mieux préciser les stratégies de prévention qui permettraient de maintenir les progrès réalisés.

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PAQUID: Personnes Agées QUID
3C: Three City
AMI: Aging Multidisciplinary Investigation
MRC CFAS: Medical Research Council - Cognitive Function and Ageing Study
PYR: Person-Year
LIC: Low Income Countries
LMIC: Low and Middle Income Countries
UMIC: Upper and Middle Income Countries
HIC: High Income Countries
DSM: Diagnostic and Statistical Manual
y.o. : years old
LE: Life Expectancy
DemFLE: Dementia-Free Life Expectancy
WHO: World Health Organization
AD: Alzheimer's disease
ADL: basic Activities of Daily Living
IADL: Instrumental Activities of Daily Living
HR: Hazard Ratio
OR: Odd Ratio
YLL: Year of Life Lost
MMSE: Mini-Mental State Examination
TMT: Trail Making Test
BVRT: Benton Visual Retention Test
DSST: Digit Symbol Substitution Test
IST: Isaacs Set Test
HRS: Health and Retirement Study
NIH: National Institutes of Health
MCAR: Missing Completely At Random
MAR: Missing At Random
MNAR: Missing Not At Random
MCI: Mild Cognitive Impairment
FCSRT: Free and Cued Selective Reminding Test
AGECAT: Automated Geriatric Examination for Computer Assisted Taxonomy
CDA: Comparative Dementia Algorithm

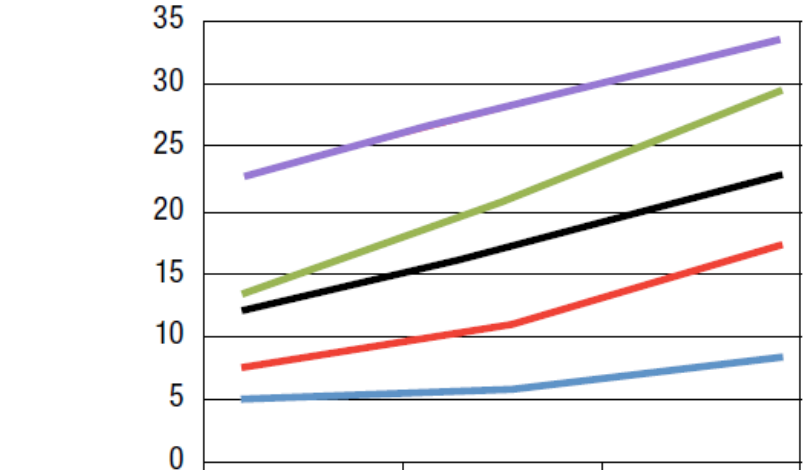
INTRODUCTION

and

OBJECTIVES

1. Introduction

In most developed countries, life expectancy (LE) at birth has been regularly increased up to 69.1 years for men and 73.7 years for women overall in 2015 (1). LE at age 60 was 18.9 for men and 21.7 for women in 2015. At age 60, an increase of around two years per decade has been evidenced (2). In France, LE at birth in 2015 was 79.0 y for men and 85.1 y for women. Additionally, LE at age 60 was of 22.9 for men and 27.3 for women (3). These life expectancies are expected to keep rising until 2030 for a high number of industrialised countries (4). This improvement has led to an aging population, with a growing proportion of elderly people (5). Indeed, 12.2% of the world population is aged 60 years and older and this number is expected to rise to 16.3% in 2030 (6). Moreover, it will not be restricted to high income countries, with all categories of country being concerned (Figure 1). In the OCDE countries, the proportion of 65+ should rise from 15% in 2010 to 25% in 2060 (7). In France, almost 25% of the 66.6 million people living in France in January 2016 are aged 60 and more (3). The number of individuals aged 60 and more could rise by 10.4 million between 2007 and 2060, with 23.6 million individuals older than 60 y.o. (8). However, chronic diseases are more frequent with age and are followed by incapacities and dependency (9). Age being a major risk factor of dementia, this would result in greater number of individuals at risk of developing dementia, with longer exposure to dementia risk.



	2015	2030	2050
LIC	5.2	6.0	8.4
L-MIC	8.1	11.2	16.3
UMIC	13.3	20.5	28.9
HIC	22.0	27.3	31.6
World	12.2	16.3	21.2

Figure 1: Percentage of the total population aged 60 years and over, by country income level, 2015 to 2050. LIC: Low Income Countries; L-MIC: Low and Middle Income Countries; UMIC: Upper and Middle Income Countries; HIC: High Income Countries. (World Alzheimer Report 2015)

- Why is dementia considered as a public health priority?

First of all, as detailed in more details later, dementia is a frequent disease in the elderly and an increasing number of people with dementia are expected. It is a serious condition with direct consequences for the subject (cognitive deterioration, disability, institutionalization and death) (10). According to the World Health Organization (WHO), deaths due to dementias more than doubled between 2000 and 2015, making it the 7th leading cause of global deaths in 2015 (11). This rise of death can be due to an increase of dementia cases or to an increased recognition of dementia as cause of death. However, dementia also has consequences for the relatives of the patient. Indeed, caregivers report increased risk of death, increased risk of depression and anxiety, and even an increased risk of dementia (12, 13). Age-related diseases such as dementia are leading to a high social and economic burden, impacting not only the

patients but also their families and societies. It is thus a costly disease, responsible for hundreds of billions for health expenses worldwide (6). Dementia is often the cause of stigmatisation, abuse and family conflicts. However, this disease is not well understood, under treated and under estimated. Aging-related diseases come with several comorbidities, making the disease difficult to identify. Results from the Three-City (3C) study evidenced that only a third of incident dementia cases have recourse to a specialist (14, 15). In Europe, only a low proportion of patients are treated with cholinesterase inhibitors, with high disparities between countries.

Dementia is thus a complex disease leading to important consequences for patients, families and society in term of health, burden and economy; and can no longer be neglected. It is therefore important to understand the evolution of this disease over time as well as the determinants associated to identify potential target to prevent or delay dementia occurrence.

1.1. Aging and dementia

Alzheimer disease has first been characterised by Alois Alzheimer in 1906. However, no real improvement on the knowledge of the disease has been made before the 80's, when the main hallmarks of the disease have been identified. At the same time, the creation of the first association of family members and the mediatisation of the disease has increased awareness around dementia as a real disease and not only the consequence of aging.

1.1.1. Definition

Dementia is commonly defined as a syndrome associating a cognitive decline and a repercussion on the ability to perform everyday life activities. Its clinical diagnosis takes into account multiple indicators including neuropsychological evaluations, neurological examinations, global medical records, as well as complementary information including neuroimaging. Clinical diagnosis is often based on consensus criteria; the most used being the Diagnostic and Statistical Manual of Mental Disorder (DSM). Until recently, the DSM-IV version for Dementia was focusing on memory impairment associated with at least one of the following deficit: aphasia, apraxia, agnosia, or disturbance in executive functioning. These cognitive deficits had to cause significant impairment in social or occupational functioning.

Mild Cognitive Impairment is defined has been defined as impairment in memory or other cognitive function greater than expected for normal aging without significant impairment of activities of daily living. In the last DSM-V version, the term Dementia disappeared and was replaced by two different levels of severity: 1) Minor Neurocognitive Disorder, allowing an intermediate state between a normal cognitive status and a severe cognitive trouble impacting activities of daily living, and 2) Major Neurocognitive Disorder, relating to the former dementia terminology. The first stage refers to mild to moderate cognitive alterations without major impact on everyday functioning. The second stage refers to cognitive deficits severe enough to impact daily living activities. Criteria from DSM IV and V are detailed in table 1.

Different aetiologies can be distinguished. Accounting for 50 to 70% of cases, Alzheimer's disease is the most frequent form of dementia. Unpublished data from the 10 year follow-up of the Three-City study (3C) confirmed this proportion (table 2). Then, the other major causes are vascular dementia, dementia with Lewy's body, and diseases related to fronto-temporal dementia. However, with aging, dementia has mainly mixed aetiology, combining Alzheimer's disease and other aetiology, in particular small vessel disease.

Table 1: Dementia definitions according to different criteria

DSM-IV criteria	**Peterson's criteria (16)**	**DSM-V criteria**	
Dementia	Mild Cognitive Impairment	Major Neurocognitive disorder	Minor Neurocognitive disorder
A. The development of multiple cognitive deficits manifested by both:	A. Impairment in memory or other cognitive function greater than expected for normal aging.	A. Evidence of **significant** cognitive decline from a previous level of performance in one or more cognitive domains (Learning and memory, Language, Executive function, …)	A. Evidence of **milder** cognitive decline from a previous level of performance in one or more cognitive domains (Learning and memory, Language, Executive function, …)
1. Memory impairment		1. Evidence of decline is based on: Concern of the individual, a knowledgeable informant, or the clinician that there has been a **significant** decline in cognitive function	1. Evidence of decline is based on: Concern of the individual, a knowledgeable informant, or the clinician that there has been a **mild** decline in cognitive function
2. At least one of the following: - Aphasia - Apraxia - Agnosia - Disturbance in executive functioning (planning, organizing, …)		2. A **substantial** impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.	2. A **mild** impairment in cognitive performance preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.
B. The cognitive deficits in A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning	B. No significant impairment of activities of daily living	B. The cognitive deficits **interfere** with independence in everyday activities (at a minimum, assistance should be required with complex instrumental activities of daily living)	B. The cognitive deficits **do not interfere** with independence in everyday activities (complex instrumental activities of daily living are preserved)

Dementia	Mild Cognitive Impairment	Major Neurocognitive disorder	Minor Neurocognitive disorder
C. The course is characterized by gradual onset and continuing cognitive decline		C. The cognitive deficits do not occur exclusively in the context of a delirium	C. The cognitive deficits do not occur exclusively in the context of a delirium
D. The cognitive deficits do not occur exclusively during the course of delirium		D. The cognitive deficits are not better explained by another mental disorder (eg, major depressive disorder, schizophrenia)	D. The cognitive deficits are not better explained by another mental disorder (eg, major depressive disorder, schizophrenia)
E. The cognitive deficits are not better explained by another mental disorder (eg, major depressive disorder, schizophrenia)			

Table 2: Distribution according to aetiology from dementia cases at the 10 year follow-up of the Three-City (3C) Study (n=90).

Aetiology	**Frequency (%)**
Probable AD	35 (38.5)
Possible AD / mixed dementia	30 (33.0)
Vascular Dementia	9 (9.9)
Parkinsonian Dementia	7 (7.7)
Dementia with Lewy Bodies	6 (6.6)
Others	4 (4.2)

In this manuscript, we will mostly focus on the dementia syndrome rather than its different aetiologies described above. First, especially in epidemiological studies, it is indeed difficult to collect all the information required to establish an exact etiologic diagnosis. Furthermore, as we get older, the probability to combine several kinds of lesions in elderly patients increases. For example, Alzheimer's lesions, that are extracellular deposits of the amyloid-β peptide and intracellular accumulation of abnormally phosphorylated tau neurofibrillary tangles, may be associated with vascular damages such as macro- and/or microscopic infarctions, atherosclerosis, arteriolosclerosis, and white matter lesions. This is leading to mixed pathological form of dementia (17, 18).

1.1.2. Epidemiology of dementia, worldwide and in Europe

In order to describe the extent of dementia as a public health priority, many population-based studies following older people over time have been implemented from the end of the 80's to the 90's. Knowledge about descriptive epidemiology of dementia and its consequences mainly come from these studies. This kind of study, with longitudinal follow-up of the participants allowing to document cognitive decline over time and active screening and diagnosis of dementia, is one of the main ways to accurately estimate prevalence and incidence of dementia. However, they are not exempt from issues such as low participation rates or drop-out over the follow-up, leading to generalisation problems.

1.1.2.1. Prevalence

The prevalence of a disease, i.e. the number of persons living with the disease at a certain time or period, depends on two indicators: the incidence (defined as the number of new cases of a disease during a defined period) and the mean duration of the disease. A change in prevalence involves a change in one of these indicators.

In 2015, the World Alzheimer Report based on prevalence study worldwide has estimated a prevalence of dementia of 46.8 million cases (6). According to projection, the number of people living with dementia is expected to rise to 74.7 million in 2030 and 131.5 in 2050. An important proportion of this projected increase will be attributable to increases of the numbers

of people with dementia in low and middle income countries (LMIC) (Figure 2). It could be explained by an accelerated demographic evolution in those countries with an important increase of the elderly population. Indeed, in 2015, 58% of all people with dementia live in LMIC, rising to 63% in 2030 and 68% in 2050. East Asia is the world region with the most people living with dementia (9.8 million), followed by Western Europe (7.4 million).

According to the World Alzheimer Report, more than one million people are living with dementia in France. This is in line with a study, based on incidence estimates from the Eurodem analyses, estimating a prevalence of 966,000 (757,000 – 1,254,000) cases of dementia in France in 2015, representing 8.1% of the 65 + population (19). The forecasted prevalence in France should be of almost 2 million in 2050. These projections of the future number of dementia cases are made under a strong hypothesis assuming that dementia incidence is stable over time.

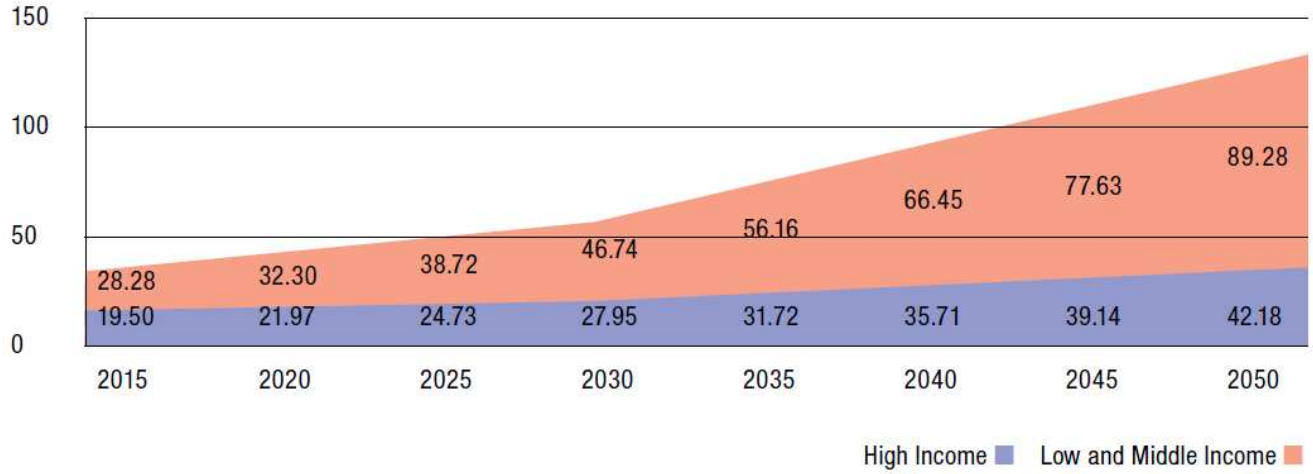


Figure 2 : The growth in numbers of people with dementia (millions) in high income (HIC) and low and middle income countries (LMIC). (World Alzheimer Report 2015)

1.1.2.2. Incidence

The most recent estimation of dementia incidence from a meta-analysis reports over 9.9 million new cases of dementia each year worldwide, meaning one new case every 3.2 seconds. The age and gender standardized global incidence for those aged 60+ is 17.30/1000 person-year (pyr). Globally, the incidence of dementia varies from 3.9/1000 person-years at

age 60-64 to 104.8/1000 pyr at age 90+. Dementia incidence appears to be higher in high incomes country than in low or middle income countries (Figure 3). Important differences are shown between world regions with 4.9 million new cases (49% of the total) in Asia, 2.5 million (25%) in Europe, 1.7 million (18%) in the Americas and 0.8 million (8%) in Africa. Differences between countries seem to be wider for higher age groups. In LIC, quality and availability of studies bring difficulties to estimate incidence or prevalence adequately. Incidence could be less precise and diagnostic criteria different compared to HIC. A selection of elderly populations with less dementia could also appear because mortality is higher in these countries.

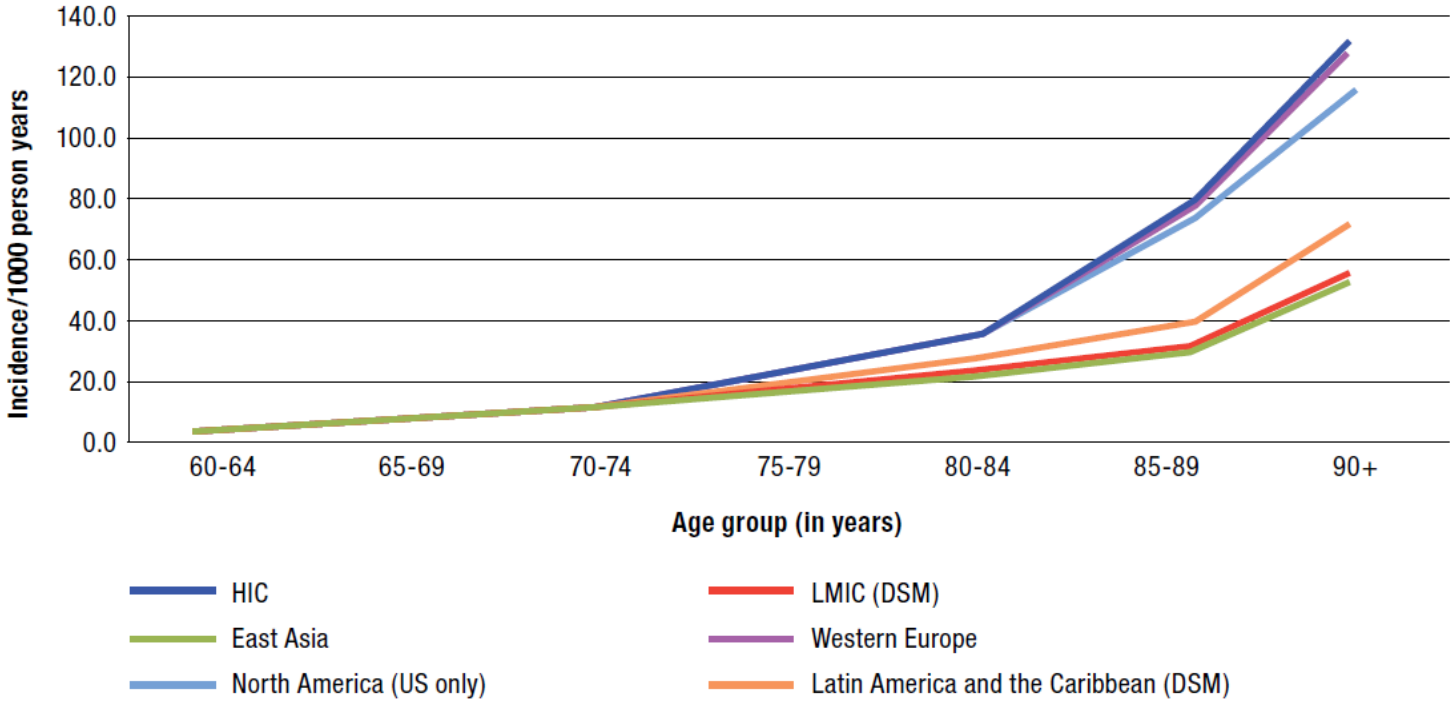


Figure 3: Estimated age-specific annual incidence of dementia, derived from Poisson random effects models, for world regions for which meta-analytical synthesis was feasible. (World Alzheimer Report 2015)

Incidence data have not recently been updated in France or in Western Europe. A collaborative incidence study based on European population-based cohorts in 2000 showed a global incidence of 2.4/1000 pyr (1.8-4.8) at age 65-69 and of 70.2/1000 pyr (54.4-77.4) at age 90+ (20). A French report on dementia in 2005 estimated the number of new dementia cases at 225,000 for the 2004 year (21).

1.1.2.3. Disability, institutionalisation

From 2050, it is predicted that there will be 613 million dependent people worldwide, of whom 277 million (45%) would be aged 60 or over (22). Dementia leading to multiple incapacities, mild at first then progressively aggravated, demented elderly need daily care to perform everyday life activities. According to WHO, people can generally expect to be in the mild or early stage of dementia (eg, forgetful, some language difficulties, and mood changes) for the first year or two, the moderate or middle stage (eg, very forgetful, increasing difficulty with speech, and help needed with self-care activities) from the second to the fourth or fifth years, and the severe or late stage (eg, serious memory disturbances and nearly total dependence and inactivity) from the fifth year onwards (11). However, the early stage can also evolve over a longer period. Developing dementia lead to increased disability as demonstrated in a French study showing that among people with dementia, 94.6% had IADL disability and 13.8% had bADL disability. Moreover, in the elderly population aged 75 years and older, 34.1% of subjects disabled in IADL and 87.8% of subjects severely disabled in ADL had dementia (10). As a result, dementia is one of the major causes of institutionalization with an increased HR of 1.5 to 5.1 and OR even higher (23, 24). Among dementia cases, the probability to reside in an institution is high (25), with an increased risk of 20% in the first year after diagnosis to 50% after 5 years. The median time until institutionalization was found around 30 months after diagnosis (26, 27). Analyses from the PAQUID study showed that among elderly in home care settings, 70% have dementia, and that 39% of demented persons live in institution (10). Because of repercussions in term of dependency, with help needed for everyday living and possibly institutionalisation, dementia thus leads to high medical and social costs for patients and society. Indeed, the worldwide costs of dementia have been reported at 818 billion US dollars in 2015 (28). However, these costs remain concentrated in HIC, even though the part of LMIC in the dementia burden is increasing. Thus, global costs of dementia are expected to keep rising in the upcoming years.

1.1.2.4. Survival

At age 65, the global life expectancy for France was 16.6 (18.42-18.78) for men and 23.0 (22.73-23.18) for women in 2010. In 2030, it is expected to rise to 21.47 (17.83-24.69) for men and 26.05 (22.43-29.01) for women (4). Developing dementia strongly increase mortality (29, 30). A French study reported a 1.8 (1.46-2.21) adjusted risk of dying after developing dementia (30). Thus, dementia leads to a reduction of duration of life. Duration of life (or survival) consists of the total number of years an individual is going to spend being demented. In a study based on European cohorts, prevalent cases had consistently lower survival rates than noncases in all age groups (31). Survival with dementia decreases with age at diagnosis, being a man and high educational level. Estimations of duration of life with dementia are heterogeneous across study. Indeed, the age range of the population, the type of the population (clinical or population-based), and the methodology applied vary across study. Duration of life is mostly comprised between 3 and 9 years before death (30, 32-35). Beyond survival with dementia, another frequently estimated indicator is life expectancy. Life expectancy with dementia quantifies the effect of dementia on the survival of the total population. This indicator corresponds to the average number of years one is expected to live with dementia. This measure accounts for both dementia incidence and expectation of life based on population-level trends rather than the trends of only those with dementia. Estimations are fluctuant between countries; however, life expectancy with dementia consistently declines with age and is higher for women and low educational attainment (36-38). A recent study from the Adult Changes in Thought (ACT) Study showed a total life expectancy of 17.1 y (0.0 – 19.1) with 88.4% being without dementia at 70 y.o. and of 5.5 y (4.7-6.6) with 77.4% being without dementia at 90 y.o. (39). The potential years of life lost (YLL) - ie, the average number of additional years a person would have lived if he or she had not died prematurely because of dementia - in people aged 75 years or older has been estimated at 3–5 years (40, 41).

1.1.3. Risk and Protective factors

Dementia is known as a multifactorial disorder, being the consequence of the interplay of genetic susceptibility and environmental factors across the lifespan (42). The exposition to multiple risk factors thus leads to an increase of the risk to develop the disease. Knowledge on risk factors mostly comes from observational studies that have identified associations between the factor and the risk of dementia or AD. For many risk factors, population studies are often converging. It is yet to mention that for some risk factors, reverse causation cannot be totally excluded and may biased associations.

1.1.3.1. Non-modifiable risk factors

- **Age**

The most important risk factor of dementia is age. Indeed, the risk to develop dementia increase exponentially with age, as well as dementia prevalence. In most of the world regions, prevalence started at almost 1% at age 60-64, rising to more than 20% at age 85+ (43, 44). Alongside with age, women tend to have higher risk of dementia than men (20). However, it is not always true in every country, with incidence of dementia being higher for men than for women in the UK for example (45).

- **Genetic**

Some genetic characteristics also predispose to dementia. The most important factor is the APOE protein, with people carrying the ε4 allele being more at risk than the other (46, 47). A meta-analysis showed an increased risk of 3.2 and 14.9 for carriers of one or two ε4 alleles, respectively (48). On the contrary, carrying the ε2 allele protects against dementia (OR=0.11 (0.02-0.50) (49). Genetic research of Alzheimer's disease has strongly developed over the last decade and other genes have been evidenced as involved in the development of AD (50, 51). However, these genes only slightly increase the risk (52). Genetic research mostly aims at identifying metabolic pathways for better understanding of physiopathology and the development of new treatments.

1.1.3.2. Modifiable risk factors

- **Psychosocial factors**

Educational level is one of the earliest factors in life influencing the risk of dementia. Indeed, people with higher educational attainment or number of years of education have a lower risk of developing dementia than people with low educational level (53-56). In addition to education, principal occupation also contribute to dementia risk through cognitive abilities (57). Cognitive activity or mentally stimulating activity has also been associated with reduced dementia risk, as well as social engagement and the maintenance of a rich social network (58, 59).

The impact of these factors has been hypothesized to be link to the notion of cognitive reserve (60). Education and mental stimulation is supposed to help building cognitive reserve that enables individuals to keep functioning at a "normal" level despite the presence of neurodegenerative pathology. It has also been evidenced by some autopsy studies that subjects with normal cognitive function presented evidence of AD neuropathology (61). Cognitive reserve of these subjects allows them to compensate the lesions.

- **Cardiovascular factors**

Cardiovascular health factors are also known to influence dementia risk (62-64).

Blood Pressure: Association between high blood pressure or hypertension and increased risk of dementia has mostly been evidenced when blood pressure at midlife is assessed (65-70). A review also showed an association between hypertension and cognitive function (71). Midlife hypertension may contribute to AD through vascular mechanisms (72, 73). Indeed, hypertension is a risk factor for small vessel disease, i.e. pathological processes affecting the small arteries, arterioles, venules and capillaries of the brain, which increase the risk of dementia.

Cholesterol: Results regarding the implication of cholesterol level in dementia risk are mixed. Several studies have reported that a high total cholesterol level in midlife increase the risk of developing dementia (74-76). On the contrary, some studies showed that a decline in serum

total cholesterol level could be associated with early stages in the development of dementia (77-79).

Diabetes: Several studies have reported that diabetes lead to an increased risk of dementia. A meta-analysis evidenced a pooled adjusted risk ratio of 1.47 (1.25-1.73) for all dementia, of 1.39 (1.16-1.66) for AD and of 2.38 (1.79-3.18) for vascular dementia (80). Similar results were found in other meta-analysis studies (81, 82). The findings of mechanistic studies suggest that vascular disease and alterations in glucose, insulin, and amyloid metabolism underlie the pathophysiology (83). Diabetes may also contribute to AD through vascular mechanisms. Other mechanisms such as blood glucose levels, insulin resistance, inflammation or alterations in beta-amyloid metabolism have also been mentioned (83, 84).

Obesity: Obesity at midlife has been linked with higher risk of dementia and AD (85, 86). A meta-analysis showed an increased risk of 1.59 (1.02-2.5) (81). Another meta-analysis study based on midlife obesity also showed a 1.91 (1.4-2.62) risk for dementia in US and China (87). However, underweight people at older ages seem to be more at risk of developing dementia (86, 88). This could be due to reverse causation because weight loss often occurs in early phase of dementia. Mid-life obesity is inter-related and all linked to vascular health through several mechanisms such as inflammation for instance (89, 90).

- **Lifestyle factors**

Several lifestyle factors have also been shown to be related to dementia.

Smoking: Smoking has been associated to an increased risk of dementia, especially with lifelong exposure (91, 92). A meta-analysis reported that current smokers had a higher risk of 1.27 (1.02-1.60) than never smokers and the association was even stronger for AD and vascular dementia. They also showed that current smokers had greater yearly declines in MMSE scores than never smokers (RR=1.70 (1.25-2.31)) (93). Smoking is most likely related to dementia through vascular diseases, as smoking contributes to a variety of vascular disorder such as atherosclerosis and cerebrovascular disease. Moreover, the chemicals contains in tobacco smoke are known to be neurotoxins and could contribute to AD through oxidative stress or inflammatory processes (94).

Physical activity: Practicing a regular physical activity has been evidenced to help reduce dementia incidence (95-99). A meta-analysis reported a reduced risk of cognitive decline of

0.65 (95% CI 0.55-0.76), and dementia of 0.86 (95% CI 0.76-0.97) (98). However, the association has not always been found significant and the definition of physical activity is quite heterogeneous across studies. Physical activity is mostly associated with healthy lifestyle and diet and is beneficial on brain structure and function. Moreover, physical activity is protective factor from several cardiovascular risk factors cited above which could impact dementia risk.

Diet: Several nutrients, in particular anti-oxidant vitamins and poly-unsaturated fatty acids have been shown to be associated with a decreased risk of dementia or cognitive decline. Adherence to a Mediterranean diet (or related diet), considered as a healthy diet, has also been associated to a reduced incidence of AD and to slower cognitive decline (100-105).

- **Depression**

Depression is strongly correlated with dementia but the temporal relation is complex: indeed, it is somehow difficult to determine if it precedes, coincides with or follows dementia onset (106-110). Several studies have though showed that depression is associated with approximately two-fold increase in risk of developing cognitive impairment or dementia (111-113). Depression could be related to dementia through vascular disease and also because of alterations in stress-related hormones, lower levels of neuronal growth factors and reduced hippocampal volume (114).

- **Other factors**

Beyond the frequently investigated factors described above, some other factors could be mentioned as increasing the risk of dementia. Some infectious diseases such as Herpes Simplex Virus or Helicobacter pylori infection have been linked to increased risk of dementia or AD (115-119). Other environmental factors such as pesticides or aluminium have been associated with increased risk of dementia (120-122). Moreover, co-morbidities are frequent with advancing age and some of them, in particular sensorial deficit, have been related to cognitive impairments (123-125).

1.1.3.3. Life course approach

A life-course approach considers factors that act during development and ageing, which might influence disease onset (126). Brain and cognitive reserve, developed early in life, and consolidated in midlife may attenuate or delay the expression of symptoms of dementia in the presence of neurodegenerative disease (60). It is therefore important to investigate associations between risk factors at mid-life and dementia. To better understand which risk factors lead to disease initiation, progression and prognosis, a life course approach to the epidemiologic study of dementia is needed (127). It also provides information on the different trajectories to health and disease in old age. There are evidences that factors as soon as foetal development and birth could be linked to cognitive function and ageing (128, 129). Moreover, several of the risk factors listed above play a role as soon as midlife (130-132). A Finnish study showed that high systolic blood pressure (≥160 mm Hg) or high serum cholesterol concentration (≥6.5 mmol/l) in midlife was significantly associated with higher risk of Alzheimer's disease in later life (66). Another study evidenced that an increasing number of midlife vascular risk factors was associated with an elevated cerebral amyloid load (133). Finally, healthy diet at midlife has also been linked to greater health and well-being in elderly people (134). These results are consistent with the impact of multiple risk factors on the brain through the whole lifespan (figure 4).

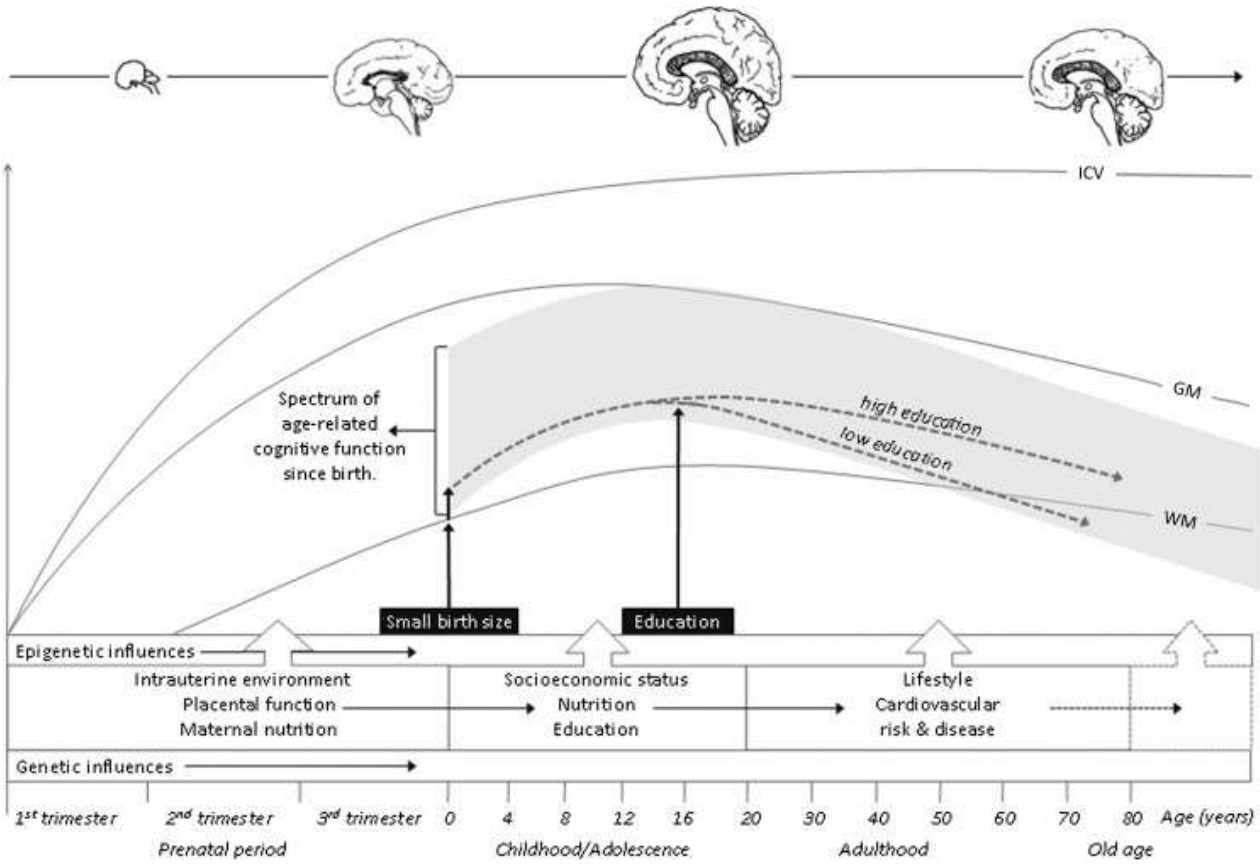


Figure 4: Hypothesized model on the origins and life course of brain aging. Several "critical periods" (prenatal period, childhood/adolescence, adulthood, and old age) are identified during which an individual is at greatest risk of damage if exposed to putative risk factors. (from Muller M et al, 2014).

1.1.4. Prevention

In the absence of effective pharmacologic treatments against dementia, prevention should target factors that can be influenced by medical interventions or individual behaviour. Prevention thus needs to focus on the modifiable risk factors listed above and commonly identified in the literature (figure 5).

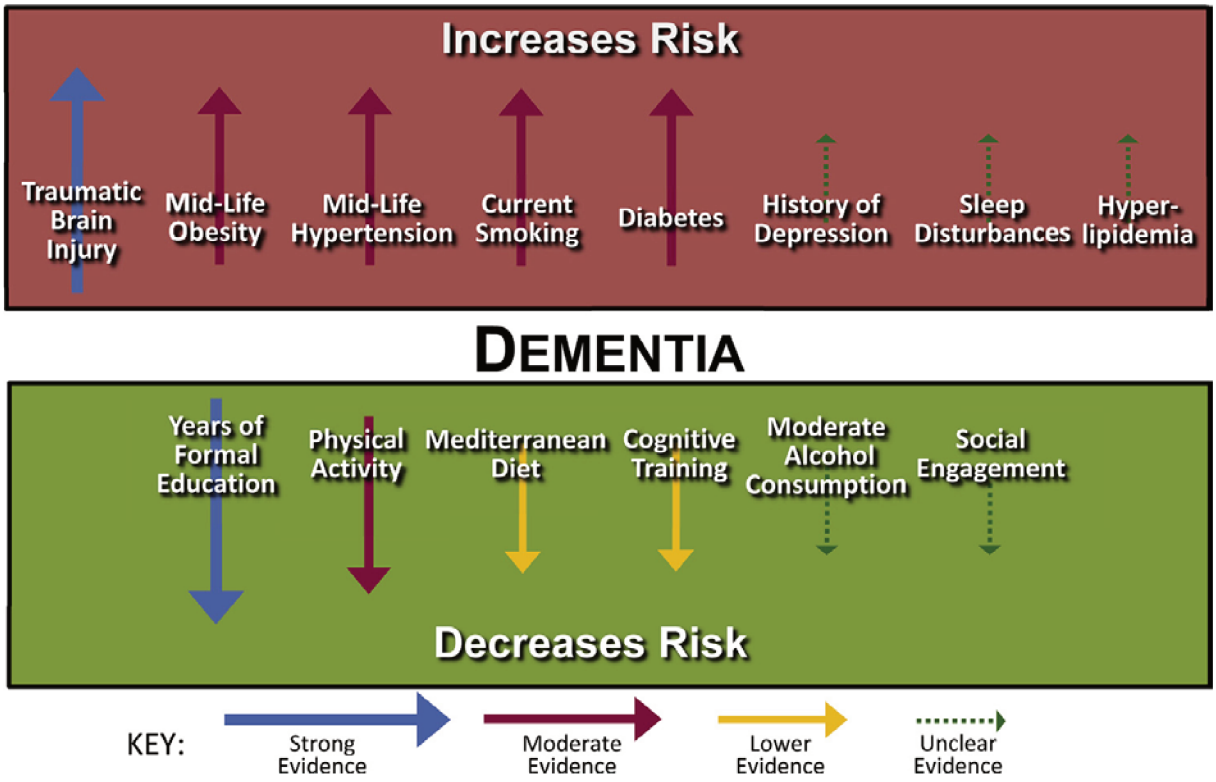


Figure 5: Strength of evidence on risk factors for dementia (from Baumgart M et al, 2015).

Most of dementia cases are at least partly attributable to some cardiovascular risk factors and psychosocial factors, which could be targeted for intervention (91, 130). A few studies have reported evidences on some modifiable risk factors to reduce cognitive decline and dementia (42, 135). Medical and public health interventions to lower various cardiovascular risk factors may lead to an additional benefit of improving cognitive health and then lower the risk of dementia. The goal of prevention will thus be to prevent, delay, or slow age related cognitive decline or clinical dementia and its subtypes. A study has reported that a delay in the onset of dementia by just 5 years might reduce the number of cases in total by up to 50% over 50 years and if onset could be delayed by 1 year, there would be nearly 800,000 fewer prevalent cases in the USA (136). A few studies have also modelled the effect of the reduction of main risk factors' prevalence on the number of dementia cases (63, 137, 138). They focused on seven modifiable risk factors (low education, smoking, diabetes, midlife hypertension, midlife obesity, depression, and physical inactivity) and reported that 28.2% (95% CI 14.2–41.5) of AD cases were attributable to these factors, which equates to 9.6 million attributable cases (95% CI 4.8–14.1 million) of 33.9 million cases. A reduction of 10% per decade in the

prevalence of each of these seven risk factors could reduce the prevalence of Alzheimer's disease in 2050 by 8.3% worldwide (137). This 10% reduction could potentially prevent up to 1.1 million cases of AD per year worldwide (63).

However, even if some risk factors have been strongly identified as increasing dementia risk, the impact of medication or care has been poorly evidenced in randomised control trials and more complex interventions should be investigated. A systematic review published in 2010 by the Agency for Healthcare Research and Quality and an associated "state of the science" conference at the National Institutes of Health (NIH) concluded that there was insufficient evidence to make recommendations about interventions to prevent cognitive decline and dementia (139). Prevention strategies will thus be further detailed in discussion.

1.2. Secular trends

As defined earlier, dementia prevalence depends on incidence and duration of the disease. The forecasted prevalence described in the first part were based on the assumption that dementia incidence remained stable over time and did not take into account possible past or future evolution. Yet, as seen in the section above, a potential evolution of several modifiable risk factors could have modified the risk of dementia and cognitive decline. The main hypothesis lay on a development or better management of these factors over the last decades (140). Indeed, prevention could have led to a reduction of their prevalence, which could lower the risk of dementia. A decrease in dementia incidence could thus be the result of the improvement of these factors. Several studies have thus investigated secular trends over the last decades in terms of prevalence, incidence of dementia and/or survival with dementia (141, 142). Dementia being characterised by cognitive decline with repercussions, it is interesting to look whether the decrease in dementia incidence is associated with an improvement in cognition and/or disability. Some studies have thus investigated more closely the cognitive and functional abilities across generations.

1.2.1. Dementia

1.2.1.1. Trends in prevalence

Trend in prevalence of dementia has been investigated in several studies from Europe and the USA. Detailed characteristics and results are shown in table 3.

Most of the prevalence studies have been based on cohort studies. Although this kind of study is probably the most appropriate way to accurately evaluate prevalence because of undiagnosed dementia, an issue when using cohort studies is that they carry biases linked to selection. With participation rates that tend to be lower in more recent cohorts, it might lead to overestimated trends.

In Sweden, three different studies have been conducted. First, a study based on two cohorts (the Kungsholmen Project (KP), n=1,700 and the Swedish National study on Aging and Care in Kungsholmen (SNAC-K), n=1,575) reported a stable prevalence between 1987-1989 and 2001-2004 (adjusted odds ratio for dementia OR=1.17 (0.95-1.46)) (143). Then, a study from Gothenburg compared participants aged 70 y.o. in 1976-1977 (n=404) and in 2000-2001 (n=579), and aged 75 y.o. in 1976-1977 (n=303) and 2005-2006 (n=753). This study did not evidence a relation between birth cohort and dementia (144). Finally, two rural populations from the Nordanstig Project (NP) in 1995-1998 (n=303) and the SNAC-Nordanstig in 2001-2003 (n=384) were compared in 78 y.o. and older and showed a trend toward a reduced prevalence of dementia (OR=0.71 (0.48-1.04)) (145).

A study in the UK compared participants aged 65 y.o. and older from the Cognitive Function and Ageing Study (CFAS) I and II in 1990-1993 and 2008-2011. They reported a decrease in prevalence with an OR of 0.7 (0.6-0.9) (146). A Spanish study of elderly aged 65 y.o. and older from the Zarademp 0 and 1 studies (n=1,080 and 3715) showed a prevalence ratio of 0.75 (0.56-1.02), with a significant decrease for men only (147). Evidence from France comparing prevalence among rural participants between the PAQUID study in 1988-1989 (n=595) and the Aging Multidisciplinary Investigation (AMI) study in 2007-2008 (n=906) were shown based on two diagnosis approaches: a clinical and an algorithmic one. The first approach showed an increase in prevalence with an OR=2.50 (1.52-4.12) and the second one a decrease of the prevalence with an OR=0.60 (0.42-0.87) (148).

In the USA, an American study compared prevalence in elderly African Americans in Indianapolis aged 70+ between 1992 and 2001 and showed a stable prevalence (rate=6.75 (5.77-7.74) and 7.45 (4.27-10.64)) (149). Then the Health and Retirement Study (HRS) was used to compare prevalence assessed by an algorithm on cognitive measures between participants aged 65 years or older from two waves: the 2000 (n=10,546) and the 2012 one (n=10,511). It reports a significant decline from 11.6% (10.7-12.7%) to 8.8% (8.2-9.4%) (150).

Finally, two studies reported prevalence of cognitive impairment rather than dementia. First, another study from the HRS compared cognitive impairment consistent with dementia between 1993-1995 (n=7406) and 2002-2004 (n=7104). In 1993 and 2002, 12.2% and 8.7% of those aged 70+ had cognitive impairment respectively, suggesting a compression of cognitive morbidity (151).

A few other prevalence studies are based on electronic health records. These data carry biases due to inadequate capture of milder cases of dementia and underdiagnoses which could lead to an important amount of missed cases. A German study based on health insurance data reported a yearly reduction between 1% and 2% in the prevalence of dementia only among women aged 75 to 84 years between 2007 and 2009 (152). Another American study reported an average decline in the prevalence of Severe Cognitive Impairment on individuals aged 65+ participating in National Long Term Care Surveys for 1982, 1984, 1989, 1994, and 1999 from 5.7% to 2.9% (153).

Table 3: Studies estimating changes in dementia prevalence over time (adapted from Wu YT et al, 2017).

1st author, year	Study population	Diagnostic methods	Cohorts (n)	Comparison	Odds ratio (95% CI)
Wiberg et al, 2013	People aged 70 years and 75 years in Gothenburg, Sweden	Clinical diagnosis (Historical criteria, similar to DSM-III-R)	*1*: 1976–1977 (*n* = 707, R = 79%) *2*: 2000–2001 (*n* = 579, R = 66%) *3*: 2005–2006 (*n* = 753, R = 63%)	2000 vs 1976 (70 y.o.)	
				Total	1.2 (0.5, 3.0)
				Men	0.5 (0.1, 3.1)
				Women	1.7 (0.6, 5.1)
				2005 vs 1976 (75 y.o.)	
				Total	1.2 (0.7, 2.2)
				Men	1.0 (0.4, 2.3)
				Women	1.4 (0.6, 3.3)
Wimo et al, 2016	People aged ≥78 years in Nordanstig, Sweden	Clinical diagnosis (DSM-III-R)	*1*: 1995–1998 (*n* = 303, R = 90%) *2*: 2001–2003 (*n* = 384, R = 77%)	2001 vs 1995	
				Total	0.7 (0.5, 1.0)
				Men	0.5 (0.2, 0.9)
				Women	0.9 (0.5, 1.4)
Qiu et al, 2013	People aged ≥75 years in Kungsholmen, Stockholm, Sweden	Clinical diagnosis (DSM-III-R)	*1*: 1987–1989 (*n* = 1,700, R = 72%) *2*: 2001–2004 (*n* = 1,575, R = 73%)	2001 vs 1987	
				Total	1.2 (0.9, 1.5)
				Men	0.9 (0.6, 1.5)
				Women	1.2 (1.0, 1.6)

1st author, year	Study population	Diagnostic methods	Cohorts (n)	Comparison	Odds ratio (95% CI)
Lobo et al, 2007	People aged ≥65 years in Zaragoza, Spain	Clinical diagnosis (DSM-III-R)	*1*: 1987–1989 (*n* = 1,080, R = 95%) *2*: 1994–1996 (*n* = 3,715, R = 64%)	1994 vs 1987 Total Men Women	 0.8 (0.6, 1.0) 0.4 (0.3, 0.6) 1.0 (0.7, 1.5)
Matthews et al, 2013	People aged ≥65 years in England (Newcastle, Nottingham, Cambridgeshire), from CFAS I and II, UK	Algorithmic diagnosis (GMS-AGECAT, similar to DSM-III-R)	*1*: 1991–1994 (*n* = 7,635, R = 80%) *2*: 2008–2011 (*n* = 7,796, R = 56%)	2008 vs 1991 Total Men Women	 0.7 (0.6, 0.9) 0.6 (0.5, 0.8) 0.8 (0.7, 0.9)
Hall et al, 2009	African- American people aged ≥70 years in Indianapolis, USA	Clinical diagnosis (DSM-III-R, ICD-10)	*1*: 1992 (*n* = 1,500, R = 86%) *2*: 2001 (*n* = 1,892, R = 44%)	2001 vs 1992 Total	 1.1 (0.9, 1.4)
Pérès et al, 2017	Farmers aged ≥65 years from PAQUID and AMI in Bordeaux, France	Clinical diagnosis (DSM-III-R)	*1*: 1988–1989 (*n* = 595, R = 69%) *2*: 2007–2008 (*n* = 906, R = 52%)	2007 vs 1988 Total	 2.3 (1.5, 3.4)
		Algorithmic diagnosis (MMSE + IADL)	*1*: 1988–1989 (*n* = 595, R = 69%) *2*: 2007–2008 (*n* = 906, R = 52%)	2007 vs 1988 Total	 0.6 (0.4, 0.7)
Langa et al, 2017	People aged ≥65 years in the HRS, USA	Algorithmic diagnosis (phone or face-to-face interview, 27-item cognitive test or proxy assessment + IADL)	*1*: 2000 (*n* = 10,546, R = 88%) *2*: 2012 (*n* = 10,516, R = 89%)	2012 vs 2000 Total Men Women	 0.8 (0.7, 0.9) 0.7 (0.6, 0.8) 0.8 (0.7, 0.9)

1.2.1.2. Trends in incidence

A growing number of studies have suggested decline in incidence of dementia (table 4). In the United States, a significant decline between 1984 and 1995 was observed in one out of four sites, suggesting a 30% decrease in 10 years but this was not supported by the 20 year data, nor other US cohort studies (Illinois and Indianapolis) (154). More recent studies from the USA confirmed the decline in dementia incidence. First, 5205 participants of the Framingham Heart Study aged 60 and over were compared across 4 periods: late 1970s-early 1980s, late 80s-early 90s, late 90s- early 2000s, and late 2000s-early2010s. Analyses evidenced a 5-year incidence decline of 22%, 38%, and 44% during the second, third and fourth epochs respectively, compared to the first one (155). Second, one study based on African Americans in Indianapolis investigated incidence from a cohorts of participants enrolled in 1992 followed until 2009 (n=1440) and another enrolled in 2001 followed until 2009 (n=1835); they reported a significantly lower incidence in the 2001 cohort compared to the 1992 cohorts (156). The same study was conducted among participants in Nigeria (1992 cohort n=1774; 2001 cohort n=1895) but did not find a significant difference.
In the Netherlands, a study has investigated incidence on individuals aged 60-90 between two periods: 1990 (n=5727) and 2000 (n=1769). A decline of 25% of 5-year dementia incidence between 1990-95 and 2000-05 has been reported, although non-significant (IRR= 0.75 (0.56-1.02)) (157). The prevalence study from Sweden calculated dementia incidence using mortality and prevalence, suggesting that stable prevalence with increased survival necessarily indicates declining incidence (143). The CFAS I and II studies were also used to compare two-year incidences and evidenced an incidence rate ratio (IRR) of 0.8 (0.6-1.0), this decline being mostly driven by a decreased incidence in men (45).
A study based on people aged 65+ and living in Chicago compared incidence of AD from 1997 through 2008 but did not find any change in the risk of AD over time (158).

As for prevalence data, beyond population-based cohorts, some studies have investigated dementia trends based on health insurance data. The German study based on health insurance data compared incidence between two periods (2004/2007 and 2007/2010) and reported a higher incidence in the first period (RR=1.10, p=0.006) (159). Another study based on health care administrative data from the Canadian Institute for Health Information reported a 7.4% (p=0.009) decrease of incidence rate between 2002 and 2013 (160). Moreover, a study based

on Medicare inpatient records from 1984 to 2001 and linked to the National Long-Term Care Survey (about 380,000 person-years totally) found an increase of dementia incidence rate over time (6.2/1000 p.y. in 1984-1990 to 9.5/1000 p.y. in 1991-2000) (161).

The growing interest for secular trends of dementia is recent and, when this thesis work was initiated, only a few studies had reported secular trends of prevalence and even less of incidence. Secular trends analyses then studied during the last few years have mostly reported decreases in dementia prevalence and incidence, or stable prevalence in some cases. However, studies in favour of a declining risk of dementia mostly took place in Europe and the USA, whereas some studies conducted in East Asian countries have mostly reported increased prevalence or incidence (162-168). For example, a study from The Hisayama Study, based on residents aged 65+ of the Japanese community, compared prevalence in 1985, 1992, 1998, and 2005. They found an increase of dementia prevalence over time: 6.0%, 4.4%, 5.3%, and 8.3% respectively (169). The most recent one from a Japanese community have reported an increased prevalence (for all-cause dementia: 6.8% in 1985, 4.6% in 1992, 5.3% in 1998, 8.4% in 2005, and 11.3% in 2012, p for trend <0.01) and an increased incidence between 1988-1998 and 2002-2012 (for all-cause dementia: HR=1.68 (1.38-2.06); for AD: HR=2.07 (1.59-2.70)) (170). Differences between countries and determinants of these trends will be further analysed in discussion.

Table 4: Studies estimating changes in dementia incidence over time. (Adapted from Wu YT et al 2017)

Study, Country	**Study population**	**Diagnostic methods**	**Cohorts (n)** Incidence duration	**Comparison**	**Hazard ratio/incidence ratio (95% CI)**
Schrijvers et al, 2012	All residents aged 60–90 years in Ommoord district of Rotterdam	Clinical diagnosis (DSM-III-R)	*1*: 1990 (*n* = 5,727, R = 73%) *2*: 2000 (*n* = 1,769, R = 67%) 5 year incidence	2000 vs 1990 Total Men Women	 0.8 (0.6, 1.0) 0.7 (0.4, 1.2) 0.8 (0.5, 1.1)
Matthews et al, 2016	People aged ≥65 years in England (Newcastle, Nottingham, Cambridgeshire) from the CFAS I and II, UK	Algorithmic diagnosis (GMS-AGECAT, similar to DSM-III-R)	*1*: 1991–1994 (*n* = 7,635, R = 80%) *2*: 2008–2011 (*n* = 7,796, R = 56%) 2 year incidence	2008 vs 1991 Total Men Women	 0.8 (0.6, 1.0) 0.6 (0.4, 0.9) 1.0 (0.7, 1.3)
Gao et al, 2016	African-American people aged ≥70 years in Indianapolis, USA	Clinical diagnosis (DSM-III-R, ICD-10)	*1*: 1992 (*n* = 1,440, R = 86%) *2*: 2001 (*n* = 1,835, R = 44%)	2001 vs 1992 Total	 0.4 (0.3-0.5)
	Yoruba aged ≥70 years in Ibadan, Nigeria	Clinical diagnosis (DSM-III-R, ICD-10)	*1*: 1992 (*n* = 1,174, R = 98%) *2*: 2001 (*n* = 1,895, R = 100%)	2001 vs 1992 Total	 0.8 (0.6, 1.1)

Study, Country	Study population	Diagnostic methods	Cohorts (n) Incidence duration	Comparison	Hazard ratio/incidence ratio (95% CI)
Satizabal et al, 2016	Longitudinal cohorts of people aged ≥60 years from the Framingham Heart Study	Clinical diagnosis (DSM-IV)	*Epoch 1*: 1977–1983 (*n* = 2,457) *Epoch 2*: 1986–1991 (*n* = 2,135) *Epoch 3*: 1992–1998 (*n* = 2,333) *Epoch 4*: 2004–2008 (*n* = 2,090) 5 year incidence	1986–1991 vs 1977–1983 Total Men Women 1992–1998 vs 1977–1983 Total Men Women 2004–2008 vs 1977–1983 Total Men Women	 0.8 (0.6, 1.0) 1.0 (0.6, 1.6) 0.7 (0.5, 1.0) 0.6 (0.5, 0.8) 0.9 (0.6, 1.4) 0.5 (0.4, 0.7) 0.5 (0.4, 0.7) 0.6 (0.4, 1.1) 0.5 (0.4, 0.8)

1.2.1.3. Trends in mortality

From a public health perspective and an individual perspective, mortality according to dementia status, life expectancy and survival with dementia are crucial knowledge. If trends in global mortality are easily known from census data in most countries, only a few studies have, however, investigated trends in dementia mortality; these results need to be updated either in time or in methodology (table 5). Moreover, almost no study investigating secular trends of survival or life expectancy without dementia have been conducted.

The Swedish study also compared survival between the KP study in 1987-1994 and the SNAC-K study in 2001-2004. The results showed a decreased mortality with hazard ratio of death being 0.71 (0.57–0.88) in subjects with dementia, 0.68 (0.59–0.79) in those without dementia, and 0.66 (0.59–0.74) in all participants (143). The other study from a rural area in Sweden reported a global decreased risk of dying between 1995-98 and 2001-03 with an adjusted hazard ratio of 0.65 (0.45-0.94), driven by the significant decrease in men (145). A non-significant decrease was also found for people with and without dementia.
Analyses from the Rotterdam Study showed a 37% decline in mortality rate in 10 years (rate ratio=0.63 (0.52-0.77)); however, mortality according to dementia status has not been investigated (157). In the Indianapolis study, the observed decrease in dementia incidence associated with a stable prevalence over time suggests an increasing duration of dementia (declining dementia mortality) (149, 156). Analyses from a Japanese elderly population aged 65+ showed an improved survival for individuals from the 1988 cohort compared to the 2002 cohort (47.3% to 65.2%, $p<0.01$) (170).

Some results regarding mortality with dementia have also been obtained from administrative databases, but with potential biases due to this kind of data. Thus, unlike results from population-based studies, results from German health insurance data showed a lower mortality with dementia in the first period compared to the second one, only significant for women (2006/2007 vs 2009/2010 RR =0.83 (0.76-0.91)). Mortality without dementia tended to decrease for men and remained stable for women (159). They also investigated trends in life expectancies, reporting that remaining life years with dementia were compressed non-significantly for men (0.96 vs 0.87, p=0.18) and significantly for women (1.87 vs 1.53, p=0.000) at age 65. At the same time, remaining life years without dementia increased non-significantly for men (14.79 vs 15.14, p=0.084) and for women (18.14 vs 18.41, p=0.148).

An American study showed that AD mortality increased by 31% from 1999 to 2004 (171). However, they used AD diagnosis from death certificate, which could have biased the results if the diagnosis of AD frequency in primary care had changed over time. Analyses from the HRS participants showed a non-significant decrease of two-year mortality among participants with moderate to severe cognitive impairment from HR=3.11 to HR=2.53 (p=0.09) between 1993-95 and 2002-04 (151).

Analyses relying on population-based studies have reported a decrease in mortality, even if results of mortality according to dementia status are more mixed. Moreover, trends in life expectancies according to dementia status have been poorly investigated. When using administrative database, the mortality with dementia tends to have increased. However, interpretation of results on these specific populations needs to be taken with caution. A study from elderly American based on medical records showed an increase in total life expectancy among men in younger ages, while it tended to be decreasing for older women between 1971 and 1980. The dementia free life expectancy increased for both sex at younger ages and thus the percentage of life free of dementia declined among male and increased among women. The life expectancy with dementia increased in men and decreased in women between 1971 and 1980 (172).

More studies on evolution of mortality and life expectancy according to dementia are thus needed to confirm the decrease in mortality with or without dementia and the increase in life expectancy free of dementia. Discrepancies between results based on population-based studies and administrative databases as well as potential bias when using administrative database will be further discussed in discussion.

Table 5: Studies estimating changes in mortality over time

1st author, year	Study population	Diagnostic methods	Cohorts (n)	Comparison	Mortality ratio (95% CI)
Schrijvers et al, 2012	All residents aged 60–90 years in Ommoord district of Rotterdam, from the Rotterdam Study (Netherlands)	Clinical diagnosis (DSM-III-R)	*1*: 1990 (*n* = 5,727, R = 73%) *2*: 2000 (*n* = 1,769, R = 67%)	2000 vs 1990	Total mortality
				Total	0.63 (0.52-0.77)
				Men	0.64 (0.50-0.82)
				Women	0.59 (0.44-0.80)
Qiu et al, 2013	People aged ≥75 years in Kungsholmen, Stockholm	Clinical diagnosis (DSM-III-R)	*1*: 1987–1989 (*n* = 1,700, R = 72%) *2*: 2001–2004 (*n* = 1,575, R = 73%)	2001 vs 1987	Total mortality
				Total	0.66 (0.59-0.74)
				Men	0.67 (0.54-0.84)
				Women	0.66 (0.57-0.75)
				2001 vs 1987	No dementia
				Total	0.68 (0.59-0.79)
				Men	0.71 (0.55-0.91)
				Women	0.67 (0.56-0.79)
				2001 vs 1987	With dementia
				Total	0.71 (0.57-0.88)
				Men	0.68 (0.40-1.14)
				Women	0.71 (0.55-0.90)

1st author, year	Study population	Diagnostic methods	Cohorts (n)	Comparison	Mortality ratio (95% CI)
Doblhammer et al, 2015	Sample from health claims data from a Germany's insurance aged 50+	-ICD-10 numbers G30, G31.0, G31.82, G23.1, F00, F01, F02, F03, and F05.1 -prescription of cholinesterase inhibitors and/or memantine	*1*: 2006-2007 (n=141092) *2*: 2009-2010 (n=135243)	2006 vs 2009 Men Women Men Women	No dementia 1.04 (p=0.075) 1.00 (p=0.935) With dementia 0.90 (p=0.084) 0.83 (p=0.000)
Wimo et al, 2016	People aged ≥78 years in Nordanstig	Clinical diagnosis (DSM-III-R)	*1*: 1995–1998 (*n* = 303, R = 90%) *2*: 2001–2003 (*n* = 384, R = 77%)	2001 vs 1995 Total Men Women 2001 vs 1995 Total Men Women 2001 vs 1995 Total Men Women	Total mortality 0.78 (0.63-0.97) 0.77 (0.61-0.98) 0.86 (0.68-1.07) No dementia 0.86 (0.67-1.11) 0.88 (0.59-1.29) 0.85 (0.60-1.20) With dementia 0.75 (0.59-1.09) 0.64 (0.34-1.21) 0.89 (0.55-1.43)
Ohara et al, 2017	Resident of a Japanese community aged 65+	Two stage survey of dementia based on the Hasegawa Dementia Scale (HDS), the HDS revised version (HDS-R), and MMSE	*1:* 1988-1998 (n=803) *2:* 2002-2012 (n=1231)	1988 vs 2002	Survival 47.3% to 65.2%, p<0.01

1.2.2. Cognition and disability

Cognitive decline and disability being the two components of dementia, evaluation of trend in these two components could allow a better understanding of the decline in dementia trend. Evolution of cognitive deficits/performances is easier to assess and has been more widely studied than evolution of cognitive decline.

1.2.2.1. Trends in cognition

Evolution over time in level and/or decline has been investigated for different cognitive domains. Table 6 summarises results on secular trends of cognitive performances.

Some studies only looked at level of cognitive abilities and were consistent toward an improvement of cognitive functions (173). A study from Germany analysed cognitive processing speed among participants aged 50 to 90 y.o. of two waves from the German Socio-Economic Panel (SOEP). It showed that the average cognitive functioning of those aged 50–90 and tested in 2012 was higher than that of the same age-group tested in 2006 (174). Another study using two cohorts of Danish nonagenarians born 10 years apart (1905 vs 1915) looked at cognitive functioning assessed by the Mini-Mental State Examination and by a composite score of 5 cognitive tests. It reported that the 1915 cohort scored significantly better on the MMSE and on the composite score than the 1905 cohort (175). Then, a French study based on two generations born more than 15 years apart (the 1991 cohort and the 2008 cohort) analysed the evolution of the Cognitive Efficiency Profile (CEP) global score and sub-scores and showed that the 2008 cohort performed better in all the different cognitive scores, except for the naming one, than the 1991 cohort (176). An English study comparing two cohorts of subjects aged 65 years or older from the MRC CFAS in 1991 (n = 9458) and the ELSA study in 2002 (n = 5196) showed that semantic verbal fluency measured by the animal naming test was higher in the 2002 cohort than in the 1991 cohort (177). Finally, two cohorts of participants from Gothenburg aged 70 y.o. born in 1901-1902 (n=381) and in 1930 (n=551) were compared with a battery of psychometric tests assessing short term memory, verbal ability, spatial ability, reasoning and executive functions. Except for one test assessing short term memory, the second cohort had better scores than the first one (178).

Several articles also investigated trends in cognitive decline. An American study based on the MoVIES and MYHAT cohorts looked at evolution of psychomotor speed, executive function, and language during the period 1987-2012. Authors pooled data from the two studies and categorized participants into four 10-year birth cohorts: those born between 1902 and 1911; between 1912 and 1921; between 1922 and 1931; and 1932 and 1943. They reported significant baseline cohort effects and evolution with age effects for every cognitive outcome: the earliest birth cohort (1902-1911) had lower baseline scores and steeper cognitive declines compared with the latest birth cohort (1932-1943) (179). An update of this work has been made on immediate and delayed recall of a 10-item Word List, assessing verbal memory. They observed that both immediate and delayed recall showed an improvement between the earliest- and latest-born cohorts' performance, at baseline and for age-associated trajectory (180). Another American study using participants from the Seattle Londitudinal Study investigated evolution on several cognitive domains such as spatial orientation, inductive reasoning, word fluency, number ability and verbal meaning between two generations: the first one born between 1883 and 1913 (n=1242) and the second one born between 1914 and 1948 (n=738). Except on number ability, later born cohorts outperformed earlier born cohorts at age 70 by up to 0.50 SD and also showed shallower rates of cognitive decline on all abilities (181). A study based on the Swedish Adoption/Twin Study of Aging compared four cognitive domains (verbal and spatial ability, memory, and speed) between two cohorts: one born in 1900-1925 and the second born in 1926-1948. Results indicated significant cohort differences in average performance at age 67.5 for all components except speed. However, unlike the previously described studies, no cohort differences were found in trajectories over time on the age compared (62 to 78 y.o.) (182). Similar conclusions were established from the Long Beach Longitudinal Study comparing to cohorts tested 16 years apart from ages 55 to 87 on reasoning, list recall, text recall, space and vocabulary (183). On the contrary, two studies found steeper decline for later born cohort. First, a study compared three different cohorts (born in 1901-02, in 1906-07 and in 1930) on logical reasoning (n=1176) and spatial abilities (n=1480). They have reported substantial cohort differences in levels of performance and significant but moderate cohort differences in rates of change. Later-born cohorts, on average, outperformed earlier-born, but also showed a steeper average decline compared with the earliest-born cohort (184). A second study from the Longitudinal Aging Study Amsterdam compared two cohorts aged 65 to 75: the first one (N = 705) was born between 1920 and 1930, whereas the second cohort (N = 646) was born between 1931 and 1941. The later born cohort had better general cognitive performance (assessed by the MMSE), inductive

reasoning, and processing speed at baseline but showed steeper decline in processing speed (185).

Table 6: Studies estimating changes in cognitive function over time.

1st author, year	Study population	Cognitive domains (test)	Cohorts (n)	Main results
Finkel et al, 2007	Participants from the Swedish Twin Registry aged 50+	-Verbal abilities (Information, Synonyms, and Analogies) -Spatial abilities (Figure logic, block design, card rotations tests) -Memory (Digit span, picture memory and Names and Faces) -Processing speed (Figure identification)	*1:* Born between 1900 and 1925 (n=425) *2:* Born between 1926-1948 (n=381)	Verbal: 1900 vs 1926: 50.53 vs 53.95 Spatial: 1900 vs 1926: 49.98 vs 53.22 Memory: 1900 vs 1926: 49.07 vs 53.42 Speed: 1900 vs 1926: 49.31 vs 49.82
Zelinski et al, 2007	Participants from the Long Beach Longitudinal Study aged 55 – 87	-Reasoning (Letter and word series) -List recall -Text recall -Space (Figure and Object Rotation) -Recognition Vocabulary	*1:* Born between 1893-1923 (n=456) *2:* Born between 1908-1940 (n=482)	Reasoning: 1893 vs 1908: 4.37 (0.82); p<.001 List: 1893 vs 1908: 7.54 (1.10); p<.001 Text: 1893 vs 1908: 1.76 (0.56); p<.001 Space: 1893 vs 1908: 1.72 (0.37); p<.001 Vocabulary: 1893 vs 1908: 0.71 (1.21); p>.05
Llewellyn et al, 2009	Community living individuals in England aged 65+	Semantic verbal fluency (animal naming test)	*1:* 1991 (n=680) *2:* 1996 (n=600)	Increase by 1.1 (0.9-1.3) extra words/min

1st author, year	Study population	Cognitive domains (test)	Cohorts (n)	Main results
Sacuiu et al, 2010	People living in Gothenburg (Sweden) aged 70 y.o.	Short term memory (Digit Span Forward, Digit Span Backward) Verbal ability (synonyms) Spatial ability (block design) Reasoning (Figure classification) Executive function (identical forms)	*1:* born in 1901-1902 (n=381) *2:* Born in 1930 (n=551)	Identical forms: 16.6 (8.3) vs 26.2 (7.7); p<.001 Synonyms: 17.1 (6.4) vs 21.6 (5.2); p<.001 Figure Classification: 12.6 (4.6) vs 17.0 (4.6); p<.001) Block design: 13.5 (6.6) vs 20.1 (6.7); p<.001 Digit Span Forward: 5.6 (1.0) 5.8 (1.2); p=0.55 Digit Span Backward: 3.8 (0.9) vs 4.3 (1.1); p=0.002
Gerstorf et al, 2011	Participants from the SLS from age 50 to age 80	-Spatial Orientation - Inductive reasoning -Word fluency -Number ability -Verbal meaning (five subtests from the 1948 PMA 11-17 version of Thurstone's Primary Mental Abilities Test)	*1:* Born between 1886 and 1913 (n=1242) *2:* Born between 1914 and 1948 (n=738)	Spatial orientation: 1914 vs 1886: 4.975 (0.361); p<.05 Inductive reasoning: 1914 vs 1886: 5.818 (0.337); p<.05 Word fluency: 1914 vs 1886: 2.353 (0.609); p<.05 Number ability: 1914 vs 1886: 0.457 (0.443); p=NS Verbal meaning: 1914 vs 1886: 5.408 (0.375); p<.05

1st author, year	Study population	Cognitive domains (test)	Cohorts (n)	Main results
Dodge et al, 2013 and 2017	Individuals aged 65+ from the Voter Registration Lists in Southwestern Pennsylvania	-Psychomotor speed (TMT-A) -Executive function (TMT-B, letter fluency) -Language (animals fluency) -Memory (Immediate and delayed recall)	*1:* Born between 1902-1911 (n=400) *2:* Born between 1912-1921 (n=1387) *3:* Born between 1922-1931 (n=1075) *4:* Born between 1932-1943 (n=718)	TMT-A: 1902 vs 1932:-0.77; p<.0001 1912 vs 1932: -0.51; p<.0001 1922 vs 1932: -0.24; p=0.002 TMT-B: 1902 vs 1932:-1.24; p<.0001 1912 vs 1932: -0.95; p<.0001 1922 vs 1932: -0.54; p<.0001 Letter fluency: 1902 vs 1932:-0.85; p<.0001 1912 vs 1932: -0.66; p<.0001 1922 vs 1932: -0.43; p<.0001 Animals fluency: 1902 vs 1932:-0.89; p<.0001 1912 vs 1932: -0.64; p<.0001 1922 vs 1932: -0.39; p<.0001 Immediate recall: 1912 vs 1902: 0.41; p=0.31 1922 vs 1902: 2.0; p=0.001 1932 vs 1902: 6.10; p<.0001 Delayed recall: 1912 vs 1902: -0.01; p=0.96 1922 vs 1902: 0.44; p=0.12 1932 vs 1902: 2.36; p<.0001

1st author, year	Study population	Cognitive domains (test)	Cohorts (n)	Main results
De Rotrou et al, 2013	Patients attending the memory clinic of the Broca hospital, Paris, France	MMSE CEP score	*1:* 1991 sample (n=204) *2:* 2008 sample (n=177)	MMSE: 27.0 (2.2) vs 29.0 (1.0) ; p<.0001 CEP global score: 63.5 (12.9) vs 77.3 (8.5); p<.0001
Christensen et al, 2013	Participants from Danemark aged 90+	Global cognition (MMSE) a composite of five cognitive tests	*1:* Born in 1905 (n=2262) Assessed at 93 y.o. *2:* Born in 1915 (n=1584) Assessed at 95 y.o.	MMSE: 21.4 (6.0) vs 22.8 (5.6); p<.0001 Composite score: 0.01 (3.6) vs 0.49 (3.6); (p=0·0003)
Steiber et al, 2015	Participants from the SOEP aged 50 to 90	Cognitive processing speed (SDT)	*1:* Tested in 2006 (n=1997) *2:* Tested in 2012 (n=2854)	Men: 2.563 (0.33) increase 2006 -> 2012 Women: 2.237 (0.32) increase 2006 -> 2012
Karlsson et al, 2015	Participants from the H70 study aged 70-79	-Logical reasoning (Figure Logic test) -Spatial ability (Block Design Test)	*1:* Born in 1901-02 (n=460) *2:* Born in 1906-07 (n=513) *3:* Born in 1930 (n=1250)	Logical reasoning: p<.001 1901: 12.67 (12.21-13.14) 1930: 16.19 (15.71-16.66) Spatial ability: p<.001 1901: 13.80 (12.97-14.63) 1906: 16.13 (15.46-16.80) 1930: 19.31 (18.70-19.92)

1st author, year	Study population	Cognitive domains (test)	Cohorts (n)	Main results
Brailean et al, 2016	Participants from the Longitudinal Aging Study Amsterdam aged 55-64	-Global performance (MMSE) -Episodic memory (15 word test) -Processing speed (DSST) -Inductive reasoning (Raven Colored Progresive Matrices)	*1:* Born between 1920-1930 (n=705) *2:* born between 1931-1941 (n=646)	Global performance: 1920 vs 1931: -0.09 (-0.02); p<0.01 Immediate recall: 1920 vs 1931: 0.27 (-0.35); p>0.05 Delayed recall: 1920 vs 1931: 0.12 (-0.18); p>0.05 Processing speed: 1920 vs 1931: -5.02 (-7.14); p<0.001 Inductive reasoning: 1920 vs 1931: -0.57 (-0.95); p<0.01

1.2.2.2. Trends in disability

Dementia has high consequences on health and disability, leading to high costs for patients and society. Several reviews have thus been conducted on health and disability trends (186-188).

Even if some studies evidenced mixed results (174, 189, 190), the majority are consistent toward an improvement of disability over time. A review confirmed the decline in any disability and IADL from eight US studies (191). The Danish study on nonagenarians showed a lower score in ADL (an 11-item self-report measure of physical disability) for the 1905 cohort than for the 1915 one, meaning a decrease in disability (175). A study from Gothenburg examined participants at age 75 in 1976-1977 (n=744) and in 2005-06 (n=731) on ADL and IADL. They reported a significantly decreased disability in both ADL (13.9 vs 5.6%) and IADL (33.4 vs 13.0%). Another study in Finland compared people aged 65-69 years in 1988 (n=362), 1996 (n=320) and 2004 (n=292) on IADL abilities and showed a significant improvement in IADL difficulties between 1988 and 1996, and between 1988 and 2004 (192). A Chinese study investigated trends in ADL and IADL among 4 waves: 1998, 2003, 2005, and 2008. They showed a decreased risk of having ADL disability in 2005 and 2008 compared to 1998 and a decreased risk of IADL disability in all period compared to 1998 (193). In the USA, individuals aged 55 to 70 from the original Framingham Heart Study (n=1760) were compared with those from the offspring cohort (n=1688). Total disability combining a physical activity component (Nagi activities), a gross motor component (Rosow-Breslau activities) and ADL scale showed a significant decrease in disability; however, disability in ADL on its own was stable (194). Two other American papers reported a decreasing trend of disability. They were based on the National Long Term Care Surveys and showed decreases in ADL or IADL disability between 1982 and 1999 (195, 196). Another study on the Longitudinal Study on Aging and the National Health Interview Survey participants reported mixed results with a prevalence of disability lower in the more recent years in the NHIS, a lower incidence of disability, but an increased prevalence at some dates after 1984 in the LSOA sample (197). Results from the French PAQUID study, comparing two generations aged 75 to 84 born between 1903-1912 and between 1913-1922 also showed no change for ADL and a decrease in IADL disability for women only (198). A study from a population aged 70+ from Gloucestershire evaluated four items: outdoor mobility at least able to go outside for short walks, managing to wash or shower independently, managing to dress

easily on own and able to cook or reheat a whole meal, between 1998 and 2008. They showed significant reductions in disability for outdoor mobility, washing difficulty, and cooking (199). Finally, the Swedish study from Gothenburg investigated ADL and IADL dependency between 1976 and 2005 and showed a significant decrease for both (200).

If improvement of cognitive performances has been evidenced in most of the studies, trends of cognitive trajectories are more conflicted. Fewer studies have investigated evolution both in level and decline and the cognitive domains highly varied as well as the neuropsychological tests used. For disability, discussion of trends is also complicated because disability can be defined and measured in many ways. Different criteria based on ADL and/or IADL have been mostly investigated and a trend toward an improvement of functional abilities has been evidenced.

Table 7: Studies estimating changes in disability over time.

1st author, year	Study population	Disability definition	Cohorts (n)	Main results
Manton et al, 1997	Participants from the National Long Term Care Surveys aged 65+	IADL and ADL scale Total disability score	*1:* 1982 assessment (n=20,485) *2:* 1994 assessment (n=19,171)	Total disability: 1982 vs 1994: 24.9% (0.31) vs 21.3% (0.29); p<.0001 IADL: 1982 vs 1994: 5.6% (0.17) vs 4.3% (0.14); 1-2 ADL: 1982 vs 1994: 6.6% (0.18) vs 5.9% (0.16); 3-4 ADL: 1982 vs 1994: 2.9% (0.12) vs 3.2% (0.12); 5-6 ADL: 1982 vs 1994: 3.6% (0.13) vs 2.8% (0.12);
Crimmins et al, 1997	Participants from the NHIS and the LSOA aged 70+	ADL and IADL items for total disability: unable to perform at least one ADL or IADL	NHIS: Assessment from 1982 to 1993 (n= almost 9000 each year) LSOA: Assessment on 1984, 1986, 1988 and 1990 (n=7527 in 84 and 5151 after)	NHIS: Years since 1982: $OR_{disability}$=0.989; p<0.01 LSOA: 1986 vs 1984: OR=1.20; p<0.05 1988 vs 1984: OR=1.15; p<.05 1990 vs 1984: OR=1.06; p>.05
Allaire et al, 1999	Participants from the Framingham Heart Study aged 55 to 70 y.o.	ADL scale Gross motor function	*1:* Subjects from the original cohort started in 1948 (n=1760) *2:* Subjects from the offspring cohort started in 1971 (n=1688)	Help in at least one ADL: Men: 1.3% vs 0.5%; p=0.17 Women: 1.0% vs 1.1%; p=0.86 Help in at least one gross motor function: Men: 16.0% vs 8.8%; p<.001 Women: 29.2% vs 17.2%; p<.001

1st author, year	Study population	Disability definition	Cohorts (n)	Main results
Manton et al, 2001	Participants from the National Long Term Care Surveys aged 65+	IADL and ADL scale Total disability score	*1:* 1982 assessment *2:* 1989 assessment *3:* 1994 assessment *4:* 1999 assessment	Total disability: 1989 vs 1982: 0.26%/y decline 1994 vs 1982: 0.38%/y decline 1999 vs 1982: 0.56%/y decline
Pérès et al, 2005	Participants from PAQUID study aged 75 to 84	ADL and IADL	*1:* Born between 1903-1912 (n=1496) *2:* Born between 1913-1922 (n=910)	IADL: Women:1903 vs 1913: OR= 0.61 (0.49-0.77) Men: 1903 vs 1913: OR=1.09 (0.81-1.48) ADL: 1903 vs 1913: OR= 0.73 (0.49-1.09)
Jagger et al, 2007	Participants from the Cambridge center of MRC CFAS study aged 65-69	Modified Townsend activities of daily living scale : nine activities and tasks, including eight ADL/IADL	*1:* Assessment in 1991-92 (n=689) *2:* Assessment in 1996-97 (n=687)	Total disability: 1996 vs 1991: OR=1.34 (0.98-1.83)

1st author, year	Study population	Disability definition	Cohorts (n)	Main results
Donald et al, 2010	Population aged 75+ of 10 general practices in Gloucestershire	4 items: outdoor mobility at least able to go outside for short walks, managing to wash or shower independently, managing to dress easily on own and able to cook or reheat a whole meal	*1:* Survey in 1998 (n=4482) *2:* Survey in 2008 (n=5290)	Unable to walk beyond gate: 1998: 19.5 (18.3-20.8) 2008: 16.1 (15.1-17.1) Difficulty/inability washing 1998: 43.7 (42.2-45.2) 2008: 29.2 (28.1-30.6) Difficulty/inability dressing 1998: 8.8 (7.9-9.7) 2008: 7.6 (6.9-8.4) Unable to prepare a meal 1998: 15.6 (14.4-16.7) 2008: 12.3 (11.4-13.2)
Seeman et al, 2010	Participants from National Health and Nutrition Examination Surveys aged 60+	4 ADL item: difficulty walking from room to room, getting in and out of bed, eating, and dressing. 3 IADL items: difficulty doing chores around the house, preparing own meals, and managing money	*1:* NHANES 1988-1994 (n=4688) *2:* NHANES 1999-2004 (n=4239)	BADL: 1999 vs 1988: 60-69y: OR=1.7 (1.4-2.2) 70-79y: OR=1.1 (0.9-1.4) 80+y: OR=1.1 (0.9-1.5) IADL: 1999 vs 1988: 60-69y: OR=1.7 (1.3-2.2) 70-79y: OR=1.4 (1.1-1.8) 80+y: OR=1.2 (0.9-1.6)
Heikkinen et al, 2011	Participants part of the Evergreen project from Finland, aged 65-69	IADL scale	*1:* Born in 1919-23 (n=451) *2:* Born in 1927-31 (n=403) *3:* Born in 1935-39 (n=400)	1996 vs 1988: OR=0.43 (0.31-0.59) 2004 vs 1988: OR=0.35 (0.25-0.48)

1st author, year	Study population	Disability definition	Cohorts (n)	Main results
Christensen et al, 2013	Participants from Danemark aged 90+	Basic activities of daily living: 11-item self-report measure such as walking around the house, walking up and down one flight of stairs, running 100 m, carrying 5 kg (The lower the worse)	*1:* Born in 1905 (n=2262) Assessed at 93 y.o. *2:* Born in 1915 (n=1584) Assessed at 95 y.o.	Total (mean): 1905 vs 1915: 1.8 (0.7) vs 2.0 (0.8); p<.0001 Men: 1905 vs 1915: 2.1 (0.8) vs 2.3 (0.9); p<.0001 Women: 1905 vs 1915: 1.7 (0.7) vs 1.9 (0.8); p<.0001
Feng et al, 2013	Participants from the Shanghai Longitudinal Survey of Elderly Life and Opinion aged 60+	ADL and IADL scales	*1:* Assessment in 1998 (n=2763) *2:* Assessment in 2003 (n=3222) *3:* Assessment in 2005 (n=1680) *4:* Assessment in 2008 (n=2195)	ADL: 2003 vs 1998: OR=1.00; p>.05 2005 vs 1998: OR=0.78; p<.05 2008 vs 1998: OR=0.64; p<.001 IADL: 2003 vs 1998: OR=0.74; p<.001 2005 vs 1998: OR=0.62; p<.001 2008 vs 1998: OR=0.36; p<.001
Falk et al, 2014	Population aged 75 from Gothenburg	ADL and IADL	*1:* Assessment in 1976-77 (n=744) *2:* Assessment in 2005-06 (n=731)	ADL: 1976 vs 2005: 13.9% vs 5.6%; p<.0001 IADL: 1976 vs 2005: 33.4% vs 13.0%; p<.0001

1.3. Methodological considerations

Investigating secular trends of dementia expose estimations to a few methodological issues and bias. Studies and analyses need to account for the following problems to try to provide the most unbiased, robust and accurate results.

1.3.1. Selection bias

Establishing accurate comparisons between the participants of different populations or cohorts requires similarity and consistency to evidence real association. The selection of different populations, either by initial different response rate or different follow-up, can produce estimates variations more linked to methodology than a real effect. However, response rates are frequently heterogeneous between studies used to establish secular trends, with even an increase of nonparticipation in more recent studies (201). Low response rates often lead to a selection of the participants included in these studies, with a trend toward the selection of healthier subjects. Indeed, consent/refusal to participate in a study is sometimes related to exposure status and/or health status. It is common that subjects that are already declining, with a high number of co-morbidities or with low educational level are more prone to refuse to be included (202). The major issue of low response rate is thus the introduction of a nonresponse/nonparticipation bias. It refers to the systematic errors introduced in the study when reasons for study participation are associated with the epidemiologic area of interest. When comparing two studies with different response rates, an under/over estimation of the investigated associations is possible.

The other selection bias is related to drop-out of subjects during the follow-up of longitudinal studies. Three different mechanisms of drop-out have been proposed, defining missing data as (203):

- Completely at random (MCAR data) when the probability to drop-out is not related to the marker trajectory (in this case, dementia or cognitive decline) or to covariates. This is the only scenario where the sample is still representative of the entire population.

- At random (MAR data) when the probability to drop-out depends on covariates as well as on past observed values of the marker. It is the case if subjects' decision to drop-out is related to their last observed cognitive scores. Participants with incomplete data shall not be excluded from analyses to assure unbiased parameters.
- Not at random (MNAR data) when the probability to drop-out depends also on unobserved characteristics of the cognitive marker trajectory, such as the current cognitive status. It is the case if subjects who deteriorated since their last visit tend to drop-out. Unfortunately, this case leads to biased parameters.

However, MAR and MNAR data are difficult to distinguish. When studying aging, MCAR data are not the principal cause for missing data. Indeed, it has been shown that individuals who dropped out for reasons other than death tended to be older and were more cognitively impaired (204). This selection based on MNAR data could bias incidence estimations and also misestimate secular trends.

1.3.2. Diagnosis instability

Dementia diagnosis is a clinical syndromic diagnosis, using diagnostic criteria; however, clear thresholds to define the level of cognitive decline and its repercussion are not given in these criteria, leaving the ultimate decision to clinical judgement. In a lot of countries, growing interest has been shown about dementia and several countries have established Alzheimer programme to enhance research and awareness. With this evolution of interest, and the increasing awareness of dementia, the diagnostic boundaries are widely believed to have significantly changed in clinical and research practice over time. During the last few years, other factors could have influence diagnosis with for example, negative results of pharmaceutical trials or better knowledge in biomarkers' research. Clinical sensitivity is also different across countries.

As an illustration, here is the case report of a patient described in the JAMA (205):

"Mrs J, age 81 years, with hypertension and hyperlipidemia, requested a referral to a neurologist, stating: "I am forgetting things I just heard."

Mrs J and her husband began noticing mild memory problems 1.5 years earlier, and report slow progression since. Her husband noticed changes in problem solving and time

management. Mrs J was easily distracted and had difficulty remembering recent conversations. She misplaced objects and spent time looking for them; she read and wrote less than before. She repeatedly asked how to do things on her computer and cell phone. Her husband reported that she exhibited no initiative, and that their home seemed more disorganized. She had difficulty planning dinner and her cooking was simpler. Both denied changes in language or speech. She continued to drive locally without accidents but had difficulty remembering directions to familiar places. Mrs J had no hallucinations or delusions. She slept well, her mood was fine, and she exhibited no behavioural problems or personality changes.

Functionally, she remained independent in all activities of daily living (ADLs). She had urinary frequency and over the past couple of months she had a few incidents of incontinence, especially when awakening from a nap. In instrumental activities of daily living (IADLs), Mr J had recently taken over paying bills. Finally, even with a compartmentalized pill-box, she occasionally forgot to take her medications (amlodipine 5 mg daily; losartan 50 mg twice daily; and ergocalciferol 1,000 units daily.)"

In this paper, this person is qualified as having a typical case of Mild Cognitive Impairment (MCI). This case has then been presented to 150 neurologists, psychiatrists and geriatricians of the French Memory Consults during a meeting in early 2015. They all considered this person had mild dementia and not MCI. This case would have been diagnosed with no dementia in France in 1990 and with mild dementia in 2000.

This greatly complicates comparisons over time, with clinical diagnosis probably not being the most adapted way to analyse time trends. Indeed, if diagnosis is made earlier in more recent population, prevalence and incidence will appear to rise, unrelated to a real increase of dementia risk. Meta-analysis of incidence or prevalence decrease is thus difficult because dementia can be defined in different ways across time and countries.

1.3.3. Mortality (competing risk of death)

When studying elderly individuals, death is expected to be frequent enough to induce selection of the surviving population. In this case, selection is even more problematic because death is known to be linked to cognitive decline, among other factors (206). Beside, several

risk factors of dementia are common risk factors of death such as age or vascular diseases. We consider death as a semi-competing risk because dementia cannot occur after death while subjects living with dementia can die. With interval censoring happening when dementia status is evaluated only at visit times, the exact time of dementia onset is unknown. Combination of competing death and interval censoring may thus lead to an underestimation of dementia incidence. Indeed, it may either prevent dementia from occurring or prevent demented subjects from being diagnosed if they die before the visit following their dementia onset. Moreover, due to the high improvement of survival, this bias may be differential between periods. The differential death rate between people with and without dementia may itself be changing. Statistical methods such as multi states models should be applied to account for semi-competing risk of death and interval censoring.

2. Study justification and objectives

The main objective of this thesis was to investigate and understand as accurately as possible the evolution of dementia over time in France.

For this purpose, several objectives were determined:

- To assess the evolution of dementia incidence based on two elderly populations from two different generations, by evaluating both the evolution of a clinical diagnosis of dementia and an algorithm diagnosis.
- To evaluate the effect of several risk factors on the evolution.
- To account for the selection of the population compared, for the evolution of dementia diagnosis over time, and for competing risk of death.
- To investigate the evolution of several “components” of dementia: cognition and disability.
- To confirm the evolution of clinical diagnosis over time and the reproducibility of our dementia algorithm
- To assess the evolution of mortality of demented and non-demented subjects, as well as the evolution of life expectancy with and without dementia and the life duration with dementia.

METHODS

3. Methods

3.1. Population

3.1.1. French cohorts

The Personnes Agées Quid (PAQUID) study and the Three-City (3C) study are two population based cohorts of randomly chosen participants aged 65 years and over. Eligible subjects were contacted by letter or phone, or even directly at home. In general, the aim of these cohorts is to regularly follow and evaluate participants, with repeated cognitive evaluations and a screening and active research of dementia cases. For both cohorts, a standardized questionnaire assessing socio-demographic, medical, cognitive, and functional data was administered at home by trained neuropsychologists during face-to-face interviews, at baseline and at each follow-up. Participants were followed-up at home every 2/3 years, even if they moved to a care home. At each follow-up, vital status was systematically recorded for all the participants. An ethical review committee has approved both studies. To limit attrition during cohort duration, lost to follow-up were regularly researched after the contact informant. Participants who dropped out during follow-up were contacted again at next visit and were included again in case of approval. The questionnaires assessed among other things educational level, treatment intakes, height and weight, stroke history, living condition, Instrumental Activities of Daily Living (IADL), Basic Activities of Daily Living (bADL), and depression. A battery of psychometric tests assessed the MMSE test, the Benton test, the Isaacs Set Test (IST), and the Wechsler code. In the 3C study, the Grober and Buschke test was also recorded. The two cohorts, PAQUID and the Bordeaux part of the 3C study, were managed by the same team.

3.1.1.1. The PAQUID study

The PAQUID study consists of a representative sample of 3,777 participants in the departments of Gironde and Dordogne (Southwest France), randomly chosen from the electoral rolls in 1988–1989 (57). Among the 5,554 persons selected initially, 3,777 (68 percent) agreed to participate in the study. Three criteria had to be met for inclusion: to be at

least 65 years of age by December 31, 1987; to be living at home at the time of the initial data collection phase; and to give informed consent to participate in the study. The participation rate was 68%. The main objective of this study was to describe and analyse normal and pathological brain aging, as well as functional status after 65 years old. For this, prevalence and incidence of dementia were estimated and cognitive and functional aging, as well as the identification of risk factors and pre-clinical symptoms of AD were investigated. Participants were followed over 25 years every 2 or 3 years, at 3, 5, 8, 10, 13, 15, 17, 20, 22 and 25 years after the baseline evaluation. The follow-up is still ongoing (figure 6).

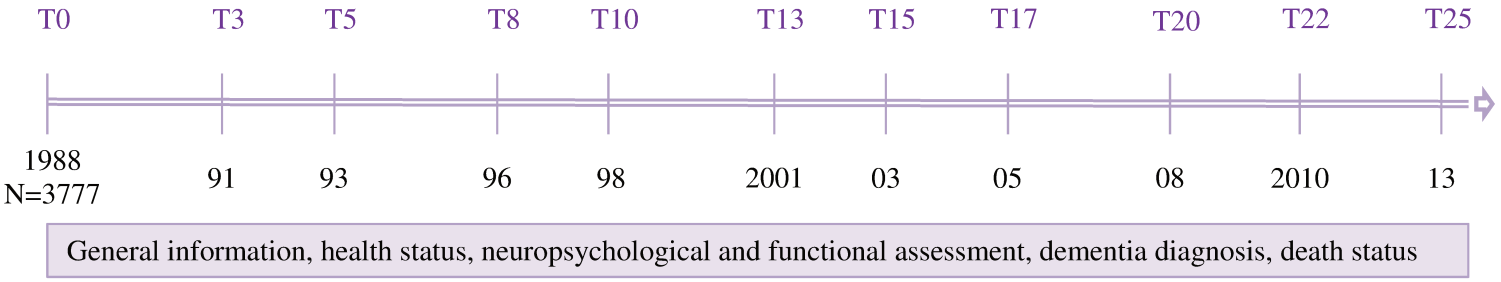


Figure 6: Study design of the PAQUID cohort.

3.1.1.2. The 3C study

The ongoing 3C Study is conducted in three areas of France: Bordeaux (South-West), Dijon (North-East) and Montpellier (South-East) (207). To be eligible for recruitment into the study, persons had to be (1) living in these cities or their suburbs and registered on the electoral rolls, (2) aged 65 years and over, and (3) not institutionalized. The objective of this study was to investigate vascular factors and their relation with dementia in a prevention goal. Twenty-four percent of the eligible persons selected on the electoral rolls (n = 34,922) could not be reached; among those contacted, the acceptance rate was 37%. A total of 9,294 persons were included: 2104 from Bordeaux, 4931 from Dijon, and 2259 from Montpellier. The cohort was recruited and examined between March 1999 and March 2001. It was then follow-up over 14 years (for Bordeaux and Montpellier, Dijon were only followed for 12 years) every 2 or 3 years, at 2, 4, 7, 10, 12, and 14 years after the baseline evaluation. The follow-up is still ongoing (figure 7). Similarly to PAQUID, numerous data were collected with a focus on medical data, especially vascular ones. Moreover, biological samples were collected, as well as brain imaging for a subsample of the cohort.

In the following works, only the Bordeaux centre has been used to facilitate comparison with the PAQUID study.

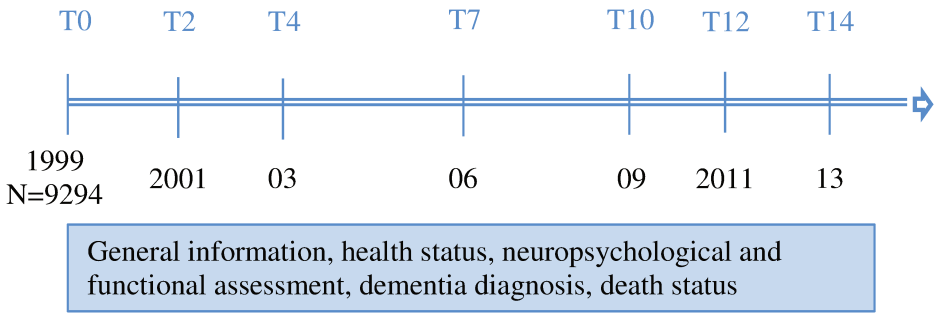


Figure 7: Study design of the Three City Study for the Bordeaux centre.

3.1.2. The Cognitive and Function Aging Study (CFAS I and II)

The MRC Cognitive Function and Aging Study (CFAS I): between 1989 and 1994, baseline interviews in populations aged 65 years and older were conducted in six geographical areas in England and Wales and subjects were followed up to ten years. A two stage process, with screening followed by diagnostic assessment, was used in CFAS I to assess dementia prevalence (Figure 8). In the following, only data from three of the English areas of MRC CFAS—Cambridgeshire, Newcastle, and Nottingham (208), where interviews were carried out between Dec, 1990, and July, 1993— were selected for comparison analyses. It provided 7,635 subjects, from which a sub-population of 1,459 subjects undergone the assessment phase. The CFAS I baseline interview included questions about sociodemographic characteristics, lifestyle, health, activities of daily living (basic and instrumental), cognition, health-care and social-care contact, and medication. A sample of 20% of those who had a baseline interview, stratified to represent the entire cognitive spectrum, was invited for assessment with the geriatric mental state (GMS) examination, a standardized interview for ascertainment of dementia and other neuropsychiatric syndromes in the older population.

Between Nov, 2008, and Oct, 2011, new fieldwork in the same geographical areas was carried out to provide CFAS II estimates on 7762 subjects, which could be directly compared with

CFAS I (146). In CFAS II, the one stage interview integrated screening and assessment phases of CFAS I.

CFAS I and CFAS II had identical sampling approaches, methods and diagnostic approach apart from the simplification of design from two stages to one stage at baseline and incidence phase through combination of screening and assessment interviews. In both studies, the population for invitation to interview was randomly sampled from primary care registration of the same geographical areas. An introductory letter from the general practitioner was followed by a visit by a named study interviewer, previously trained to deliver the standardized interviews. The response rate of CFAS I was 80% compared to 56% in CFAS II.

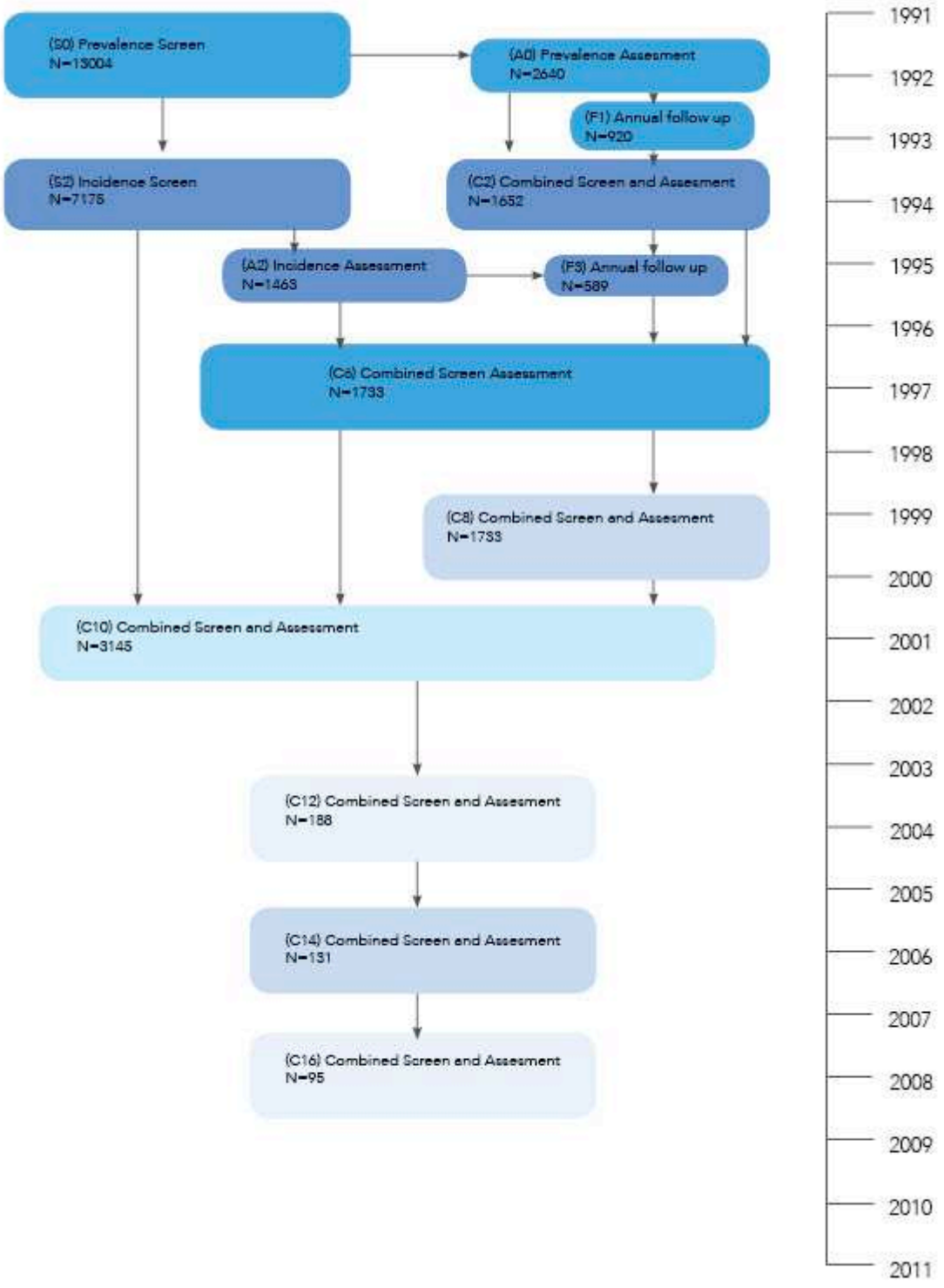


Figure 8: Design and follow-up of the CFAS I study.

3.2. Cognitive and functional evaluation in the French cohorts

3.2.1. Psychometric tests

Cognition was evaluated based on a battery of psychometric tests assessing several cognitive domains: the Mini-Mental State Examination (MMSE), the Isaacs Set Test (IST), the Benton Visual Retention Test (BVRT), and the Digit Symbol Substitution Test (DSST; in PAQUID only). These tests were assessed and collected at every follow-up, except for the DSST, missing at the 3 year follow-up of PAQUID.

The MMSE assesses global cognitive functioning through several domains: time and space orientation, recall, attention and concentration, praxis, constructional capacity and language (annexe 1) (209, 210). It is composed of 30 items and scores ranged from 0 (much altered performance) to 30 (good performance).

The IST assesses semantic verbal fluency (211). In the following, the 15 seconds version has been used: participants have to pronounce a list of words from a semantic category in 15 seconds. Four categories are proposed: cities, fruits, animals and colours. The higher the score is, the better are the performances.

The BVRT defines visual working memory, necessary to realize complex cognitive activities (212). This test consists in recognizing the previously seen figure among four proposed figures (Figure 9). Fifteen figures are successively presented. The BVRT score ranged from 0 (much altered performance) to 15 (good performance).

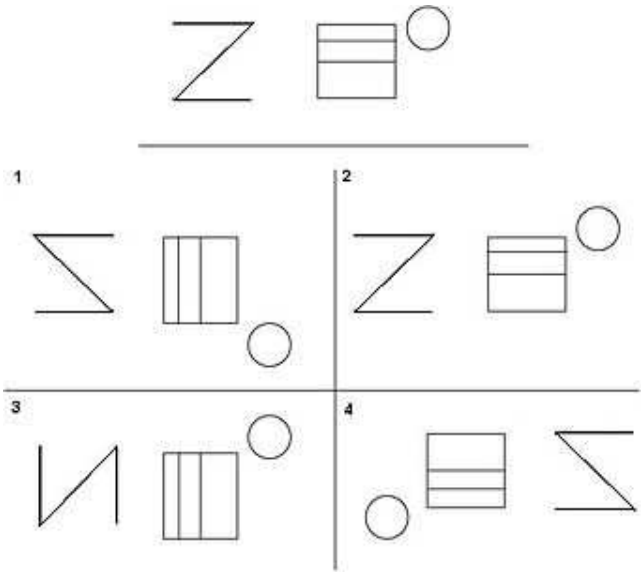


Figure 9: The Benton Visual Retention Test

The DSST evaluates processing speed which is the pace at which you take in information, make sense of it and begin to respond. This test requires the patient to copy, into spaces below rows of numbers, the symbols that are matched to each number according to a key located on the top of the page (Figure 10). The test is timed and the score is the number of success performed in 90 seconds. A high score represents good performance.

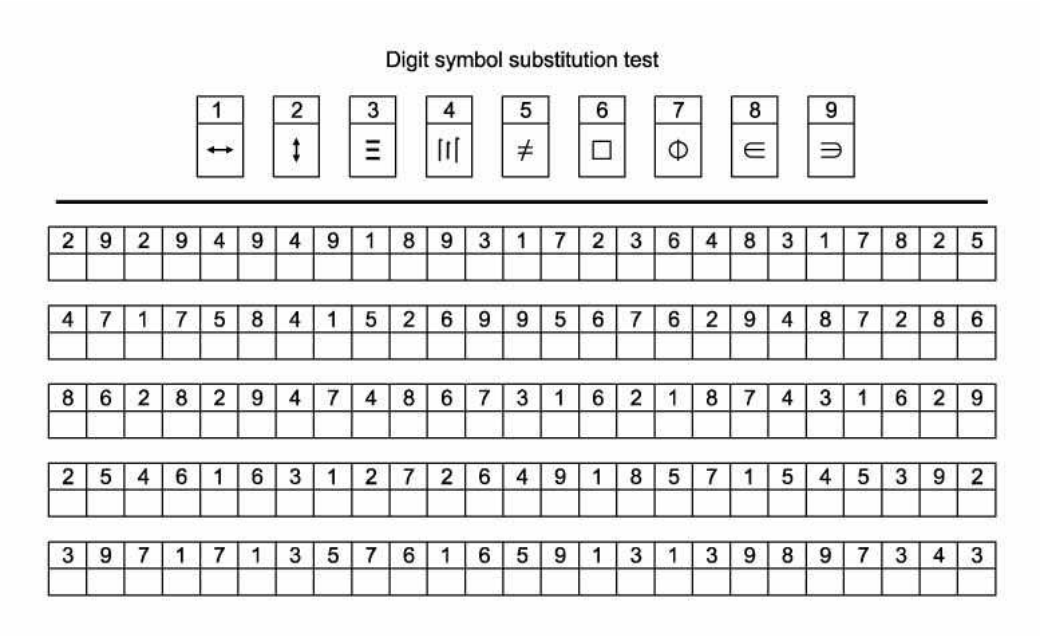


Figure 10: The Digit Symbol Substitution Test

3.2.2. Disability scales

Even if multiple scales assessing disability have been developed, the most frequently used in the literature assessing IADL is the Lawton and Brody scale (213). The Lawton scale includes 8 complex activities involving motor functions and cognitive function (table 8). Cognitive abilities such as memory, attention, language, executive functioning, and visuospatial function are necessary to process information necessary to realize specific tasks. It covers the following tasks: telephoning, transporting, shopping, and handling budget and medication. Three additional items are specifics to women: cooking, doing laundry and cleaning. According to activities, three or five answer modalities are proposed. A subject is considered as disabled if at least one IADL is impaired. Each activity has its own impairment threshold.

In the following works, we considered only the four activities which have been shown to be the most correlated with cognitive function in previous work (214): telephoning, transporting, handling budget and handling medications.

Table 8: Instrumental Activities of Daily Living (IADL) Scale with disability thresholds

Laundry		**Ability to use telephone**	
1. Does personal laundry completely	1	1. Operates telephone on own initiative ; looks up and dials numbers	1
2. Launders small items, rinses socks, stockings, etc	0	2. Dials a few well-known numbers	1
3. All laundry must be done by others	0	3. Answers telephone, but does no dial	1
		4. Does not use telephone at all	0
Shopping		**Responsibility for own medications**	
1. Takes care of all shopping needs independently	1	1. Is responsible for taking medication in correct dosages at correct time	1
2. Shops independently for small purchases	0	2. Takes responsibility if medication is prepared in advance in separate dosages	0
3. Needs to be accompanied on any shopping trip	0	3. Is not capable of dispensing own medication	0
4. Completely unable to shop	0		
Food Preparation		**Ability to handle finances**	
1. Plans, prepares, and serves adequate meals independently	1	1. Manages financial matters independently (budgets, writes checks, pays rent and bills, goes to bank); collects and keeps track of income	1
2. Prepares adequate meals if supplied with ingredients	0	2. Manages day to day purchases, but needs help with banking, major purchases, etc	1
3. Heats and serves prepared meals or prepares meals but does not maintain adequate diet	0	3. Incapable of handling money	0
4. Needs to have meals prepared and served	0		
Housekeeping		**Mode of transportation**	
1. Maintains house alone with occasion assistance (heavy work)	1	1. Travels independently on public transportation or drives own car	1
2. Performs light daily tasks such as dishwashing, bed making	1	2. Arranges own travel via taxi, but does not otherwise use public transportation	1
3. Performs light daily tasks but cannot maintain acceptable level of cleanliness	1	3. Travels on public transportation when assisted or accompanied by another	1
4. Needs help with all home maintenance tasks	1	4. Travel limited to taxi or automobile with assistance of another	0
5. Does bit participate in any housekeeping tasks	0	5. Does not travel at all	0

1: Ability to perform the activity; 0: Disability for the activity

3.3. Dementia Diagnosis

3.3.1. Clinical diagnosis in the French cohorts

The clinical diagnosis was made following a 3-step procedure for both PAQUID and 3C-Bordeaux studies. The first step was the cognitive evaluation made by the neuropsychologist through a series of psychometric tests and the functional evaluation. Participants, who were suspected of dementia based on their neuropsychological performances, decline relative to a previous examination and clinical impression of neuropsychologist, were then examined by a senior neurologist. The diagnosis of dementia was based on the DSM-III-R and the DSM-IV criteria. In case of refusal or death between the first and second step, additional information was gathered from the informant and the medical practitioner. Then, each case was discussed by a validation committee composed of neurologists, geriatrician and directed by JFD to definitely classify the case. Information on cognitive decline was included based on follow-up data.

3.3.2. Algorithmic diagnosis

To prevent the instability of the clinical diagnosis we defined an algorithmic diagnosis, based on cognitive and functional assessments using the Mini Mental State Examination (MMSE) and the 4 Instrumental Activities of Daily Living (IADL) (ability to use the telephone, transportation, responsibility for medications and ability to manage its budget). For each activity, participants were considered disabled for the first level of disability; thus the score range from 0 for a subject completely unimpaired to 4 for a person dependent for the four activities. Considering the old age of the participants and the associated high proportion of subjects restricted in the activity of transport, we considered restriction in activities from at least two restricted activities out of the four (215). These four IADL were selected because they have been shown to be the most cognitive activities and the most associated to dementia in a previously published paper (214). The algorithmic diagnosis of dementia was then defined by a MMSE score <24 (or a missing MMSE score for "cognitive reason") AND a 4 IADL score ≥2. However, these four IADL are not always recorded in international cohorts

and the algorithm thus needs to be adapted according to functional items available. For example with the CFAS data, disability was assessed by some IADL and ADL. Although cognitive decline is part of dementia definition, the algorithm use the global cognitive performance as it is more convenient and more reproducible, available not only in incidence studies but also in prevalence studies.

3.3.3. AGECAT

The Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT) algorithm used in the English studies is based on the Geriatric Mental State examination (GMS) that provides relevant information to determine dementia syndrome in older population (216). Missing data within an interview could prevent the algorithmic diagnosis and for individuals with missing data, the same approach was taken for CFAS II as for CFAS I, which was a review of all available information by diagnostician (Carol Brayne), applying DSM-IIIR criteria. Many of these individuals with missing data had severe cognitive impairment and were not able to respond to the interview questions. The GMS-AGECAT has been validated against internationally accepted earlier diagnostic criteria (DSM-IIIR) (217).

3.4. Statistical methods

3.4.1. Multi-state modelling: Illness-death model

In the following work, incidence analyses were performed using a multi-state model, the Illness-Death model (218). In this model, individuals start out as healthy (state 0), they may become demented (move to state 1) and afterwards they may die (state 2) (figure x). Individuals may also die without first becoming demented (transition from state 0 to state 2). Transition intensities can be interpreted as instantaneous risks of the onset of a given event at time t. Transition intensity 01 represents the age-specific incidence of dementia.

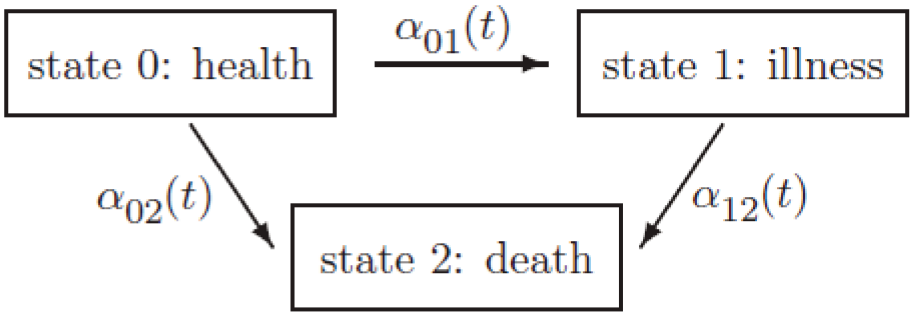


Figure 11: The illness-death model. Transition intensity 01 (a01(t)) represents age-specific incidence of dementia. Transition intensities 02 (a02(t)) and 12 (a12(t)) represent age-specific mortality rates for healthy or demented subjects, respectively.

Transition intensities between states are defined as follow:

$$\alpha 01(t|Z) = \alpha 01,0(t) \exp(\boldsymbol{\beta} 01T\ \boldsymbol{Z}),$$

$$\alpha 02(t|Z) = \alpha 02,0(t) \exp(\boldsymbol{\beta} 02T\ \boldsymbol{Z}),$$

$$\alpha 12(t|Z) = \alpha 12,0(t) \exp(\boldsymbol{\beta} 12\ T\ \boldsymbol{Z}),$$

With:

$(t|Z)$ being transition intensity from a state k to a state l at time t for a subject with a covariate vector Z,

$\alpha kl,0(t)$ being unspecified transition intensity at the beginning of the follow-up (at diagnosis) between k and l

and $\boldsymbol{\beta} kl$ being the vector of regression coefficients measuring the effect of Z on transition intensity k to l.

This model takes into account interval censoring of age at dementia due to the fact that dementia is assessed only at the visits, competing risk of death, right censoring, and left truncation due to the selection of subjects alive and non-demented at inclusion. Beyond providing transition intensities, it has also been programmed to perform other relevant indicators, such as probabilities according to dementia and death status, as well as life expectancies and life duration with dementia.

3.4.2. Linear Mixed Effects model

For cognitive and functional evolutions, analyses were performed using the linear mixed models theory (219). This model enables analysis of individual trajectories among a population. It studies the linear relation between a variable of interest and explanatory variables, taking individual variability into account.

The general formulation of a linear mixed model is defined as follow for subject *i*, $i = 1, \ldots, N$ at time t_{ij}, $j = 1, \ldots, n_i$:

$$Y_{ij} = X^T_{ij}\beta + Z^T_{ij}\gamma_i + \varepsilon_{ij} \text{ with } \gamma_i \sim N(0, B) \text{ and } \varepsilon_i \sim N(0, R_i)$$

With **Yij** being the observed values of the marker for individual i at time j. The vectors **Xij** and **Zij** include covariates with fixed and random effects respectively. $\boldsymbol{\gamma_i}$ are the subject-specific random effects, with B the variance matrix. Random effects represent long term individual trend. The random intercept is defined as the difference between the mean intercept of the total population and the intercept of subject *i*. The random slope takes into account the inter-individual difference so that all individuals can have different slopes. $\boldsymbol{\varepsilon_{ij}}$ represents the residual error or measurement error. $\boldsymbol{\beta}$ represents the fixed-effect parameters to estimate. This model uses the whole information available and measurement numbers and time can differ between individuals. The variances of estimated parameters account for inter- and intra-subjects' correlation of repeated data thanks to random effects.

Due to the nature of some psychometric tests, ceiling and floor effects, as well as curvilinearity (unequal interval scaling) can intervene and biased the results. These characteristics thus need to account for with models including spline transformations to normalize the different scores (220). The scores are transformed and normalized to fit linear assumptions of linear mixed models. In the following work, each score used was transformed and analysed with linear mixed models assuming a linear mean trajectory with time and including individual correlated random effects on intercept and slope. The simple effect of a variable quantified the "baseline" scores according to this variable while the interaction with time quantified the effect of variable on the score change over the follow-up period.

RESULTS

4. Results

4.1. Secular trends of dementia incidence and related factors

4.1.1. Introduction

Dementia being a syndrome known for its high consequences not only for patients and family but also at an economic level, projection of number of cases expected in the next decades has been frequently estimated worldwide. These projections are based on the prevalence of the disease and assume that the incidence has been stable over the last decades and that it will remain stable. However, this work was initiated following the report of a trend toward a decrease in dementia prevalence or incidence in a few studies. Moreover, an improvement in care of health-related risk factors of dementia has been evidenced; with for example a decrease in the stroke prevalence, higher proportions of people treated again hypertension or hypercholesterolemia. Moreover, access to education also improved over time. Nevertheless, other factors such as obesity or diabetes became more frequent in the population. The hypothesis leading to secular trends' work was that the modification of risk factors could have influenced the risk of developing dementia. A decrease of dementia incidence could lead to an overestimation in projections of the number of people with dementia in the future and would reinforce the potential for prevention of risk factors involved.

To date, several studies reported a decline in the prevalence or incidence of dementia (45, 145-147, 150, 155-157). However, only a few tried to identify factors involved in this decline (150, 155) and few analyses investigated the stability of dementia diagnosis or the impact of low response rate (45, 146).

4.1.2. Methods

To investigate the possible evolution of dementia prevalence and incidence, we analysed data from participants 10 years apart from the same geographic areas of the PAQUID (**the 1990's population**) and the 3C studies (**the 2000's population**). As PAQUID was performed on a larger geographic area (departments of Gironde and Dordogne) than 3C, we included only a subsample of the PAQUID participants, those living in the same geographic areas as the 3C

participants. To evaluate factors involved in the evolution, models were adjusted on several risk factors differing between the two studies. To take into account the potential evolution of clinical diagnosis of dementia, two different definitions of dementia were used: first, the clinical diagnosis established by neurologists and consensus group and second, an algorithmic diagnosis which definition was a MMSE score <24 (or a missing MMSE score for "cognitive reason") AND a 4 IADL score ≥2. The illness-death model was applied to account for death, interval censoring and left truncation. Several sensitivity analyses were also performed to validate our results. First, we defined other algorithms to diagnose dementia to test the MMSE threshold chosen : 1) a MMSE score <23 (or a missing MMSE score for "cognitive reason") AND a 4 IADL score ≥2; 2) a MMSE score <25 (or a missing MMSE score for "cognitive reason") AND a 4 IADL score ≥2; 3) a MMSE score <24 (or a missing MMSE score for "cognitive reason") for low education level or MMSE score <26 for high education level AND a 4 IADL score ≥2. Then, we ran analyses on participants aged 65 to 85 years old to make the populations more similar, as participants aged 85 + from 3C where under-represented. Finally, we have simulated sample with different dementia risk, to account for the low response rate of 3C-Bordeaux.

4.1.3. Article

Alzheimer's & Dementia 12 (2016) 272-280

Featured Article

Trends in dementia incidence: Evolution over a 10-year period in France

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Abstract

Introduction: Few recent studies have suggested declining trends in dementia frequency. French cohorts with long follow-up allowed us to explore incidence evolution trends.
Methods: Two different populations of subjects aged ≥65 years included in 1988–1989 (n = 1469) and 1999–2000 (n = 2104) were followed up over 10 years, with systematic assessment for cognition and dementia. Multistates illness-death models were used to compare dementia incidence using both clinical and algorithmic diagnoses.
Results: Using the algorithmic diagnosis, incidence declined significantly overall and for women (age-adjusted hazard ratio [HR] = 0.62; confidence interval (CI) = 0.48–0.80 for women between the two populations). Differences in education, vascular factors, and depression accounted only to some extent for this reduction (women full-adjusted HR = 0.73; CI = 0.57–0.95). No significant decreasing trends were found for men or when using the clinical diagnosis for either sex.
Discussion: Our study provides further support for a decrease in dementia incidence in women using algorithmic diagnosis. Changes in diagnostic boundaries mask this reduction.

Keywords: Dementia; Incidence; Time trends; Diagnosis; Risk factors

1. Introduction

Over the past 10 years, the number of people living with dementia worldwide has been estimated to rise to 81 million by 2040 [1]. The estimates being used at present are based on the assumption of stable incidence of dementia and have not taken the potential for decreased prevalence and incidence into account. It is possible that better risk factor management could lower the risk of dementia and lead to smaller rises [2].

Some published studies have supported the hypothesis of a declining dementia trends or an improvement of cognitive performances [3–9]. Most of these have been prevalence studies, with only a few yet reporting incidence [4,5]. Others report no change in dementia or even a rise [10,11]. Any studies attempting to examine change over time must deal with methodological concerns. Included here is the potential major effect of changes in dementia diagnosis over time, and mortality competing risks which might prevent the occurrence of dementia. Previous studies did not take both these concerns into account. Moreover, there might be different effects for men and women as their health profiles change over time. Indeed, age-specific incidence of dementia differs between women and men, as well as age-specific risk of death and living conditions improvement.

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Recently, the potential impact on dementia prevalence of several modifiable risk factors has been highlighted, showing that about one-third of Alzheimer's disease cases might be attributable to these risk factors [12]. Among these factors, cardiovascular risk factors, physical activities, diet, and educational level are of particular interest [13–16]. A decrease in dementia incidence could be the result of the improvement of these factors.

This study aimed to evaluate the possible decrease of dementia incidence dealing with several methodological concerns. Two French surveys of elderly community dwellers have been compared in the same urban area over the past two decades, one that started in 1988 and the other one in 1999. We also determined how some risk factors could explain this evolution of dementia incidence.

2. Methods

2.1. Study population

This study is based on two prospective population-based cohorts in the Bordeaux area of France (Personnes Agées Quid [PAQUID] and Three-City [3C]). Participants aged ≥65 years living in the community were randomly chosen from the electoral rolls for both cohorts.

The PAQUID cohort was formed in 1988–1989 with a representative sample of 3777 participants living at home in the departments of Gironde and Dordogne. The selection was stratified by sex, age, and size of urban unit. For this article, only participants from the Urban Community of Bordeaux (n = 1469) have been selected from PAQUID. The 3C cohort started in 1999 and recruited 2104 participants from the Urban Community of Bordeaux, within 10 districts. For both cohorts, a standardized questionnaire assessing sociodemographic, medical, cognitive, and functional data was administered by trained neuropsychologists during face-to-face interviews, at baseline, and at each follow-up (3, 5, 8, and 10 years for PAQUID and 2, 4, 7, and 10 for 3C; Supplementary Fig. 1). Participants were followed up even if they moved to a care home. At each follow-up, vital status was systematically recorded for all the participants. Full details of the studies have been described elsewhere [17,18].

The study population was, thus, composed of 1469 subjects from PAQUID (named 1990s population in the following, baseline screening response rate 60%) and 2104 from 3C (named 2000s population, baseline screening response rate 39%; Fig. 1).

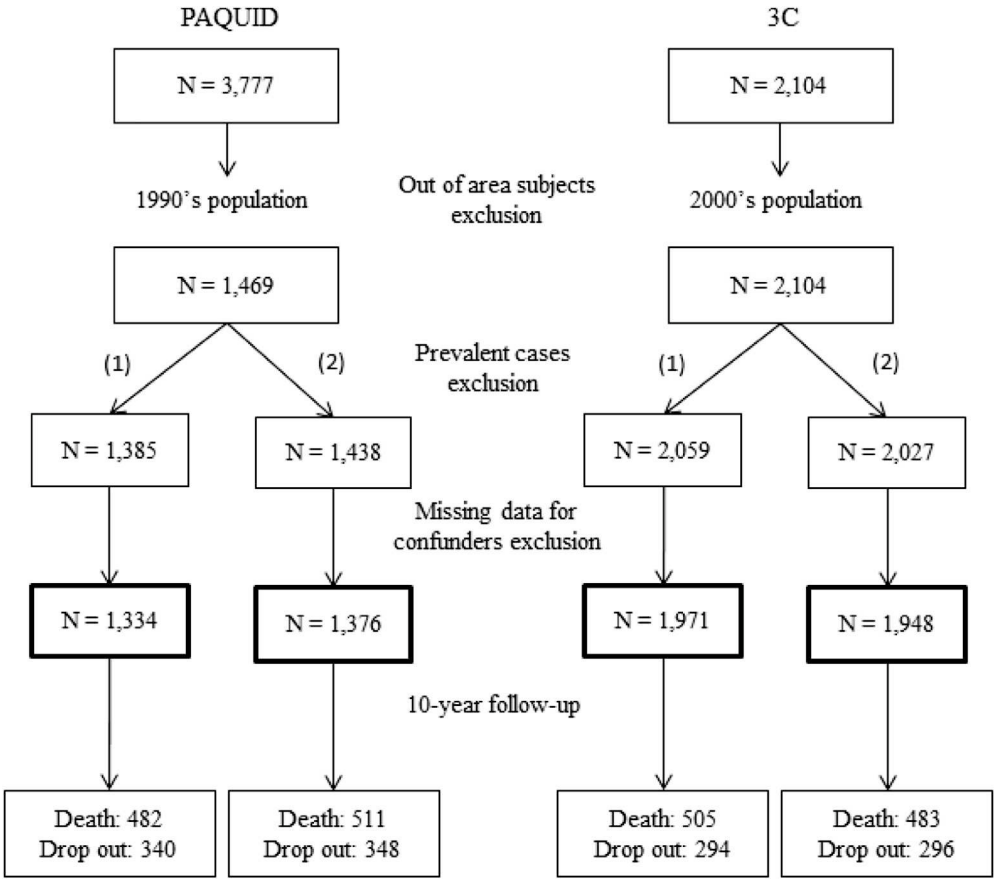

Fig. 1. Flow chart of the study. The 1990s population (left) and the 2000s population (right) are represented for algorithmic (1) and clinical (2) diagnoses. Analyzes have been realized on the bold boxes numbers. Abbreviations: 3C, Three City study; PAQUID, Personnes Agées Quid.

2.2. Diagnosis of dementia

At baseline, as at each follow-up, participants underwent a complete functional and cognitive evaluation as well as an active screening for dementia. Although diagnostic criteria have not fundamentally changed, there have been substantial societal and clinical shifts in dementia awareness. To take this into account, two definitions of dementia have been used in this study: a clinical diagnosis and an algorithmic diagnosis, both considered as nonreversible diagnosis.

The clinical diagnosis was made after a three-step procedure for both 1990s and 2000s populations. The first step was a cognitive evaluation made by the neuropsychologist through a series of psychometric tests. Participants who were suspected of dementia, based on their neuropsychological performances or decline relative to a previous examination, were then examined by a senior neurologist. The diagnosis of dementia was based on the *Diagnostic and Statistical Manual of Mental Disorders - Third Edition, Revised* and the *Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition* criteria. In case of refusal or death between the first and second step, additional information was gathered from the informant and the medical practitioner. Then, each case was discussed by a validation committee composed of neurologists, geriatricians, and directed by J.-F.D. to definitely classify the case.

The algorithmic diagnosis was based on cognitive and functional assessments, using the mini mental state examination (MMSE) [19] and the four instrumental activities of daily living (IADL; ability to use the telephone, transportation, responsibility for medications, and ability to manage its budget). For each activity, participants were considered disabled for the first level of disability; thus, the score range from 0 for a subject completely unimpaired to 4 for a person dependant for the four activities. Considering the old age of the participants and the associated high proportion of subjects restricted in the activity of transport, we considered restriction in activities from at least two restricted activities of the four [20]. The algorithmic diagnosis of dementia was then defined by an MMSE score <24 (or a missing MMSE score for "cognitive reason") and a four IADL score ≥ 2.

2.3. Baseline characteristics

Initial interview data provided numerous factors similarly collected in PAQUID and 3C: educational level divided into three categories (validated primary school level or short secondary school level, long secondary school level or more, vs. no diploma); smoking habits (current, former vs. never smoker); body mass index (BMI, reported weight/reported height^2), categorized into four classes (<21, 21–27, [reference] 27–30, and ≥ 30); history of stroke; drug use collected using a standardized questionnaire as well as visual inspection of the participant's medicine packs, allowing to evaluate treated hypertension; treated diabetes; and use of lipid-lowering drugs and antidepressants. Depressive symptomatology was assessed using the Center for Epidemiologic Studies–Depression scale, considering a score >16 for men and >22 for women for depressive symptomatology [21]. A depressive status was considered for subjects either using antidepressants or having a depressive symptomatology.

2.4. Statistical analyses

Data from 1990s and 2000s populations were pooled. For each of these two populations, data from the first 10 years of follow-up were analyzed (1988–1989 to 1998–1999 for the 1990s population and 1999–2001 to 2009–2010 for the 2000s population). Both populations were compared on sociodemographic characteristics, MMSE and 4-IADL scores at baseline, and on the previously described variables (chi square and Student tests). Data regarding follow-up and attrition of each population were provided. Diagnosis of dementia was determined separately for each of the two diagnosis criteria, using exactly the same definition for prevalent and incident cases.

Then, incidence analyses were performed using a multistate model, the illness-death model [22]. In this model, individuals start out as healthy (state 0), they may become demented (move to state 1), and afterward they may die (state 2; Fig. 2). Individuals may also die without first becoming demented (transition from state 0 to state 2). Transition intensity 01 represents the age-specific incidence of dementia. This model takes into account interval censoring of age at dementia owing to the fact that dementia is assessed only at the visits, competing risk of death, right censoring, and left truncation due to the selection of subjects alive and nondemented at inclusion. Age was used as the basic time scale in the analyses, so the risks of dementia were adjusted nonparametrically for age. Because of mortality and incidence differences between sexes, analyses have been performed overall and for men and women separately using both diagnostic methods. We first measured incidence evolution between the two populations (2000s population vs. 1990s population) adjusted only for age and for sex on overall analyses. The models were then additionally adjusted for (1) educational level; (2) vascular factors (BMI, stroke, antihypertensive, antidiabetic, and lipid-lowering drugs intake); (3) depressive status; (4) and all these potential risk factors to see the degree to which they might explain any changes. Finally, sensitivity analyses were performed. First, we used different algorithmic

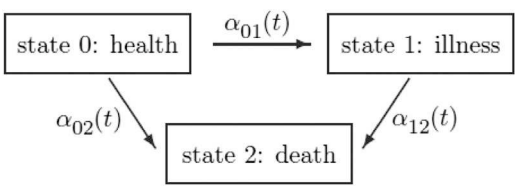

Fig. 2. The illness-death model. Transition intensity 01 ($\alpha_{01}(t)$) represents age-specific incidence of dementia. Transition intensities 02 ($\alpha_{02}(t)$) and 12 ($\alpha_{12}(t)$) represent age-specific mortality rates for healthy or demented subjects, respectively.

diagnoses, considering different thresholds for MMSE score (<23 and <25; or depending on education level [<24 for low level and <26 for high level]). Second, we explored the effect of a potential response bias on incidence changes. To complete the 2000s sample and reach response rate of 60% as in the 1990s sample, several samples of refusals were, thus, simulated using a Weibull distribution, estimated on the 2000s responders, assuming a higher risk of dementia of 1.25, 1.5, or 2 for refusals than for participants. Statistical analyses were performed with SAS statistical software version 9.3 and R package SmoothHazard. Third, we re-ran the analyses excluding participants aged ≥85 years at baseline to make the populations more similar. Fourth, we re-ran the analyses including the maximum of participants without missing data for each analysis.

3. Results

3.1. Description

Mean age did not differ between the two populations, although there were fewer participants aged <70 and >80 years in the 2000s population (Table 1). The 2000s population was higher educated, had a higher BMI, and was more often former smoker than the 1990s population. They had less history of stroke, took more antihypertensive and lipid-lowering drugs, and had less often a depressive symptomatology but took more antidepressant drugs. At baseline, participants in the 2000s population were less disabled on the 4-IADL score and had higher MMSE scores than those in the 1990s population. The proportion of participants visited at least once over the follow-up was higher in the

Table 1
Comparison between the 1990s and the 2000s populations at baseline, overall, and by sex, n = 3573

	1990s (n = 1469)			2000s (n = 2104)			
n (%) or mean (SD)	Overall	Men	Women	Overall	Men	Women	*P* value
Sex	1469 (59.9)	562 (38.3)	907 (61.7)	2104 (41.1)	816 (38.8)	1288 (61.2)	NS
Age							<.0001
65–70	457 (31.1)	184 (32.7)	273 (30.1)	468 (22.2)	197 (24.1)‡	271 (21.0)‡	
70–75	323 (22.0)	148 (26.3)	175 (19.3)	690 (32.8)	286 (35.0)	404 (31.4)	
75–80	341 (23.2)	115 (20.5)	226 (24.9)	615 (29.2)	216 (26.5)	399 (31.0)	
80–85	202 (13.8)	78 (13.9)	124 (13.7)	269 (12.8)	91 (11.2)	178 (13.8)	
85 and older	146 (9.9)	37 (6.6)	109 (12.0)	62 (3.0)	26 (3.2)	36 (2.8)	
Mean (SD)	75.0 (7.0)	74.2 (6.5)	75.5 (7.2)	74.64 (5.1)	74.3 (5.1)	74.9 (5.1)	NS
Education*							<.0001
No diploma	375 (25.5)	100 (17.8)	275 (30.3)	262 (12.5)	73 (9.0)‡	189 (14.7)‡	
Intermediate school level	880 (59.9)	340 (60.5)	540 (59.5)	1141 (54.5)	417 (51.1)	724 (56.4)	
High school level	214 (14.6)	122 (21.7)	92 (10.1)	696 (33.2)	325 (39.9)	371 (28.9)	
Stroke*	81 (5.5)	41 (7.3)	40 (4.4)	78 (3.7)	42 (5.17)	36 (2.8)†	0.01
Smoking habits*							<.0001
Current	155 (10.6)	104 (18.6)	51 (5.6)	115 (5.5)	275 (33.7)‡	1078 (83.7)‡	
Former	394 (26.9)	325 (58.0)	69 (7.6)	635 (30.2)	479 (58.8)	156 (12.1)	
Never	915 (62.5)	131 (23.4)	784 (86.7)	1353 (64.3)	61 (7.5)	54 (4.2)	
BMI*							<.0001
<21	253 (17.8)	51 (9.2)	202 (23.3)	256 (12.6)	46 (5.7)‡	210 (17.0)‡	
21–26	853 (60.1)	369 (66.7)	484 (55.9)	1192 (58.5)	485 (60.4)	707 (57.2)	
27–29	208 (14.7)	94 (17.0)	114 (13.2)	384 (18.8)	196 (24.4)	188 (15.2)	
≥30	105 (7.4)	39 (7.0)	66 (7.6)	206 (10.1)	76 (9.5)	130 (10.5)	
Antihypertensive drugs	766 (52.1)	285 (50.7)	481 (53.0)	1206 (57.3)	479 (58.7)†	727 (56.4)	0.002
Antidiabetics drugs	101 (6.9)	50 (8.9)	51 (5.6)	160 (7.6)	88 (10.8)	72 (5.6)	NS
Lipid-lowering drugs	165 (11.2)	66 (11.7)	99 (10.9)	656 (31.2)	250 (30.6)‡	406 (31.5)‡	<.0001
Antidepressants drugs	46 (3.1)	11 (2.0)	35 (3.9)	198 (9.4)	43 (5.3)†	155 (12.0)‡	<.0001
Depressive symptomatology*	201 (14.0)	77 (14.0)	124 (13.9)	160 (7.7)	49 (6.1)‡	111 (8.7)‡	<.0001
Depressive status*	234 (16.2)	86 (15.6)	148 (16.6)	312 (15.0)	85 (10.6)†	227 (17.8)	NS
4 IADL*							<.0001
0 (not disabled)	1076 (73.4)	459 (82.1)	617 (68.0)	1753 (83.5)	704 (86.6)	1049 (81.6)‡	
1	224 (15.3)	51 (9.1)	173 (19.1)	234 (11.2)	67 (8.2)	167 (13.0)	
2	80 (5.5)	21 (3.8)	59 (6.5)	61 (2.9)	21 (2.6)	40 (3.1)	
3	37 (2.5)	10 (1.8)	27 (3.0)	27 (1.3)	11 (1.3)	16 (1.2)	
4 (disabled for the 4 activities)	49 (3.3)	18 (3.2)	31 (3.4)	24 (1.1)	10 (1.2)	14 (1.1)	
MMSE							<.0001
Mean (SD)	26.2 (3.3)	26.7 (3.0)	25.80 (3.4)	27.2 (2.4)	27.3 (2.3)‡	27.11 (2.5)‡	

Abbreviations: SD, standard deviation; NS, nonsignificant; BMI, body mass index; IADL, instrumental activities of daily living; MMSE, mini-mental state examination.

NOTE. Significant differences between the two populations by sex: †$P < .05$, ‡$P < .001$.

*Missing data: Education (n = 5); stroke (n = 12); BMI (n = 116); smoking habits (n = 6); depressive symptomatology (n = 66); depressive status (n = 59); four IADL (n = 8); and MMSE (n = 23).

2000s population (91% vs. 69% for the 1990s population) and the proportion of deaths lower (27.5% vs. 41.7% for the 1990s population, $P < .0001$).

3.2. Clinical diagnosis incidence

Using clinical diagnosis, 31 prevalent cases in the earlier population (2.1%) and 77 (3.7%) in the 2000s were excluded as well as participants with at least one missing value for adjustment factors (n = 141). Analyzes were, thus, performed on 3324 subjects. Over the 10 years of follow-up, 251 incident cases for 13,508 person-year (PA) have been diagnosed in the 2000s population compared with 123 for 7139 PA in the 1990s population.

The age-adjusted risk of developing dementia did not differ for the 2000s compared with the 1990s population, overall (hazard ratio [HR] = 0.92 [0.73–1.15]) and whatever the sex (HR = 1.21 [0.76–1.93] for men and HR = 0.90 [0.69–1.17] for women; Table 2). Adjustment on each factor separately did not modify this risk of dementia incidence between the 2000s and the 1990s population. When adjusted on all the potential risk factors, there was still no difference in dementia incidence between the 2000s and the 1990s population (overall HR = 1.06 [0.82–1.36], HR = 1.54 [0.94–2.55] for men and HR = 1.10 [0.83–1.42] for women).

3.3. Algorithmic diagnosis incidence

Using algorithmic diagnosis, 84 prevalent cases (5.7%) in the 1990s population and 45 (2.1%) in the 2000s have been identified, which is much higher than earlier clinical diagnosis estimates. After exclusion of these prevalent cases as well as of participants with at least one missing value for adjustment factors (n = 139), analyzes were, thus, performed on 3305 subjects. Over the 10 years of follow-up, 217 incident cases for 13,747 PA have been diagnosed in the 2000s population compared with 155 for 6835 PA in the 1990s population.

Incidence rates of dementia by age are presented in Fig. 3 for the 1990s and the 2000s populations, separately for men and women.

A significant decrease of dementia incidence between the 1990s and the 2000s population was found overall (HR = 0.65 [0.53–0.81] for 2000s population compared with 1990s) and for women (HR = 0.62 [0.48–0.80]) on age-adjusted analyses, whereas the risk did not differ for men (HR = 1.10 [0.69–1.78]; Table 2). Comparison between the different models showed that education explained only a small part of this decrease in dementia incidence as did vascular factors. The difference of incidence remains significant in the fully adjusted model (overall HR = 0.77 [0.61–0.97] and women's HR = 0.73 [0.57–0.95]). In men, the risk of developing dementia did not differ between the 2000s and the 1990s population regardless of the adjustment.

3.4. Sensitivity analyses

Sensitivity analysis using a different algorithmic diagnostic criterion using different MMSE cut points did not alter the findings (Supplementary Table 1). Sensitivity analysis assuming a higher risk of dementia for the refusals was performed for women (Supplementary Table 2). Dementia incidence decrease remained significant when an increased risk of 1.25 was applied to refusals (age and education-adjusted HR = 0.78 [0.63–0.98]). For an increased risk of dementia of 1.5 among refusals, age-adjusted dementia incidence decrease was still significant

Table 2
Incidence evolution between the 1990s and the 2000s population, for both diagnoses, overall and by sex

	Overall*		Men		Women	
Diagnosis of Dementia	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Clinical diagnosis	(n = 3324)		(n = 1299)		(n = 2025)	
2000s versus 1990s						
Adjusted on age	0.92 (0.73–1.15)	.46	1.21 (0.76–1.93)	.42	0.90 (0.69–1.17)	.43
Adjusted on age + education	0.97 (0.77–1.23)	.82	1.28 (0.79–2.07)	.31	0.98 (0.73–1.32)	.88
Adjusted on age + vascular factors†	0.96 (0.76–1.21)	.73	1.28 (0.78–2.11)	.32	0.98 (0.72–1.33)	.89
Adjusted on age + depressive status	0.93 (0.73–1.18)	.55	1.24 (0.78–1.97)	.37	0.90 (0.69–1.17)	.43
Fully adjusted‡	1.06 (0.82–1.36)	.66	1.54 (0.94–2.55)	.09	1.10 (0.83–1.42)	.50
Algorithmic diagnosis	(n = 3305)		(n = 1301)		(n = 2004)	
2000s versus 1990s						
Adjusted on age	0.65 (0.53–0.81)	<.0001	1.10 (0.69–1.78)	.68	0.62 (0.48–0.80)	.0002
Adjusted on age + education	0.71 (0.57–0.88)	.002	1.00 (0.48–2.11)	.99	0.70 (0.54–0.89)	.004
Adjusted on age + vascular factors†	0.69 (0.56–0.86)	.0009	1.27 (0.79–2.05)	.32	0.66 (0.52–0.85)	.001
Adjusted on age + depressive status	0.64 (0.51–0.79)	<.0001	1.13 (0.70–1.82)	.61	0.59 (0.46–0.76)	<.0001
Fully adjusted‡	0.77 (0.61–0.97)	.02	1.27 (0.76–2.11)	.36	0.73 (0.57–0.95)	.02

Abbreviations: HR, hazard ratio; CI, confidence interval; BMI, body mass index.
*Additionally adjusted for sex.
†Adjusted for BMI, stroke, antihypertensive, antidiabetic, and lipid-lowering drugs intake.
‡Adjusted for age, education level, BMI, stroke, antihypertensive, antidiabetic and lipid-lowering drugs intake, and depressive status.

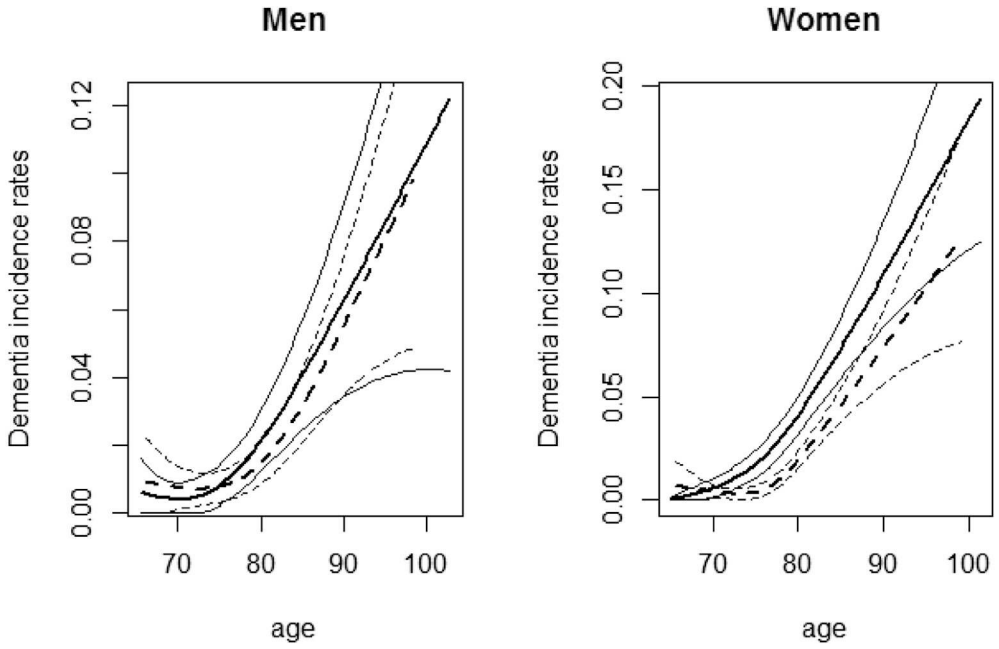

Fig. 3. Comparison of incidence rates of dementia and confidence intervals by age, for the 1990s (solid lines) and the 2000s population (dotted lines), for men (left) and women (right), based on algorithmic diagnosis.

(HR = 0.73 [0.59–0.92]) but became nonsignificant after further adjustment on education (HR = 0.83 [0.67–1.04]). Sensitivity analysis excluding participants ≥85 years showed the same result as the main analysis (fully adjusted HR = 0.71 [0.54–0.92] for women; Supplementary Table 1). Sensitivity analysis including the maximum of participants without missing data for adjustment factors also showed the same result (age-adjusted HR = 0.66 [0.52–0.83] for women).

4. Discussion

We found a significantly lower risk of dementia in the 2000s compared with the 1990s population wholly accounted for by a decrease in women using the algorithmic diagnosis. Adjustment for education level and vascular factors only partially explained the decrease of incidence among women. Using clinical diagnosis, no decrease has been found, with a suggestion of estimated risk for men higher in the 2000s population after adjustments. These findings were robust to sensitivity analyses where the algorithmic method was modified and with believable bias assumed in the refusal groups.

Our study has potential limitations. First, the sampling was not exactly the same for the 1990s and 2000s cohort. However, these cohorts covered the same geographic area (the Urban Community of Bordeaux) using the same database (electoral rolls) for randomization. They were managed by the same principal investigator (J.-F.D.) with partly the same team using same procedures for collecting the data. Second, the lower response rate of the 2000s cohort will potentially have led to selection bias, with participants differing somewhat from the population in age, sex, and socioeconomic level distributions [18]. This could be due (1) to more complicated procedures to participate in the research in the 2000s study due to regulations, with more detailed written inform consent which might have discouraged the eligible subjects; (2) and to a rise of telephone solicitations for sales prospecting, which conduct selected people to be more prone to refuse during phone contact; (3) and to a more detailed communication about medical examinations in the 2000s population than in the 1990s population.

If the adjusted risk of dementia was higher among refusals than respondents, this could have overestimated the decrease of dementia incidence in our results. However, sensitivity analyses showed that an increase of 50% of the risk of dementia among refusals would be necessary to balance the decrease of dementia incidence in the 2000s population, which is unlikely. Moreover, sensitivity analyses excluding participants aged ≥85 years who were under-represented in the 2000s population provided similar results as the main analysis. Third, attrition of the cohort was higher in the 1990s population, partly due to a decrease of mortality rates over a 10-year period. Moreover, it is possible that participants who are not followed up are at higher risk of dementia; thus, this is likely to have led to an underestimation of the incidence decrease. Fourth, although potential measured confounders were accounted for, residual confounding cannot be excluded because of measurement error and unmeasured confounders.

Secular trends analyses encounter many difficulties including consistency of the diagnosis over time and competing risk of death. Dementia diagnosis is a clinical syndromic diagnosis, using diagnostic criteria; however, clear thresholds to define the level of cognitive decline and its repercussion are not given in these criteria, leaving the ultimate decision to clinical judgment. With the evolution of interest, and the increasing awareness of dementia, the diagnostic boundaries are widely believed to have significantly changed in clinical and research practice over time; contemporary diagnosis is made at an earlier phase of the disease than in the 1990s. This greatly complicates comparison over time, with clinical diagnosis probably not being the most adapted way to analyze time trends. This explains the higher proportion of prevalent cases in the 2000s population (5.7%) compared with the 1990s (2.1%) using the clinical diagnosis, although these numbers are the opposite (2.1% in the 1990s and 3.7% in the 2000s) using the algorithmic diagnosis. In our study, using the clinical diagnostic approach, stable estimates were found for women with even an increased estimates for men, whereas for the algorithmic method, a decrease for women was found but no change for men. Algorithmic diagnostic methods avoid such a measurement bias and have been used in a small number of other studies (e.g., HRS, CFAS) [7]. The algorithm we used matches the definition of dementia which associates cognitive decline and functional impairment. This algorithm considered only the MMSE to evaluate cognitive decline and may, thus, have some limitations. However, the MMSE explores the global cognition and seems, thus, more appropriate to define a "demented state" than other tests exploring specific cognitive domains. In addition, to increase its predictive value, we combined it with the IADL functional evaluation. Moreover, sensitivity analyses using different cutoffs of MMSE showed consistent results. Second, death is a competing risk; thus, it may either prevent dementia from occurring or prevent demented subjects from being diagnosed if they die before the visit after their dementia onset. Combination of competing death and interval censoring may, thus, lead to an underestimation of dementia incidence. Owing to a higher mortality in the 1990s population, this bias may be differential between periods. The differential death rate between people with and without dementia may itself be changing. The multistate model allowed taking both competing risk and interval censoring into account. One limit of this model is that it assumes proportionality of transition intensities between the two periods, which is a strong assumption. However, when interval censoring occurs, it has been shown that this model provides better estimations of incidence than a standard survival model [23].

A small number of studies have suggested decline in incidence of dementia. In the United States, a significant decline between 1984 and 1995 was observed in one of four sites, suggesting a 30% decrease in 10 years but this was not supported by the 20-year data, nor other US cohort studies (Illinois and Indianapolis) [4]. In the Netherlands, a decline of 25% of 5-year dementia incidence between 1990–1995 and 2000-2005 has been reported but this was nonsignificant [5]. These figures are very similar to our 27% decrease in women. A prevalence study in Sweden calculated dementia incidence using mortality and prevalence, suggesting that stable prevalence with increased survival necessarily indicates declining incidence [6]. An English study with three geographical sites reported consistent reductions in prevalence over two decades [7]. Finally, a German study using routine data also reported decreasing prevalence of dementia, but over a period of only 3 years [9].

In contrast to these findings, other studies have showed an increased incidence or prevalence of dementia over time [24–27]. Until now, studies in favor of a declining risk of dementia took place mostly in Europe and the USA [4–7,9], whereas studies that showed an increasing dementia incidence were mostly conducted in China or Japan [25–27]. However, the recent meta-analysis of China studies does not support significant increases once methodological factors were taken into account [28].

Our results showed a different trend between men and women, with a decreasing incidence only for women. Few studies have analyzed dementia trends according to sex, with inconsistent results. Lobo et al. showed a significant decline in prevalence for men but not for women, whereas the German study found a slight nonsignificant decrease for men and a significant decrease for women. Qiu et al. and Schrijvers et al. failed to find any differences according to sex. One explanation for the sex difference incidence evolution in our results could be that improvement of education and risk factor management could have been greater in women than in men over the past decades, leading, thus, to a lower risk of dementia in women. Moreover, women were less disabled at baseline in the 2000s population than in the 1990s population which is in accordance with previous French results showing a significant decline in IADL disability prevalence over 10 years, particularly for women [29].

The two main hypotheses proposed for the observed decrease of dementia incidence are the improvement of education, which is largely implicated in cerebral and cognitive reserve [30], and the improvement in the management of risk factors, in particular vascular factors [5,6]. However, previous articles have not specifically explored these hypotheses. In our data, the 2000s population was higher educated and more medicated against vascular problems with less history of stroke. However, despite adjustment, these factors only partly explained the decreasing dementia incidence in our

results. Yet, it is possible that variables included do not catch all the beneficial impact of education and health behavioral changes.

Important strengths of our study are the comparison of two large independent cohorts, with identical design and procedures of data collection, and the comparison of a clinical and an algorithmic diagnosis. We have also taken into account several potential confounders and considered mortality evolution and interval censoring using multistate models.

Our study supports the hypothesis of a decline of dementia incidence for women, but not for men, between the 1990s and the 2000s; this decline seems only partly explained by potential modifiable factors. Further research is needed to clearly identify which factor change and at what age are influencing these changes across time. Such understanding will allow better policies on risk reduction for dementia across populations. In the context of an increase of risk factors such as diabetes and obesity in industrialized countries, better understanding of risk, protection, and compensation across the life course is important.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jalz.2015.11.001.

RESEARCH IN CONTEXT

1. Systematic review: We searched PubMed for articles on secular trends of dementia published in any language up to January 31, 2015, using the search terms: "dementia" or "Alzheimer's disease" and "incidence" or "prevalence" or "change" or "trends."
2. Interpretation: This work strengthens the evidence of a decline in dementia incidence over time but only for women. Moreover, our results provide an insight into the impact of some modifiable risk factors on this dementia incidence decline, although these risk factors accounted only to some extent for this decline. The decrease is in line with improved prevention and treatments of cardiovascular diseases and improved education and lifestyle. The use of multistate models allows taking competing risk of death and interval censoring into account. The use of algorithmic diagnosis allows stable comparison of cases between different periods.
3. Future directions: This finding will help producing more accurate projections of the number of individuals with dementia and care needs and could help targeting effective prevention measures. Our study suggests the potential for prevention to reduce the number of cases with dementia.

References

[1] Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, et al. Global prevalence of dementia: A Delphi consensus study. Lancet 2005;366:2112–7.

[2] Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of Alzheimer's disease. Alzheimers Dement 2007;3:186–91.

[3] Lobo A, Saz P, Marcos G, Dia JL, De-la-Camara C, Ventura T, et al. Prevalence of dementia in a southern European population in two different time periods: The ZARADEMP project. Acta Psychiatr Scand 2007;116:299–307.

[4] Rocca WA, Petersen RC, Knopman DS, Hebert LE, Evans DA, Hall KS, et al. Trends in the incidence and prevalence of Alzheimer's disease, dementia, and cognitive impairment in the United States. Alzheimers Dement 2011;7:80–93.

[5] Schrijvers EM, Verhaaren BF, Koudstaal PJ, Hofman A, Ikram MA, Breteler MM. Is dementia incidence declining? Trends in dementia incidence since 1990 in the Rotterdam Study. Neurology 2012;78:1456–63.

[6] Qiu C, von Strauss E, Bäckman L, Winblad B, Fratiglioni L. Twenty-year changes in dementia occurrence suggest decreasing incidence in central Stockholm, Sweden. Neurology 2013;80:1888–94.

[7] Matthews FE, Arthur A, Barnes LE, Bond J, Jagger C, Robinson L, et al. A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: Results of the Cognitive Function and Ageing Study I and II. Lancet 2013;382:1405–12.

[8] Christensen K, Thinggaard M, Oksuzyan A, Steenstrup T, Andersen-Ranberg K, Jeune B, et al. Physical and cognitive functioning of

people older than 90 years: A comparison of two Danish cohorts born 10 years apart. Lancet 2013;382:1507–13.
[9] Doblhammer G, Fink A, Fritze T. Short-term trends in dementia prevalence in Germany between the years 2007 and 2009. Alzheimers Dement 2015;11:291–9.
[10] Hebert LE, Bienias JL, Aggarwal NT, Wilson RS, Bennett DA, Shah RC, et al. Change in risk of Alzheimer disease over time. Neurology 2010;75:786–91.
[11] Rorsman B, Hagnell O, Lanke J. Prevalence and incidence of senile and multi-infarct dementia in the Lundby Study: A comparison between the time periods 1947-1957 and 1957-1972. Neuropsychobiology 1986;15:122–9.
[12] Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: An analysis of population-based data. Lancet Neurol 2014;13:788–94.
[13] Middleton LE, Yaffe K. Targets for the prevention of dementia. J Alzheimers Dis 2010;20:915–24.
[14] Qiu C, Xu W, Fratiglioni L. Vascular and psychosocial factors in Alzheimer's disease: Epidemiological evidence toward intervention. J Alzheimers Dis 2010;20:689–97.
[15] Sahathevan R, Brodtmann A, Donnan GA. Dementia, stroke, and vascular risk factors: A review. Int J Stroke 2012;7:61–73.
[16] Willis KJ, Hakim AM. Stroke prevention and cognitive reserve: Emerging approaches to modifying risk and delaying onset of dementia. Front Neurol 2013;4:13.
[17] Dartigues JF, Gagnon M, Letenneur L, Barberger-Gateau P, Commenges D, Evaldre M, et al. Principal lifetime occupation and cognitive impairment in a French elderly cohort (Paquid). Am J Epidemiol 1992;135:981–8.
[18] 3C Study Group. Vascular factors and risk of dementia: Design of the Three-City Study and baseline characteristics of the study population. Neuroepidemiology 2003;22:316–25.
[19] Gagnon M, Letenneur L, Dartigues JF, Commenges D, Orgogozo JM, Barberger-Gateau P, et al. Validity of the mini-mental state examination as a screening instrument for cognitive impairment and dementia in French elderly community residents. Neuroepidemiology 1990;9:143–50.
[20] Peres K, Chrysostome V, Fabrigoule C, Orgogozo JM, Dartigues JF, Barberger-Gateau P. Restriction in complex activities of daily living in MCI: Impact on outcome. Neurology 2006;67:461–6.
[21] Radloff L. The CES-D scale: A self-report depression scale for research in the general population. Appl Psychol Meas 1977;1:385–401.
[22] Touraine C, Helmer C, Joly P. Predictions in an illness-death model. Stat Methods Med Res 2013 [Epub ahead of print].
[23] Leffondre K, Touraine C, Helmer C, Joly P. Interval-censored time-to-event and competing risk with death: Is the illness-death model more accurate than the Cox model? Int J Epidemiol 2013;42:1177–86.
[24] Ukraintseva S, Sloan F, Arbeev K, Yashin A. Increasing rates of dementia at time of declining mortality from stroke. Stroke 2006;37:1155–9.
[25] Li S, Yan F, Li G, Chen C, Zhang W, Liu J, et al. Is the dementia rate increasing in Beijing? Prevalence and incidence of dementia 10 years later in an urban elderly population. Acta Psychiatr Scand 2007;115:73–9.
[26] Sekita A, Ninomiya T, Tanizaki Y, Doi Y, Hata J, Yonemoto K, et al. Trends in prevalence of Alzheimer's disease and vascular dementia in a Japanese community: The Hisayama Study. Acta Psychiatr Scand 2010;122:319–25.
[27] Chan KY, Wang W, Wu JJ, Liu L, Theodoratou E, Car J, et al. Epidemiology of Alzheimer's disease and other forms of dementia in China, 1990-2010: A systematic review and analysis. Lancet 2013;381:2016–23.
[28] Wu YT, Lee HY, Norton S, Chen C, Chen H, He C, et al. Prevalence studies of dementia in mainland China, Hong Kong and Taiwan: A systematic review and meta-analysis. PLoS One 2013;8:e66252.
[29] Peres K, Helmer C, Letenneur L, Jacqmin-Gadda H, Barberger-Gateau P. Ten-year change in disability prevalence and related factors in two generations of French elderly community dwellers: Data from the PAQUID study. Aging Clin Exp Res 2005;17:229–35.
[30] EClipSE Collaborative MembersBrayne C, Ince PG, Keage HA, McKeith IG, Matthews FE, Polvikoski T, et al. Education, the brain and dementia: Neuroprotection or compensation? Brain 2010;133:2210–6.

Supplementary table 1: Sensitivity analyses for incidence evolution between the 1990's and the 2000's population, for both sexes.

	Hommes		Women	
	HR (95% CI)	p value	HR (95% CI)	p value
Analyzes with algorithm 1				
2000's vs 1990's	(n=1,290)		(n=1,981)	
Adjusted on age	1.25 (0.82 – 1.89)	0.30	0.62 (0.50 – 0.78)	<.0001
Adjusted on age + education	1.23 (0.80 – 1.90)	0.34	0.68 (0.54 – 0.85)	0.0008
Adjusted on age + vascular factors*	1.32 (0.87 – 2.01)	0.20	0.65 (0.51 – 0.81)	0.0002
Adjusted on age + depressive status	1.26 (0.83 – 1.92)	0.27	0.60 (0.48 – 0.75)	<.0001
Fully adjusted†	1.37 (0.89 – 2.10)	0.15	0.69 (0.54 – 0.87)	0.002
Analyzes with algorithm 2				
2000's vs 1990's	(n=1,304)		(n=2,020)	
Adjusted on age	1.06 (0.62 – 1.79)	0.83	0.58 (0.45 – 0.75)	<.0001
Adjusted on age + education	0.86 (0.49 – 1.51)	0.60	0.64 (0.49 – 0.83)	0.0009
Adjusted on age + vascular factors*	1.36 (0.82 – 2.27)	0.23	0.61 (0.46 – 0.79)	0.0003
Adjusted on age + depressive status	1.07 (0.63 – 1.81)	0.80	0.56 (0.43 – 0.72)	<.0001
Fully adjusted†	1.11 (0.65 – 1.89)	0.70	0.67 (0.51 – 0.88)	0.004
Analyzes with algorithm 3				
2000's vs 1990's	(n=1,294)		(n=1,988)	
Adjusted on age	1.07 (0.71 – 1.63)	0.74	0.60 (0.47 – 0.75)	<.0001
Adjusted on age + education	0.97 (0.62 – 1.51)	0.89	0.67 (0.53 – 0.84)	0.0006
Adjusted on age + vascular factors*	1.20 (0.79 – 1.82)	0.40	0.61 (0.48 – 0.77)	<.0001
Adjusted on age + depressive status	1.08 (0.71 – 1.63)	0.72	0.57 (0.46 – 0.72)	<.0001
Fully adjusted†	1.21 (0.72 – 2.03)	0.47	0.69 (0.54 – 0.87)	0.002
Analyzes on 65 - 85 years old participants				
2000's vs 1990's	(n=1,251)		(n=1,906)	
Adjusted on age	1.18 (0.72 – 1.92)	0.52	0.64 (0.49 – 0.82)	0.0006
Adjusted on age + education	1.04 (0.63 – 1.72)	0.87	0.69 (0.53 – 0.89)	0.004
Adjusted on age + vascular factors*	1.32 (0.82 – 2.13)	0.25	0.67 (0.52 – 0.88)	0.003
Adjusted on age + depressive status	1.22 (0.75 – 1.99)	0.42	0.61 (0.47 – 0.78)	0.0001
Fully adjusted†	1.35 (0.83 – 2.20)	0.23	0.71 (0.54 – 0.92)	0.01
Analyzes including all available participants for each analysis				
2000's vs 1990's				
Adjusted on age	(n=1,333) 1.08 (0.68 – 1.71)	0.74	(n=2,111) 0.66 (0.52 – 0.83)	0.0005
Adjusted on age + education	(n=1,332) 1.00 (0.77 – 1.29)	0.97	(n=2,109) 0.73 (0.58 – 0.93)	0.01
Adjusted on age + vascular factors*	(n=1,313) 1.28 (0.81 – 2.03)	0.28	(n=2,027) 0.66 (0.51 – 0.85)	0.001
Adjusted on age + depressive status	(n=1,319) 1.17 (0.73 – 1.88)	0.52	(n=2,087) 0.63 (0.50 – 0.80)	0.0001

HR: Hazard Ratio ; IC: Confidence Interval

* Adjusted for BMI, stroke, antihypertensive, antidiabetic and lipid-lowering drugs intake

† Adjusted for age, education level, BMI, stroke, antihypertensive, antidiabetic and lipid-lowering drugs intake and depressive status

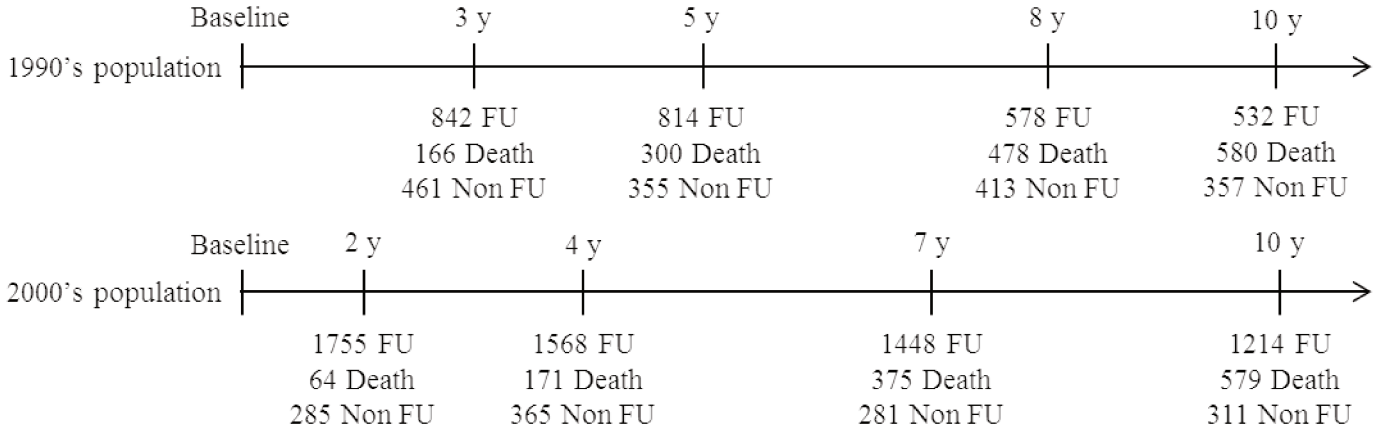
Algorithm 1: Algorithm depending on education: without diploma: MMSE <24 and 4IADL≥2; with diploma:

MMSE <26 and 4IADL≥2
Algorithm 2: MMSE<23 and 4IADL≥2
Algorithm 3: MMSE<25 and 4IADL≥2

Supplementary table 2: Incidence evolution between the 1990's and the 2000's population, assuming different risks of dementia among non-respondents.

Women	**Initial analysis**		**Non-respondent over risk=1.25**		**Non-respondent over risk=1.5**		**Non-respondent over risk=2.0**	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Algorithmic diagnosis	(n=2,004)		(n=2,648)		(n=2,648)		(n=2,648)	
2000's vs 1990's								
Adjusted on age	0.62 (0.48 – 0.80)	0.0002	0.70 (0.56 – 0.87)	0.001	0.73 (0.59 – 0.92)	0.006	0.83 (0.67 – 1.03)	0.09
Adjusted on age + education	0.70 (0.54 – 0.89)	0.004	0.78 (0.63 – 0.98)	0.03	0.83 (0.67 – 1.04)	0.11	0.92 (0.75 – 1.14)	0.46

HR: Hazard Ratio ; IC: Confidence Interval



Supplementary figure 1: Follow up for each population with number of subjects seen at each follow up (FU), cumulative number of deaths and non-cumulative number of subjects not seen at each follow up (Non FU) (n=3573). Non FU subjects at one time can be seen at a following time.

4.1.4. Supplementary results

Beside the incidence trend analysis, prevalence estimates at baseline for the two populations and both diagnosis were performed. Prevalence rates of the 3C population were standardized according to age and sex distribution of the PAQUID population. Prevalence rates are shown in table 9.

Table 9: Age and sex standardised prevalence rates of dementia in % according to dementia definition and population

		Total N=3573	**Men N=1378**	**Women N=2195**
Clinical diagnosis				
	1990's	2.1 (1.4 – 2.8)	3.0 (1.6 – 4.4)	1.5 (0.7 – 2.3)
	2000's	3.8 (3.0 – 4.6)	3.9 (2.6 – 5.3)	3.7 (2.6 – 4.7)
Algorithmic diagnosis				
	1990's	5.7 (4.5 – 6.9)	4.4 (2.7 – 6.2)	6.5 (4.9 – 8.1)
	2000's	2.2 (1.6 – 2.8)	2.5 (1.4 – 3.5)	2.0 (1.2 – 2.8)

According to clinical diagnosis, the 2000's population had a higher prevalence than the 1990's population, whereas it is the contrary with the algorithmic definition. These results are in line with the clinical diagnosis in 3C made earlier than in the PAQUID study. We can also remark that prevalence was really different according to gender in the 1990's population, whereas it became more similar in the 2000's population. The diagnostic drift seemed more important in women than in men.

In addition to this incidence study, I have also contributed to the prevalence analysis comparing two rural populations from the PAQUID study in 1988 and the Aging Multidisciplinary Investigation (AMI) study in 2008. (*Pérès K, Brayne C, Matharan F, **Grasset L**, Helmer C, Letenneur L, et al. Trends in the prevalence of dementia in French farmers from two epidemiological cohorts. J Am Geriatr Soc. 2017;65(2):415-20*). Prevalence was also defined according to the two diagnostic procedures: the clinical and the algorithmic ones. The prevalence of clinical dementia has increased from 5.7% to 11.3% between the

1988 and the 2008 populations. However, the prevalence using algorithmically-defined dementia has decreased from 23.8% to 13.0%. These results have also demonstrated the shift in clinical boundary of diagnosis between PAQUID and AMI toward less cognitively and functionally impaired states. Older farmers are different from the general population in many ways, such as occupational exposures, lifestyle, educational level, and access to care, but nevertheless provide insight into change over time.

4.1.5. Discussion

This work brings further evidence toward a decreasing trend of dementia incidence and prevalence. However, our results did not show a decrease of incidence in men and the risk factors accounted for in the analyses did not fully explain the decrease observed in women.

The decrease evidenced may be explained by a global improvement of health status between generations. However, a selection bias in the 3C-Bordeaux population cannot be totally excluded, even if sensitivity analyses reported consistency of results. The issue of participation rates differences between populations compared is frequent in the published papers: 56 vs 80% between the CFAS studies, 95 vs 64% in the Spain studies, and 86 vs 44% in the Indianapolis-Ibadan Dementia Project for example (146, 147, 156). As developed in introduction, a low response rate can lead to a selection of the population toward the inclusion of healthier participants than the global population. With lower participation rate in the later populations, the selection could lead to over estimation of the reduction evidenced. Even if in our study and in others (146), authors tried to take into account this by sensitivity analyses, such analyses could not replace similar response rates.

Even if most of the studies support the declining trend of dementia incidence, gender results are more mixed. In our study, the decrease in incidence is driven by a decreased incidence in women. Similar results were shown in the Framingham Heart Study with significant decline in women between all the period, and a non-significant decline in men between 2004-2008 and 1977-1983 only. In the Rotterdam study, the non-significant decline was similar between men and women. However, in the CFAS study, the decline in incidence was significant for men only. In the article, it is shown that men had higher incidence rates than women in CFAS I and that this difference was less strong in CFAS II. Unlike CFAS, women had higher incidence rates than men in PAQUID and 3C studies, even if the difference was smaller in the

3C study. In the prevalence studies, the Zaragoza study also showed a decreased prevalence in men only.

In the literature, three additional studies investigated the effect of several risk factors on the decrease of incidence. First, analyses from the FHS were adjusted for educational level, midlife blood pressure, BMI and diabetes, stroke history, cardiovascular disease and atrial fibrillation. These factors only slightly explained the decrease of incidence by less than 10% each. They have also found that the decrease was observed among individuals with at least a high school diploma only. Then in the HRS study, prevalence analyses were adjusted on education, cardiovascular risks of stroke, diabetes, hypertension, and heart disease, and BMI. In line with other results, these factors partially explained the decrease in prevalence; however, the decrease was still significant. In the Rotterdam study, intracranial volume, total brain volume, and volume of white matter lesions were compared and showed an increased total brain volume and less cerebral small vessel disease (nonsignificant in men). This is in line with an increase of cerebral reserve and an improvement of cerebrovascular health. Population Attributable Risk (PAR) were also calculated in another paper for the two cohorts and showed a reduced PAR by smoking and cholesterol level, a stable PAR by education and cardiovascular disease and an increased PAR by diabetes and hypertension (138).

The decreasing trends in dementia incidence and prevalence are promising and highlight the potential for prevention of modifiable risk factors. However, the increasing trends of diabetes and obesity could reverse this trend in the future. It is therefore critical to replicate secular trends analyses and focus on factors associated to this decline.

4.2. Secular trends of cognition and disability

4.2.1. Introduction

With accumulating evidence in favour of a decrease of dementia incidence and prevalence, it is therefore important to seek for a better understanding of this evolution. Due to its definition, dementia is closely related to and directly affects cognitive and functional abilities. Looking more closely at components of the disease over time could help having a better comprehension of mechanisms involved. It has been shown that cognitive impairment can be identified many years before dementia onset (221). It is thus of interest to investigate evolution of cognition and function between generations. Cohort effect could be seen in term of level or trajectory over time.

When referring to cognition, reserve is an important concept. As defined in introduction, the concept of reserve refers to the ability of a physiologic system to maintain function despite damage from injury or disease. In the context of dementia, reserve refers to the ability to maintain cognitive function despite the accumulation of the various pathologies that contribute to cognitive impairment. We can distinguish the neural reserve and the cognitive reserve. Neural reserve is more quantitative, like for example, more neurons or bigger brain volumes. The brain can tolerate more pathology before it reaches a critical threshold for clinical symptoms to appear (222). In cognitive reserve, the brain actively attempts to cope with brain damage by using pre-existing cognitive processing approaches or by enlisting compensatory approaches (60, 223-225). Related to this, the improvement over time of educational level could have improved cognitive reserve and lead to better cognitive performances. Indeed, subjects with better cognitive reserve maintain better cognitive performances through lesion processes, and cope better with these lesions up to a certain level of pathology. For vascular risk factors, the hypothesis relies on a better health of the brain. Decrease in vascular disease could imply less brain structure damages and thus greater abilities to perform cognitive task.

The aim of this work was thus to investigate the cognitive and functional abilities in level and decline of two generations 10 years apart, as well as the effect of several risk factors on the evolution.

4.2.2. Methods

In this work, we have decided to compare cognitive and functional abilities between two generations of the PAQUID study only. This limits the participation rates difference between PAQUID and 3C, even if a selection due to comparison of surviving individuals in the second generation can occur. However, an inconvenient is the limited age range available for comparison. One difficulty when studying cognitive tests evolution over time is first-passing effect. This effect conducts to an increase of the performance at the second assessment. The issue with our population was that this learning effect was present only in the first generation. To avoid biased comparison, we have chosen to investigate scores evolution from the three-year follow-up for the first generation up to the 15-year follow-up and from the 13-year follow-up to the 25-year follow-up for the second generation.

Four cognitive domains were assessed: 1) global cognitive functioning with the MMSE; 2) semantic verbal fluency with the Isaacs Set Test (IST); 3) visual working memory with the BVRT; and 4) processing speed with the DSST. For function, we decided to investigate the evolution on the four IADL highly related to cognition, with a 15-point scale summing the score at each of the 4 activities. Linear mixed models were used to look at the evolution of cognitive and functional scores over time. Scores have been transformed to be normalised using splines transformations.

4.2.3. Article

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Title: Time trends in level and decline of cognition and function of elderly people: the PAQUID study

Article Type: Research Article

Keywords: Cognitive Aging, disability, trends, cohort studies

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Abstract: Introduction: To compare cognitive and functional evolution between two generations 10 years apart and to evaluate the effect of specific risk factors on this evolution.
Methods: Two "generations" of elderly aged 78-88 years, included 10 years apart in the Paquid cohort (n=612 in 1991-92 and n=628 in 2001-02) were followed-up over 12 years with repeated assessment for cognition and function. Mixed effects models were used.
Results: The second generation had higher performances at baseline than the first one for the four cognitive tests (from p=0.005 to p<.0001). For the MMSE and the verbal fluency tests, these differences were mostly explained by educational level improvement, but not for the tests of working memory and processing speed. No difference was observed for cognitive decline. Regarding function, despite a trend, no significant differences were found.
Discussion: Cognitive state of the French elderly population has changed, partially due to improvement of educational level.

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To The Editors of Alzheimer's & Dementia
Bordeaux, May 4th 2017

Dear Sir, Madam,

Please find enclosed the manuscript entitled "Time trends in level and decline of cognition and function of elderly people: the PAQUID study" by Leslie Grasset, Hélène Jacqmin-Gadda, Cécile Proust-Lima, Karine Pérès, Hélène Amieva, Jean-François Dartigues, and Catherine Helmer, that we would like to submit for publication to Alzheimer's & Dementia.

The close relationship between dementia and cognitive and functional performance make the study of their evolution over time of high interest. However, previous reports of trajectories of cognitive and functional abilities showed mixed results. In this paper, we aimed to analyze the secular trends of cognition and function, comparing two generations of elderly people in the same age group 10 years apart, followed over a 12-year period. Moreover, we aimed to assess possible determinants of these trends. Several cognitive domains have been studied to precisely understand the impact of generation.

Knowledge on cognitive and functional evolution seems indeed essential to a better understanding of the mechanism behind the decline of dementia incidence. Moreover, identifying risk factors that have potentially led to an improvement of cognitive capacities and reduction of disabilities will help to find effective target to enhance healthy aging.

This manuscript is an original article. It has not been published, considered for publication, or sent to be considered for publication elsewhere. All authors actively participated in the discussion and manuscript revision, and had access to the data. All the authors approved the final version of the paper. LG is the guarantor for this paper.

Thank you in advance for taking this paper into consideration.

Best regards,

For the authors,

Leslie Grasset.

Time trends in level and decline of cognition and function of elderly people: the PAQUID study

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Abstract

Introduction: To compare cognitive and functional evolution between two generations 10 years apart and to evaluate the effect of specific risk factors on this evolution.

Methods: Two "generations" of elderly aged 78-88 years, included 10 years apart in the Paquid cohort (n=612 in 1991-92 and n=628 in 2001-02) were followed-up over 12 years with repeated assessment for cognition and function. Mixed effects models were used.

Results: The second generation had higher performances at baseline than the first one for the four cognitive tests (from p=0.005 to p<.0001). For the MMSE and the verbal fluency tests, these differences were mostly explained by educational level improvement, but not for the tests of working memory and processing speed. No difference was observed for cognitive decline. Regarding function, despite a trend, no significant differences were found.

Discussion: Cognitive state of the French elderly population has changed, partially due to improvement of educational level.

Key Words: Cognitive Aging, disability, trends, cohort studies

1. Introduction

Because of important health and economic consequences of population aging [1], up-to-date estimation of future dementia burden has become crucial for societies to estimate the need of health care and social services. Accurate evaluation of the evolution of dementia-related processes over time can provide such information. Indeed, forecasts indicated that by 2050 the number of people living with dementia should be around 131.5 million [1]. However, some studies have found evidences of a trend toward a decline of prevalence or incidence of dementia over the last decades [2-9]. Even if hypotheses for a decline in dementia frequency are based on changes of modifiable risk factors across decades [10,11], such as educational level, vascular factors, or healthy life style, the few studies analyzing the role of these risk factors on the dementia decrease did not enable to fully explain such a decrease [8,9].

Dementia is defined by impairment of cognitive performance with repercussions on capacity to perform daily living activities. Cognitive impairment has been shown to begin more than 15 years before the diagnosis [12]. Thus, evaluating trends of cognition and function in daily living activities over time could bring arguments to better understand secular trends of dementia.

Furthermore, living conditions and health profiles have highly evolved and improvement of factors such as education or vascular diseases could have an impact on secular trends of cognition and function. Determinants may impact cognition or function at different periods of life and may differentially impact cognitive domains. Indeed, education may intervene early in life span while vascular risk factors probably intervene later, at midlife or after 65 years old. Thus, evolution of trends in cognition and function in old age may be due either to a difference in baseline performances or to a differential decline over time.

This study aimed to analyze the secular trends of cognition and function, comparing two generations of elderly people in the same age group 10 years apart, followed over a 12-year period. Moreover, we aimed to assess possible determinants of these trends.

2. Methods

2.1 Study population

This study was based on a prospective population-based cohort, the Personnes Agées Quid (PAQUID) study, which consists of a representative sample of 3,777 participants in the departments of Gironde and Dordogne (Southwest France), randomly chosen from the electoral rolls in 1988–1989. Three criteria had to be met for inclusion: to be at least 65 years of age by December 31, 1987; to be living at home at the time of the initial data collection phase; and to give informed consent to participate in the study. Participants were followed over 25 years every 2 or 3 years, at 3, 5, 8, 10, 13, 15, 17, 20, 22 and 25 years after the baseline evaluation. Among the 5,554 persons selected, 3,777 (68 percent) agreed to participate in the study. Full details of the study have been given elsewhere [13]. A standardized questionnaire assessing socio-demographic, medical, cognitive, and functional data was administered at home by trained neuropsychologists during face-to-face interviews, at baseline and at each follow-up. An ethical review committee has approved the PAQUID study.

In this study, time trends of cognition have been studied 10 years apart. To avoid first-passing effect inherent to cognitive tests [14], we did not consider the baseline evaluation. Thus, two generations (G1 and G2) have been selected and compared: G1 included subjects born between 1903 and 1912 and thus aged 78-88 years in 1991-1992 (at the three-year follow-up of the cohort, T3) and G2 those born between 1913 and 1922, thus aged 78-88 years in 2001-2002 (T13) (Cf. figure 1). For each of these two generations, the 12 subsequent years of

follow-up have been analyzed. The follow-up at T3 for the first generation and the follow-up at T13 for the second one are further referred to as "baseline" for G1 and G2. For each generation, participants with a prevalent dementia at "baseline" were excluded. As we previously evidenced that clinical diagnosis of dementia had changed over time, these prevalent cases were excluded based on an algorithmic diagnosis (MMSE<24 and disability for at least 2 activities of the 4-IADL scale: telephone, transports, medications and finances) [8]. The study population was thus composed of 1238 subjects: 612 for the first generation and 628 for the second one.

2.2 Adjustment factors

Demographic factors included age, sex and educational level (divided into three categories: no diploma, validated primary school level or short secondary school level and, long secondary school level or more). At the "baseline" visit (i.e. at T3 for G1 and T13 for G2) medication consumptions have been collected using a standardized questionnaire, as well as a visual inspection of the medical prescriptions and the participant's medicine packs; anti-hypertensive drugs, anti-diabetics and lipid-lowering drugs were controlled for in the present study (taken as a proxy of cardiovascular diseases, diabetes and, hypercholesterolemia).

2.3 Cognition and function assessment

At baseline and at each follow-up, participants underwent a complete cognitive and functional evaluation.

Cognition was evaluated using four cognitive tests: 1) the Mini Mental State Examination (MMSE) [15], from 0 to 30, assessing global cognitive functioning; 2) the 15-second version of the Isaacs Set Test (IST) [16], assessing semantic verbal fluency; 3) the Benton Visual Retention Test (BVRT) [17], from 0 to 15, measuring visual working memory; 4) and the

Digit symbol substitution test (DSST), evaluating processing speed; this test was underwent at each time apart from T3. Functional abilities were evaluated using four Instrumental Activities of Daily Living (4 IADL: ability to use the telephone, transportation, responsibility for medications, and ability to manage finances), assessing cognitive-specific functions [18]; a score from 4 to 15 was used. High cognitive scores represent good performances whereas high functional score represent high disabilities.

2.4 Statistical analyses

For each of the two generations, cognitive and functional abilities were analyzed over a 12-year period of follow-up (from 1991-92 to 2003-04 for the G1 and from 2001-02 to 2013-14 for G2) (Cf. figure 1). Both populations were compared on sociodemographic characteristics, MMSE, BVRT, IST, DSST and 4 IADL scores at "baseline", and on intake of the three specific drug categories (anti-hypertensive, anti-diabetic and lipid-lowering treatments) using Chi-square and Student t tests. Data regarding follow-up and attrition of each population were provided (Cf. figure 1).

For cognitive and functional evolutions, analyses were performed using the linear mixed models theory [19]. Due to ceiling and floor effects and curvilinearity (unequal interval scaling), the models included spline transformations to normalize the different scores [20]. Each score was transformed and analyzed in separated one-step models assuming a linear mean trajectory with time and including individual correlated random effects on intercept and slope. Time was the number of years of follow-up (time since "baseline"). Interaction with sex was tested but data were analyzed globally as it was non-significant. A first model was systematically adjusted for generation (G2 vs. G1), age, sex and included an interaction between generation and time (Model 1). The simple effect of generation quantified the difference in the "baseline" scores while the interaction with time quantified the generation

effect on the score change over the follow-up period. Then, models were additionally adjusted for educational level (Model 2) and vascular factors (antihypertensive, antidiabetic, and lipid-lowering drugs) (Model 3). Interaction between time and adjustment factors were tested and added in models when significant. The goodness-of-fit of each model was assessed using residual plots.

Statistical analyses were performed with SAS statistical software version 9.3 and R packages lcmm 1.7.5 [21].

3. Results

3.1 Study sample description

Sex distribution did not differ between the two generations (table 1). G2 was slightly younger, had a higher educational level and took more antihypertensive and lipid-lowering drugs than G1. "Baseline" performances in terms of MMSE, BVRT and DSST (mean at T5 and T15 as DSST is not available at T3) were significantly higher for the second generation and "baseline" 4IADL significantly lower (better function). The 12-year mortality was also lower in G2 (66.9% vs 80.6%) (Cf. figure1).

3.2 Cognitive and functional evolution between generations

Results of the linear mixed effect regressions for each psychometric and functional test are presented in table 2. Estimates are given in the normalized scales of the tests. Figure 2 illustrates the predicted score trajectory according to generation, based on model 1, in the natural scale of each test.

For MMSE and IST, model 1 showed that the generation was associated with the mean transformed scores (respectively p=0.0007 and p=0.005), meaning that the second generation had better scores at baseline. Time variable was also significant whatever age and sex (using

multivariate Wald test), indicating that scores declined over time. However, this decline did not differ according to the generation (respectively p=0.73 and p=0.24). After adjustment for education (model 2), generation was no longer significantly associated with "baseline" mean transformed scores (respectively p=0.21 and p=0.30); results regarding decline over time remained unchanged. Additional adjustment in model 3 did not modify this result.

For BVRT and DSST, the generation was associated with the mean transformed scores (respectively p<.0001 and p=0.0001): G2 had higher scores than G1 at "baseline". This association between generation and baseline performance remained significant after additional adjustment for education (model 2) and vascular treatment (model 3, respectively p<.0001 and p=0.003). As for MMSE and IST, the cognitive performances significantly declined with time whatever age and sex (using multivariate Wald test) but the intensity of change over time did not significantly differ according to generations.

For 4IADL score, the mean functional state at baseline did not significantly differ between generations, even in the first model (p=0.10). A significant increase in the score with time whatever age and sex (using multivariate Wald test) indicated an increase in mean disability over the follow-up. This increase in disability tended to be slower for G2 than for G1, although non-significantly (p=0.08).

4. Discussion

The main finding of this study is an improvement of performance in global cognitive functioning, verbal fluency, working memory and processing speed between two generations of subjects aged 78-88 evaluated 10 years apart, but without any difference in the rates of decline for these cognitive domains. For global cognition and verbal fluency, the improvement was mostly explained by the increase of educational level, but not for visual working memory and processing speed. Despite our hypothesis, anti-hypertensive, anti-

diabetes and lipid-lowering treatments were not significantly associated with baseline scores or with decline over time and only slightly explained the relationship between generation and cognition. For functional capacities in activities of daily living, no difference was found between generations on the initial level and on disability progression.

Supporting the decrease in dementia occurrence, cognitive performance increased between generations, involving a global improvement of cognitive functions in 10 years. Educational level was highly improved over the two generations (31.4% had no diploma in G1 vs. 18.2% in G2) and it was found to explain a large part of the baseline score differences between the two generations. However, the intensity of age-related cognitive decline over time did not vary between the two generations. This discrepancy between improvements of baseline performances without improvement of decline over time could be partly explained by the effect of education that probably intervenes early in life span. Indeed, educational level was highly associated with the mean score at baseline, but was not associated with the decline over time (data not shown). It is in line with a review showing that education is highly associated with cognitive performance but does not moderate age-associated cognitive decline [22]. These findings are consistent with the Flynn effect, described as an improvement of intellectual quotient with improvement of education [23,24]. The improvement of cognitive functions with generations has already been found in previous studies [25-32]. However, results on cognitive decline are more conflicted. Indeed, previous authors also found that cohort improvement (improvement over generations) did not mitigate age decline [26,27]. In contrast, Gerstorf et al. showed a smaller age-related decline among individuals born later for spatial orientation, reasoning, word fluency and verbal meaning [31].

In our results, education explained the improvement in baseline cognitive performance between the two generations for tests exploring global cognition and verbal fluency but not

for tests exploring visual memory and executive function. Similar results for baseline performance have been found in a recent study from the Longitudinal Aging Study Amsterdam [32]. However, in this later study, the authors also found a steeper decline for the second generation for processing speed (DSST) not explained by education. Depending on the cognitive domains implicated in each test, it makes sense that some tests are more influenced by educational level. The IST test, evaluating semantic memory, highly depends on education, whereas the DSST, evaluating more executive functions, is probably less influenced. Although education has also been found to influence BVRT [33], a difference between generations remained. This suggests that other factors beyond education may contribute to the improvement of cognitive level over time. Indeed, many aspects of our environment have changed over time, requiring an increasing level of cognitive capacities, mainly executive ones, leading thus to an improvement of tests evaluating executive functions.

Overall, persons from older generations have higher cognitive performances and thus, despite a similar cognitive decline rate, may reach the clinical threshold later than the more recent generations and experience a delayed occurrence of dementia. These higher cognitive performances are in some domains partly explained by their higher level of education. This is in line with our previous results regarding dementia incidence evolution, with a decreased risk of dementia partially explained by education [8]. However, more complicated processes seem to be involved in dementia decrease and improvement of cognition, with other factors than educational level implicated. Even if we failed to evidence that vascular factors could explain this cognitive improvement over generations, we cannot exclude an inappropriate measurement of these factors (we only had drug consumptions, analyzed as proxies). Thus, individual factors such as vascular factors and behavioral habits, as well as environmental factors may be implicated. Moreover, progression toward dementia is a very long process,

beginning several years before clinical dementia onset [12]; the understanding of this process would need a lifelong evaluation of cognitive performance.

Regarding functional abilities, they were not significantly improved between generations, although the trajectory of disability over time tended to be slightly better for the second generation. Unlike our results, a few studies have evidenced a significant improvement in the level of functional abilities between cohorts [30,34-36]. In contrast, Jagger et al. found a non-significant trend to an increase in disabilities in 5 years interval cohorts [37], and Steiber showed a decrease in physical health score (lower physical performance) in subjects aged 50 – 90 years and born 6 years apart [25]. These differences between studies could be due to the use of different assessment of functional status. Thus, mild disability (in instrumental activities of daily living) may have decreased whereas more severe disability (in basic activities of daily living) may have risen due to a longer survival of frail people. In the present study, we focused only on four Instrumental activities with high cognitive demand. It might explain the difference with the study also based on PAQUID which found a significate decline of disability on the Lawton IADL [36]. The differences could also be due to different age range and generations, or to the fact that assessment of instrumental activities of daily living may have evolved over time, as the way to perform tasks such as driving, telephoning or handling the budget. Although non-significant, our results are in favor of a slight better functional aging, occurring in advanced ages (more than 78 years old), that may be more related to an improvement of care than to determinants. On the contrary, cognition may be more related to a lifelong effect of the improvement of determinants (before 65 years old). This difference could be explained by a delay between cognitive improvement effects and impact on function.

This study has several limits. First, the study sample was aged 78-88 years at baseline and results might be different for younger subjects, although a recent study on subjects aged 65 to

75 years old showed concordant results [32]. Then, results for function were not significant and conclusions regarding functional abilities need to be taken with caution. This could be explained by the fact that the 4 IADL score is not sensitive enough to changes. Finally, for slope estimation, differential attrition between the two populations could have led to a bias; however, as attrition is lower in the second generation, it would have biased the results towards an underestimation of the generation effect.

An important strength of this study is that the two generations are from the same population-based prospective cohort, with up to 6 assessments of cognition and function over a 12-year follow-up period for each generation. Moreover, to increase comparability between the two generations and to avoid first passing effect for cognitive test, we excluded the first visit in the present study. Follow-up questionnaires were administered by trained neuropsychologists, managed by the same team over time. Appropriate statistical models were used to take normality problems into account avoiding large bias highlighted when studying decline over time of cognitive scores with asymmetric distribution [20].

Conclusion

Our analyses indicate that initial cohort differences in cognitive performance are maintained throughout aging but are not exacerbated with advancing age. Thus, the improvement of the basic cognitive state more than a lesser decline in cognitive performances in old age, may explain a possible decrease in incidence of dementia. The real link between cognition and function still needs to be investigated.

Declaration of interests

Leslie Grasset – Reports no disclosure

Hélène Jacqmin-Gadda – Reports no disclosure

Cécile Proust-Lima – Reports no disclosure

Karine Pérès – Reports no disclosure

Hélène Amieva – Reports no disclosure

Jean François Dartigues – Research Grants from IPSEN and Roche, outside the submitted work.

Catherine Helmer – Reports no disclosure

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The funders had no role in study design, in data collection, analysis, and interpretation, or in writing of report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication

References:

[1] I. Alzheimer's Disease. World Alzheimer Report London: ADI; 2015.

[2] F.E. Matthews, A. Arthur, L.E. Barnes, J. Bond, C. Jagger, L. Robinson, et al. A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II. Lancet 2013;382:1405-12.

[3] C. Qiu, E. von Strauss, L. Bäckman, B. Winblad, L. Fratiglioni. Twenty-year changes in dementia occurrence suggest decreasing incidence in central Stockholm, Sweden. Neurology 2013;80:1888-94.

[4] A. Lobo, P. Saz, G. Marcos, J.L. Dia, C. De-la-Camara, T. Ventura, et al. Prevalence of dementia in a southern European population in two different time periods: the ZARADEMP Project. Acta psychiatrica Scandinavica 2007;116:299-307.

[5] G. Doblhammer, A. Fink, T. Fritze. Short-term trends in dementia prevalence in Germany between the years 2007 and 2009. Alzheimers Dement 2015;11:291-9.

[6] E.M.C. Schrijvers, B.F.J. Verhaaren, P.J. Koudstaal, A. Hofman, M.A. Ikram, M.M.B. Breteler. Is dementia incidence declining?: Trends in dementia incidence since 1990 in the Rotterdam Study. Neurology 2012;78:1456-63.

[7] W.A. Rocca, R.C. Petersen, D.S. Knopman, L.E. Hebert, D.A. Evans, K.S. Hall, et al. Trends in the incidence and prevalence of Alzheimer's disease, dementia, and cognitive impairment in the United States. Alzheimers Dement 2011;7:80-93.

[8] L. Grasset, C. Brayne, P. Joly, H. Jacqmin-Gadda, K. Peres, A. Foubert-Samier, et al. Trends in dementia incidence: Evolution over a 10-year period in France. Alzheimer's & Dementia 2016;12:272-80.

[9] C.L. Satizabal, A.S. Beiser, V. Chouraki, G. Chene, C. Dufouil, S. Seshadri. Incidence of Dementia over Three Decades in the Framingham Heart Study. N Engl J Med 2016;374:523-32.

[10] H. Jacqmin-Gadda, A. Alperovitch, C. Montlahuc, D. Commenges, K. Leffondre, C. Dufouil, et al. 20-Year prevalence projections for dementia and impact of preventive policy about risk factors. European journal of epidemiology 2013;28:493-502.

[11] S. Norton, F.E. Matthews, D.E. Barnes, K. Yaffe, C. Brayne. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. Lancet Neurol 2014;13:788-94.

[12] H. Amieva, H. Mokri, M. Le Goff, C. Meillon, H. Jacqmin-Gadda, A. Foubert-Samier, et al. Compensatory mechanisms in higher-educated subjects with Alzheimer's disease: a study of 20 years of cognitive decline. Brain 2014;137:1167-75.

[13] J.F. Dartigues, M. Gagnon, L. Letenneur, P. Barberger-Gateau, D. Commenges, M. Evaldre, et al. Principal lifetime occupation and cognitive impairment in a French elderly cohort (Paquid). Am J Epidemiol 1992;135:981-8.

[14] H. Jacqmin-Gadda, C. Fabrigoule, D. Commenges, J.F. Dartigues. A 5-year longitudinal study of the Mini-Mental State Examination in normal aging. Am J Epidemiol 1997;145:498-506.

[15] M.F. Folstein, S.E. Folstein, P.R. McHugh. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-98.

[16] B. Isaacs, A.T. Kennie. The Set test as an aid to the detection of dementia in old people. The British journal of psychiatry : the journal of mental science 1973;123:467-70.

[17] A. Benton. Manuel pour l'application du test de retention visuelle. Applications cliniques et expérimentales. Deuxième édition française. Paris : Centre de Psychologie Appliquée.1965.

[18] P. Barberger-Gateau, D. Commenges, M. Gagnon, L. Letenneur, C. Sauvel, J.F. Dartigues. Instrumental activities of daily living as a screening tool for cognitive impairment and dementia in elderly community dwellers. J Am Geriatr Soc 1992;40:1129-34.

[19] N.M. Laird, J.H. Ware. Random-effects models for longitudinal data. Biometrics 1982;38:963-74.

[20] C. Proust-Lima, J.F. Dartigues, H. Jacqmin-Gadda. Misuse of the linear mixed model when evaluating risk factors of cognitive decline. Am J Epidemiol 2011;174:1077-88.

[21] C. Proust-Lima, V. Philipps, B. Liquet. Estimation of extended mixed models using latent classes and latent processes: the R package lcmm. J Stat Softw 2016;In press.
[22] M.E. Lenehan, M.J. Summers, N.L. Saunders, J.J. Summers, J.C. Vickers. Relationship between education and age-related cognitive decline: a review of recent research. Psychogeriatrics 2014.
[23] T.A. Salthouse. Implications of the Flynn Effect for Age-Cognition Relations. Intelligence 2015;48:51-7.
[24] V. Skirbekk, M. Stonawski, E. Bonsang, U.M. Staudinger. The Flynn effect and population aging. Intelligence 2013;41:169-77.
[25] N. Steiber. Population Aging at Cross-Roads: Diverging Secular Trends in Average Cognitive Functioning and Physical Health in the Older Population of Germany. PloS one 2015;10:e0136583.
[26] E.M. Zelinski, R.F. Kennison. Not your parents' test scores: cohort reduces psychometric aging effects. Psychol Aging 2007;22:546-57.
[27] D. Finkel, C.A. Reynolds, J.J. McArdle, N.L. Pedersen. Cohort differences in trajectories of cognitive aging. The journals of gerontology Series B, Psychological sciences and social sciences 2007;62:P286-94.
[28] J. de Rotrou, Y.H. Wu, J.B. Mabire, F. Moulin, L.W. de Jong, A.S. Rigaud, et al. Does cognitive function increase over time in the healthy elderly? PloS one 2013;8:e78646.
[29] S. Sacuiu, D. Gustafson, M. Sjogren, X. Guo, S. Ostling, B. Johansson, et al. Secular changes in cognitive predictors of dementia and mortality in 70-year-olds. Neurology 2010;75:779-85.
[30] K. Christensen, M. Thinggaard, A. Oksuzyan, T. Steenstrup, K. Andersen-Ranberg, B. Jeune, et al. Physical and cognitive functioning of people older than 90 years: a comparison of two Danish cohorts born 10 years apart. Lancet 2013;382:1507-13.
[31] D. Gerstorf, N. Ram, C. Hoppmann, S.L. Willis, K.W. Schaie. Cohort differences in cognitive aging and terminal decline in the Seattle Longitudinal Study. Developmental psychology 2011;47:1026-41.
[32] A. Brailean, M. Huisman, M. Prince, A.M. Prina, D.J. Deeg, H. Comijs. Cohort Differences in Cognitive Aging in the Longitudinal Aging Study Amsterdam. The journals of gerontology Series B, Psychological sciences and social sciences 2016.
[33] N. Le Carret, C. Rainville, N. Lechevallier, S. Lafont, L. Letenneur, C. Fabrigoule. Influence of education on the benton visual retention test performance as mediated by a strategic search component. Brain and cognition 2003;53:408-11.
[34] H. Falk, L. Johansson, S. Ostling, K. Thogersen Agerholm, M. Staun, L. Host Dorfinger, et al. Functional disability and ability 75-year-olds: a comparison of two Swedish cohorts born 30 years apart. Age Ageing 2014;43:636-41.
[35] E. Heikkinen, M. Kauppinen, T. Rantanen, R. Leinonen, T.M. Lyyra, T. Suutama, et al. Cohort differences in health, functioning and physical activity in the young-old Finnish population. Aging clinical and experimental research 2011;23:126-34.
[36] K. Pérès, C. Helmer, L. Letenneur, H. Jacqmin-Gadda, P. Barberger-Gateau. Ten-year change in disability prevalence and related factors in two generations of French elderly community dwellers: data from the PAQUID study. Aging clinical and experimental research 2005;17:229-35.
[37] C. Jagger, R.J. Matthews, F.E. Matthews, N.A. Spiers, J. Nickson, E.S. Paykel, et al. Cohort differences in disease and disability in the young-old: findings from the MRC Cognitive Function and Ageing Study (MRC-CFAS). BMC public health 2007;7:156.

Research in context

Systematic review: We searched Pubmed for articles on secular trends of cognitive and functional abilities published in any language up to 31st Dec 2016 using the search terms: "cognition" or "disability" or "function" and "change" or "trends".

Interpretation: This work strengthens the evidence of an improvement of cognitive performances over time but no change in cognitive decline between generations. Moreover, our results provide an insight into the impact of some modifiable risk factors on this trend, with educational level explaining the improvement for global cognitive functioning and verbal fluency but not for working memory or processing speed. Early life factors such as education seems to have an impact on late life cognition. Vascular factors however had no impact. Despite a tendency, no significant improvement of IADL functioning has been found.

Future directions: This finding will improve the understanding of the mechanism behind the decline of dementia incidence. The next step will be to better identify the factors explaining this improvement, to help finding effective target to enhance healthy aging.

Table 1

Table 1: "Baseline"* characteristics for the two generations

n (%) or mean (s.d.)

	First generation (G1) N=612	Second generation (G2) N=628	P value Chi² for % Student for means
Sex			0.94
Women	361 (59.0)	368 (58.8)	
Mean age	82.4 (2.4)	81.95 (2.7)	0.0007
Education			<.0001
No diploma	192 (31.4)	114 (18.2)	
Intermediate school level	364 (59.5)	402 (64.2)	
High school level	56 (9.1)	110 (17.6)	
Antihypertensive drugs	383 (62.6)	440 (70.3)	0.004
Antidiabetics drugs	50 (8.2)	35 (5.6)	0.07
Lipid-lowering drugs	70 (11.4)	154 (24.6)	<.0001
Mean "Baseline"* MMSE	26.6 (2.4)	27.1 (2.2)	<.0001
Mean "Baseline"* IST15	26.9 (5.4)	27.5 (6.1)	0.08
Mean "Baseline"* BVRT	10.3 (2.4)	11.24 (2.2)	<.0001
Mean "Baseline + 2 years"* DSST	24.0 (9.2)	27.0 (10.0)	<.0001
Mean "Baseline"* 4IADL	5.2 (1.9)	4.9 (1.6)	0.006

*Baseline time corresponds to the three-year follow-up for the first generation and the 13-year follow-up for the second one. For DSST, as it was not available at the three-year follow-up, we compare here DSST at five and 15 years).
MMSE: Mini Mental State Examination
IST15: Isaacs Set Test truncated at 15 seconds
BVRT: Benton Visual Retention Test
IADL: Instrumental Activities of Daily Living

Table 2

Table 2: Parameter estimates of score changes in their normalized scales and generation effect from the linear mixed models

	MMSE		IST 15		BVRT		DSST		4 IADL	
	β	P value	β	P value	β	P value	β	P value	β	P value
	N=1221		N=1187		N=1140		N=891		N=1237	
Model 1										
Generation (G2 vs. G1)	0.29	0.0007	0.28	0.005	0.51	<.0001	0.70	0.0001	-0.14	0.10
Time	-0.12	<.0001	-0.19	<.0001	-0.06	0.003	-0.24	<.0001	0.12	<.0001
Generation*Time	0.005	0.73	0.02	0.24	0.02	0.16	-0.02	0.44	-0.03	0.09
Model 2										
Generation (G2 vs. G1)	0.10	0.21	0.10	0.30	0.35	<.0001	0.43	0.008	-0.04	0.65
Time	-0.12	<.0001	-0.19	<.0001	-0.06	0.005	-0.24	<.0001	0.12	<.0001
Generation*Time	0.005	0.72	0.02	0.25	0.02	0.16	-0.01	0.50	-0.03	0.08
Model 3										
Generation (G2 vs. G1)	0.07	0.38	0.07	0.49	0.35	<.0001	0.48	0.003	-0.02	0.80
Time	-0.12	<.0001	-0.19	<.0001	-0.05	0.005	-0.24	<.0001	0.12	<.0001
Generation*Time	0.005	0.73	0.02	0.25	0.02	0.15	-0.01	0.49	-0.03	0.08

Model 1: Adjusted for age and sex
Model 2: Adjusted for age, sex and education level
Model 3: Adjusted for age, sex, education level, antihypertensive, antidiabetic and lipid-lowering drugs intake
Due to score transformation, parameters cannot be interpreted according to scores' natural scale.
MMSE and IADL: each model adjusted for interaction between time and age and time and sex
IST15, BVRT: each model adjusted for interaction between time and age
Time variable: values are for age and sex variable in 0 (men of 75 y.o.) in the interactions with time.

Figure 1

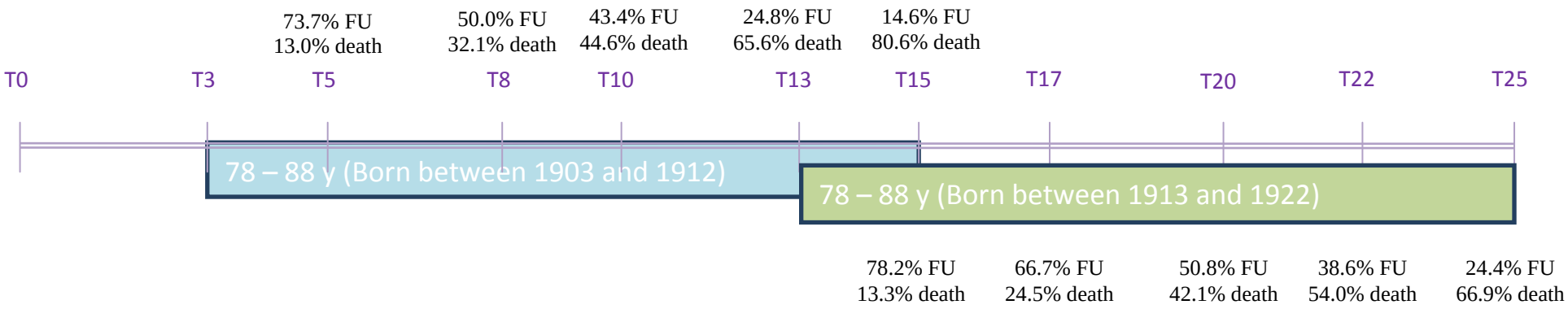

Figure 1: Repartition of subjects in the two generations with percentage of subjects seen (FU) and death (cumulated) at each follow-up time.

Figure 2

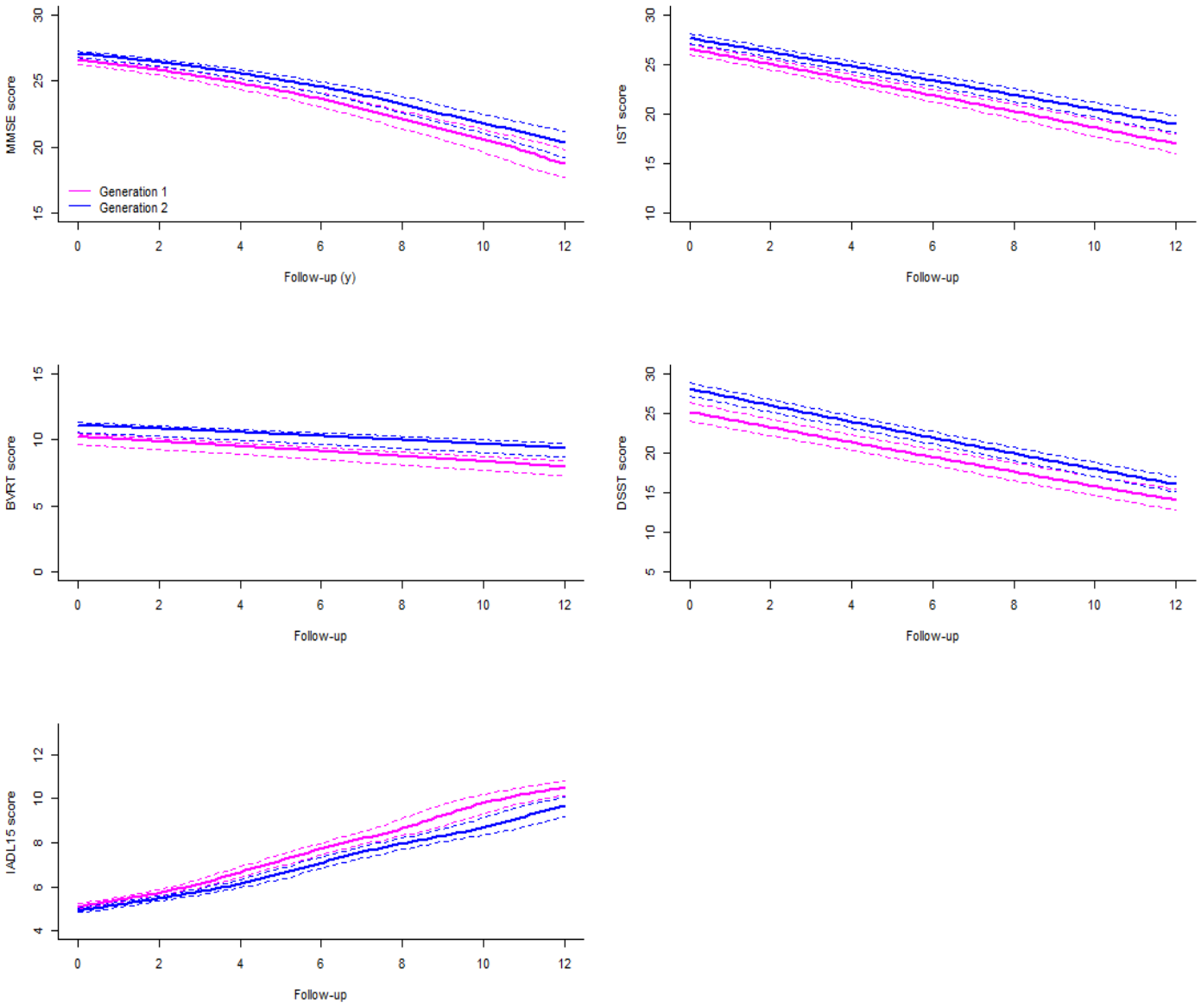

Figure 2: Non-adjusted predicted mean trajectories for each score in its natural scale for the two generations with its 95% confidence bands.

4.2.4. Complementary results

As part of the revision process for this article, the problem of differential attrition between the two generations needed further investigation. Indeed, the second generation had lower mortality rate and lower drop-out. The lower attrition in the second generation could have led to a lower number of missing values for this generation. Thus, the second generations could have a more important decline than the observed decline, as attrition is often not at random and unobserved participants may have lower cognitive performance. We have thus decided to jointly model the trajectory of the longitudinal markers with the attrition risk. The R package JM has thus been used to perform joint model for each cognitive test and the disability scale. With this package, two sub-models (a longitudinal mixed model and a survival model) are used in the joint model. The survival model for attrition risk has been adjusted for generation, sex, age at baseline and educational level. The three models presented in table 10 had the same adjustment as the original analyses.

Table 10: Parameter estimates of score changes in their normalized scales and generation effect from joint modelling

	MMSE		IST 15		BVRT		DSST		4 IADL	
	β	P value	β	P value	β	P value	β	P value	β	P value
	N=1221		N=1187		N=1140		N=891		N=1237	
Model 1										
Generation (G2 vs. G1)	0.29	0.0006	0.27	0.006	0.51	<.0001	0.56	0.0017	-0.14	0.08
Time	-0.15	<.0001	-0.23	<.0001	-0.07	0.0001	-0.27	<.0001	0.18	<.0001
Generation*Time	0.01	0.35	0.03	0.04	0.02	0.04	0.001	0.95	-0.04	0.02
Model 2										
Generation (G2 vs. G1)	0.10	0.21	0.08	0.42	0.35	<.0001	0.34	0.04	-0.04	0.59
Time	-0.15	<.0001	-0.23	<.0001	-0.07	0.0002	-0.27	<.0001	0.18	<.0001
Generation*Time	0.01	0.34	0.03	0.04	0.02	0.04	0.003	0.90	-0.04	0.02
Model 3										
Generation (G2 vs. G1)	0.07	0.40	0.052	0.59	0.34	<.0001	0.34	0.04	-0.03	0.72
Time	-0.15	<.0001	-0.23	<.0001	-0.07	0.0002	-0.27	<.0001	0.18	<.0001
Generation*Time	0.01	0.35	0.03	0.04	0.02	0.04	0.003	0.90	-0.04	0.01

Model 1: Adjusted for age and sex
Model 2: Adjusted for age, sex and education level
Model 3: Adjusted for age, sex, education level, antihypertensive, antidiabetic and lipid-lowering drugs intake
Due to score transformation, parameters cannot be interpreted according to scores' natural scale.
MMSE and IADL: each model adjusted for interaction between time and age and time and sex
IST15, BVRT and DSST: each model adjusted for interaction between time and age
Time variable: values are for age and sex variable in 0 (men of 75 y.o.) in the interactions with time.

For the MMSE and the DSST, taking attrition into account did not significantly change the results: the score at baseline has improved between the generation and the rate of cognitive decline remained similar with time. However, changes in significance appeared for the Isaacs Set Test, the BVRT and the 4 IADL score. For IST and BVRT, the performance at baseline remained significantly better for the second generation than for the first one, but the decline with time became significantly slower for the second generation than for the first one (IST: β=0.03, p=0.04 ; BVRT: β=0.02, p=0.04), whereas it was non-significant with the simple linear mixed model. However, beta estimates are similar. For the 4 IADL score, the disability level at baseline remained similar between the two generations, but the trend toward a less important disability rates for the second generation became significant (β=-0.04; p=0.02).

4.2.5. Discussion

This work evidences an improvement of the overall cognitive performances between the two generations. For some cognitive domains, this improvement can be explained by the improvement of educational level between generations, but not for all of them. With attrition accounted for, cognitive decline improved between generation for the IST 15 and the BVRT. For functional abilities, an improvement of functional decline over the follow-up has been shown between generations when taking attrition into account; however, the improvement for functional performances at a time was non-significant.

The improvement of cognitive performances has been quite documented. It is coherent with the Flynn effect, which refers to the observed rise over time in standardized intelligence test scores, documented in a study on intelligence quotient (IQ) score gains (226). However, previous results on cognitive decline are more conflicted. Some studies found an improvement in cognitive decline between generations (179-181), whereas others showed that later-born generation had more important decline (184, 185). Finally, others have shown similar decline rates between generations (182, 183). Different reasons can be proposed to explain these different results: 1) no difference in decline may be that the cohort differences in levels of cognitive performances last similarly across the life span, resulting in parallel rates of cognitive decline between cohorts; factors influencing cognitive performances early in life are involved; 2) slower decline could be that individuals with higher performance levels are able to better cope with aging-related decline and will present lower rates of cognitive decline; 3) on the contrary, we can hypothesize that individuals showing more important

cognitive decline are the one dealing with more aging pathology and are no longer able at some point to cope with brain damage. Regarding our findings, our results are in line with a similar evolution of cognition with age and even a slower decline when taking attrition into account, with more recent generations performing at a higher level than older generations. These results suggest that individuals from younger generations would achieve the clinical threshold of dementia later than the older generations. When looking at the age at dementia diagnosis, the second generation is diagnosed 1.62 year later than the first generation ($p<.0001$).

For functional abilities, the scale used could be not adequate enough to show an improvement of disability. It is assessing mild functional dependency, where more important disability has been used in the published literature. Moreover, these tasks could have become more complex with availability of internet, smartphone, or public transportation. Even with cognitive improvement between generations, these activities could now require more cognitive abilities.

These results are in favour of better cognitive health for younger generations lasting through aging. However, due to mixed results from the literature, further investigation of secular trends of cognitive trajectories as well as disability trajectories should be realised.

4.3. Diagnostic evolution and algorithmic comparison

4.3.1. Introduction

Investigation of secular trends of dementia is of high interest for a better understanding of risk factors impact and life course risk. These analyses request population-based studies with different time period. However, studying changes in dementia incidence and prevalence over time is challenging, mainly because varying methodological approaches can bias prevalence and incidence estimates. Evolution of dementia diagnosis is thus a critical topic to deal with. Indeed, differences in diagnostic approaches between time and geographical location can affect prevalence or incidence estimates and lead to misestimated trends. First, diagnostic criteria have changed across the last decades with several revision of the consensus criteria from the DSM. Then, dementia diagnosis is mostly influenced by clinical judgement, even with the support of cognitive and functional information. Finally, increasing awareness of dementia from the public but also from professionals has been associated with changes in diagnostic boundaries. However, recent failures of therapeutic trials to find efficient treatments could have also led to questioning early diagnosis usefulness for patient. All these factors could have influenced diagnosis timing (227). Thus, we need to keep in mind that a stable diagnosis is critical to assess time trends in the incidence or prevalence of dementia.

Trying to solve the issue of diagnostic drift, we have thus decided to use an algorithmic approach. Cohort studies in the UK are also using an algorithmic diagnosis, the AGECAT algorithm, to diagnose dementia cases. This algorithm has been validated against DSM III R criteria (217). In the first work of this thesis, we have established a simple algorithm based on performance on MMSE test and cognitive IADL dependency.

The aim of this work was first to investigate the evolution of clinical diagnosis of dementia in the French cohorts and to compare cases diagnosed by the clinical diagnosis and the algorithmic one on several characteristics. The second part of this work aimed at applying our MMSE-IADL (Comparative Dementia Algorithm CDA) algorithm on the CFAS studies, to compare prevalence and incidence estimates with those based on the AGECAT diagnosis.

4.3.2. Methods

For the first objective, clinical diagnosis over the 27 years of follow-up from PAQUID and the 14 years of follow-up from 3C-Bordeaux was compared based on the MMSE. For every incident case of dementia diagnosed in the two cohorts, we compared the MMSE score at time of diagnosis. Linear splines regression model was used for this purpose. With this model, we could identify changes in the pattern of cognitive performance at diagnosis over time and studies, adjusting for essential factors.

For the second objective, we applied the MMSE-IADL algorithm to the CFAS I and II participants and established prevalence and incidence estimates of dementia for both studies. Incidence analyses were performed using Poisson regression models and every analysis was weighted to account for the selection of populations and for attrition, as in the CFAS's published papers on trends.

4.3.3. Article

Evolution of dementia diagnosis over time (1988 – 2013): Evidence from French and English cohorts

Implication for secular trends analyses

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Abstract

Introduction: To establish how secular trends in dementia can be tested robustly requires use of consistent diagnostic approaches over time. This study aimed to examine the evolution of clinical dementia diagnosis over three decades. To account for possible variation in clinical diagnosis over time, we compared two stable, and recently used, algorithmic approaches: the easy to use "Comparative Dementia Algorithm (CDA)", matching dementia syndromic criteria, and the validated GMS-AGECAT algorithm.

Methods: Four cohorts covering a period ranging from 1988 to 2013 were used: the PAQUID study (n=3777, which started in 1988), the Three-City-Bordeaux study (n=2104, since 1999), and CFAS I (n=7635, since 1990) and II (n=7762, since 2008). To examine possible change in clinical diagnosis over time, Mini Mental State Examination (MMSE) scores at time of clinical diagnosis were compared over a 24-year follow-up period in PAQUID and 3C-Bordeaux using linear regression (with or without splines). To evaluate the algorithmic approach, the CDA method, (algorithm based on cognition and disability), was applied to CFAS I and II to provide prevalence and incidence estimates using weighted Poisson regression, accounting for participation rate and attrition, and then compared with the AGECAT estimations.

Results: For PAQUID, a significant increase of the MMSE score was evidenced before 2001 and a significant decrease after 2001. A significant decline in the MMSE score at clinical diagnosis was found for the 3C-Bordeaux between 2000 and 2010. The CDA methods established a prevalence of 8.8% for CFAS I compared to a prevalence of 8.3% showed in previously published AGECAT estimations. For CFAS II, a prevalence of 6.5% estimated using CDA was compared to 5.7% in previously published AGECAT estimations. The two-year incidence rate was estimated at 31.2/1000 (95%CI=28.0 – 34.8) for CFAS I (AGECAT algorithm: 20.0; 95% CI 16.9 – 23.8) and 15.0/1000 (95%CI=13.5 – 16.7) for CFAS II (AGECAT algorithm: 17.7; 95%CI 15.2 – 20.9).

Discussion: Clinical diagnosis of dementia within and across cohorts has varied during the last 30 years. Applying a stable algorithm to cohort across time can provide a robust method for the estimation of time trends. Simple algorithmic approaches such as CDA provide similar results to an internationally validated algorithm.

Dementia is a syndrome consisting of deterioration in cognitive functions sufficient to impair a person's daily life and activities. In order to describe the extent of dementia as a public health priority, many population-based studies following older people over time have been implemented during the past 30 years (1, 2). Research on the descriptive epidemiology of dementia has identified several challenges in the field: standardization of diagnostic approaches for dementia subtype and mild forms of cognitive decline; dealing with selection and attrition, differential mortality and incidence for prevalence estimations; dementia at the end of life and terminal decline; substantial under-diagnosis by the health care system (3) Diagnosis of the dementia syndrome is sensitive to such challenges (4, 5). Recently researchers have evaluated changes in dementia over time (6-14). However, to provide accurate estimations, consistent dementia diagnosis across studies and time is required. The relationship of clinical and consensus diagnosis of dementia can be examined across time, and also in relation to other types of measurement. The diagnosis of dementia is a clinical syndromic diagnosis, based on a clinical diagnostic process, usually a version of the Diagnostic and Statistical Manual of Mental Disorders (DSM) (15). These diagnostic criteria do not have clear thresholds or specific measures to define the level of cognitive decline and its consequences, leaving the ultimate decision to clinical judgement or consensus diagnosis. Although diagnostic criteria have not fundamentally changed, there have been substantial societal and clinical shifts in dementia awareness, likely to have resulted in inter- and intra-clinician variability. Recently, a few studies on the evolution of dementia over time have hypothesised that the diagnosis of dementia is likely to have evolved over time and that algorithmic diagnosis could be more stable (16-18). Changes in prevalence and incidence of any disorder, including dementia, are known to be influenced when diagnostic processes change over time, resulting in systematically different estimations (e.g. diabetes mellitus, hypertension) (19). The studies presented in this work have determined dementia cases using

two different algorithms in place of or in addition to clinical diagnosis: the Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT) algorithm, a well-known and validated automated computer algorithm used in the British cohorts CFAS I and CFAS II (20, 21); and a "Comparative Dementia Algorithm (CDA)" developed from French cohorts (17). Clinical diagnoses in French cohorts showed no change in dementia incidence over two decades whereas the algorithmic diagnosis revealed a decrease, supporting the evolution hypothesis and highlighting the importance of using a stable diagnosis of dementia.

This paper aimed 1) to examine the evolution of clinical dementia diagnosis over three decades, by analysing the cognitive performance of people given a study diagnosis of incident dementia. A comparison of these with the cases diagnosed by a CDA method on French data was also conducted to establish the nature of change, if any; 2) as a validation of this algorithm, an adaptation was also applied to the British data to perform prevalence and incidence analysis, in order to provide a comparison with the validated AGECAT algorithm.

Methods

1) Study populations

Participants, aged 65 years and older, from four different population-based cohorts from France (PAQUID and Three-City) and UK (CFAS I and II) have been used in this study (Cf Supplementary Figure).

The Personnes Agées Quid (PAQUID) cohort was formed in 1988–1989 with a representative sample of 3,777 participants living at home in the departments of Gironde and Dordogne. The selection was stratified by sex, age and size of urban unit. Respondents have been followed for 27 years. The Three-City (3C-Bordeaux) cohort, starting in 1999, recruited 2,104 participants from the Urban Community of Bordeaux, within 10 districts. Participants have been followed for 14 years. For these two French cohorts, standardized questionnaires

assessing socio-demographic, medical, cognitive, and functional data were administered by trained neuropsychologists during face-to-face interviews, at baseline and at each follow-up. Participants were followed-up every two to three years even after institutionalization. At each follow-up vital status was systematically recorded for all the participants.

The MRC Cognitive Function and Ageing Study (CFAS I): between 1989 and 1994, baseline interviews were conducted in six geographical areas in England and Wales and subjects were followed for ten years. A two stage process, with screening followed by diagnostic assessment, was used in CFAS I weighted across the cognitive performance as Mini Mental State Examination (MMSE) and AGECAT original items in screen. Data from three of the English areas of MRC CFAS—Cambridgeshire, Newcastle, and Nottingham (22), where interviews were carried out between Dec, 1990, and July, 1993— were selected for analyses, providing 7,635 subjects, from which a sub-population of 1,459 individuals underwent assessment. Between Nov, 2008, and Oct, 2011, new fieldwork in the same geographical areas was carried out to provide CFAS II estimates on 7762 subjects, which could be directly compared with CFAS I. CFAS I and CFAS II had identical sampling approaches, methods and diagnostic approach apart from the simplification of design from two stage to one stage at baseline and incidence phase through combination of screening and assessment interviews.

Full details of the studies have been described elsewhere (16, 22-24).

2) Diagnostic methods

In the French cohorts, a clinical diagnosis was available, whilst in the British cohorts, the AGECAT algorithm was applied. Moreover, in the four studies, a Comparative Dementia Algorithm (CDA) was applied.

For both PAQUID and 3C populations, the clinical diagnosis was made following a 3-step procedure. The first step was a cognitive evaluation made by the neuropsychologist through a

series of psychometric tests. Participants who had a high likelihood of dementia, based on their neuropsychological performances or decline relative to a previous examination, were then examined by a senior neurologist. The diagnosis of dementia was based on the DSM-III-R or the DSM-IV criteria. In case of refusal or death between the first and second step, additional information was gathered from the informant and the medical practitioner. Then, each case was discussed by a validation committee composed of neurologists, geriatrician and directed by JFD to provide a final diagnosis.

In CFAS I and II, the AGECAT algorithm used was based on the Geriatric Mental State examination (GMS) that provides relevant information to determine dementia syndrome in older population (20, 25). Missing data within an interview could prevent the algorithmic diagnosis and for individuals with missing data, the same approach was taken for CFAS II as for CFAS I, which was a review of all available information by diagnostician (CB), applying DSM-IIIR criteria. Many of these individuals with missing data had severe cognitive impairment and were not able to respond to the interview questions. The GMS-AGECAT has been validated against internationally accepted earlier diagnostic criteria (DSM-IIIR) (21).

The Comparative Dementia Algorithm (CDA) approach was a cognition-disability algorithm. For the French data, we used a previously published algorithm (17). This diagnosis was based on cognitive and functional assessments using MMSE and four Instrumental Activities of Daily Living (4IADL) associated with cognition (ability to use the telephone, transportation, responsibility for medications and ability to manage its budget) to fit dementia definition. The algorithmic diagnosis was then defined by a MMSE score <24 (or a missing MMSE score for "cognitive reason" such as major aphasia, mutism, comprehension problem) AND a 4 IADL score >1 (disability, even mild, for more than one activity out of the 4). For the English data, information on disability was not recorded in the same way as in France, so the algorithm has been adapted for comparative purposes. It was based on the MMSE score and on disability on

IADL and ADL (Ability to wash all over or bath, to prepare and cook a hot meal, and to put on shoes and socks or stockings). The algorithm was defined by a MMSE score <24 AND if the respondent need more than partial help with at least one of the three abilities.

3) Statistical analyses

Socio-demographic characteristics, MMSE and disability score at baseline have been compared between populations.

To explore evolution of the clinical diagnosis over time, cognitive status at diagnosis using the MMSE score was described. The scores of incident clinical cases at each follow-up of the whole PAQUID and 3C-Bordeaux studies were described using mean scores according to study and educational level. Prevalent cases at inclusion were removed and only incident cases at each follow-up were kept. Linear splines regression of MMSE scores according to time, age at diagnosis, gender, study and educational level were also performed.

The cases diagnosed during the first ten years of follow-up from PAQUID and 3C-Bordeaux were then classified according to the concordance or divergence of clinical and algorithmic diagnosis. A comparison of the characteristics of discordant cases was analysed with socio-demographic, cognitive and functional factors according to two categories: dementia in clinical diagnosis but no dementia in the algorithmic approach, and no dementia in clinical diagnosis but dementia in the algorithmic approach.

Finally, in order to validate the cognition-disability algorithm (CDA), prevalence and incidence in both CFAS I and II have been estimated and discussed in relation to previously published prevalence and incidence results obtained based on AGECAT algorithm. For CFAS I, the prevalence was provided from the first wave (inclusion) on all subjects. For CFAS II, prevalence was provided from the first wave on all subjects. Prevalence has been weighted and standardised on the age and sex repartition of the 2011 UK population. Two-year

incidence has been estimated with a weighted Poisson regression on all subjects for both CFAS I and II. An inverse probability weighting has been used based on both the probability of being included in the study, taking participation rate difference into account, and the probability of having a diagnosis, taking attrition into account. Comparisons of both prevalence and incidence between CFAS I and CFAS II are provided.

Results

1) Population characteristics

Global characteristics of the four cohort populations are presented in Table 1 (including the CFAS I sub-population). The mean age at inclusion was around 75 years old with more women than men. PAQUID and CFAS I participants reported less years of education and had a lower MMSE at baseline than 3C and CFAS II. Flow charts of the four populations are presented in Supplementary Figure 1.

2) Evolution of the clinical diagnosis

In total, 1318 incident cases where clinically diagnosed in 3C and PAQUID over the follow-up, with 1250 with values allowing for adjustment of MMSE score at diagnosis. The crude means of the MMSE at clinical diagnosis for each follow up in PAQUID and 3C-Bordeaux are shown in Figure 1. The means of the MMSE at diagnosis were higher in higher-educated subjects of 3C-Bordeaux than in lower-educated subjects of 3C and in PAQUID at all follow-up times. Overall, the regression model showed a significant increase in the MMSE score at diagnosis before 2001 (β=0.30/y, p<.0001) and then a significant decrease of the MMSE score after 2001 (β=-0.34/ y, p<.0001), adjusted on age at diagnosis, sex, study and educational level. Subjects from 3C had significantly higher levels of MMSE score at diagnosis (β=1.16, p=0.006), as well as subjects with higher educational level compared to those without diploma (β=2.87, p<.0001).

3) Characteristics of diagnostic discordance

Cases from the ten-year follow-up of 3,777 subjects of PAQUID and 2104 subjects of 3C-Bordeaux have been classified according to both clinical and algorithmic diagnosis (CDA). On the 5,881 subjects, 4,801 (81.6%) did not have dementia at either diagnosis and 535 (9.1%) were diagnosed with dementia by the two diagnosis over the ten-years follow-up. 389 (6.6%) subjects were algorithmic cases only and 156 (2.6%) subjects were clinical cases only. The characteristics of discordant cases are described in table 2. In 3C-Bordeaux, people were more likely to be diagnosed by clinical diagnosis than algorithm. They were also better educated and had less disability than the cases diagnosed by the algorithm. Age at diagnosis was the same for both categories but MMSE score at diagnosis was higher for subjects diagnosed by clinical diagnosis than for the one diagnosed by algorithm only.

4) CFAS prevalence and incidence estimates: the cognition-disability algorithm approach. Comparison with AGECAT estimations.

- Prevalence

In CFAS I total population at baseline; the algorithm was incomplete for 274 individuals. On the 7,365 remaining individuals, 601 were classified as having the algorithmic diagnosis of dementia (CDA) (weighted and standardised percentage= 8.8%). Previously published results on CFAS based on the AGECAT algorithm revealed a prevalence of 8.3%. Of the CFAS II total population at baseline, 404 of the 7762 had incomplete data for the CAD and were not in the analysis. CDA then classified 367 as having dementia (weighted and standardised percentage=5.7%). Previously published results on CFAS II based on the AGECAT algorithm reported a prevalence of 6.5%.

Based on the CDA, dementia prevalence has declined by 35% between 1990-93 and 2008-11.

- Incidence

For CFAS I, 4,648 out of the 6,135 respondents without prevalent dementia (CDA defined) were seen at the two-year follow-up. Of these, 247 (5.3%) individuals had developed dementia (based on the CDA definition) during the two years. For CFAS II, 4964 out of 6574 without prevalent dementia defined by CDA were re-interviewed at two years, out of whom 137 (2.7%) individuals fulfilled the CDA. The two-year age and sex adjusted incidence rates were thus 31.2/1000 (95%CI=28.0 – 34.8) for CFAS I and 15.0/1000 (95%CI=13.5 – 16.7) for CFAS II. Previously published results on CFAS based on the AGECAT algorithm have found an incidence of 20.0/1000 (95%CI=16.9 – 23.8) for CFAS I and 17.7/1000 (95% CI=15.2 – 20.9) for CFAS II. Incidence rates and confidence intervals per age and sex based on the CDA definition have been provided for both CFAS I and II in Table 3. CFAS II incidence estimates were lower than CFAS I, for both men and women and each age category, and women always had a higher incidence rate than men, even though somewhat reduced in CFAS II compared to CFAS I.

Discussion

This paper has described the evolution over time of the cognitive status of incident cases of dementia when they were diagnosed based on clinical diagnosis. Compared with cases diagnosed by Comparative Dementia Algorithm (CDA) only, those with a clinical diagnosis only were more highly educated and diagnosed with a higher MMSE score. Prevalence and incidence estimates were a little higher using the CDA approach compared with the AGECAT algorithm on CFAS I and similar on CFAS II.

An important strength of this study was the use of four well-recognized cohort studies, with longitudinal follow-up covering a 25-year period and with high number of subjects. Moreover, results are based on three different diagnostic approaches already published, one clinical and two algorithmic. Among the different algorithms used, gold standards will depend

on purpose and motivation for diagnosis and whether research or clinical settings. However, the CDA approach has the advantage of being simple and easy to use in a large number of studies. It needs to be stated that the diagnostic approach must be appropriate for the purpose (26). When studying secular trends of dementia, stability of the diagnosis over time is the main requirement. A limitation is that our results on possible evolution or boundary creep of dementia diagnosis are only based on the two French studies with a clinical diagnosis available. Further replication on other population studies is necessary to confirm our results. Another issue is a limit of our CDA definition that does not allow disentangling the part of functional and/or cognitive deficits attributable to co-morbidities unrelated to dementia. For example, disabilities due to comorbidities such as blindness, Parkinson's disease or stroke are similarly accounted for by the algorithm as disabilities due to repercussion of cognitive impairment. This could explain part of the difference between cases diagnosed by clinic and by algorithm only (6.6% CDA+/clin-).

The analysis of MMSE scores at clinical diagnosis from the beginning of the 90's to the beginning of 2010 demonstrates an evolution of cognitive status of participants at time of dementia diagnosis across time and study in France. Between 1992 and 2001 in PAQUID, we found that subjects were increasingly diagnosed earlier - at a less severe stage - over time. The improvement of disease knowledge and the introduction of treatments may have led to diagnosis at earlier stage. A German study based on memory clinics also found a trend to earlier diagnosis between 1985 and 2009 (27). After 2001 however in the French studies, we found that incident cases were progressively diagnosed when more severely cognitively impaired over time. This decrease may be the result of the aging of the whole cohorts, even though regression models have been adjusted on age at diagnosis. Failure to find new efficient treatments and public perception of the impact of diagnosis on patients could also be possible explanations for this change. The diagnosis of dementia was made earlier in 3C than in

PAQUID. The higher educational level of the 3C participants partly explains this difference. It may also be explained by the introduction of the Free and Cued Selective Reminding Test (FCSRT) in the 3C questionnaires (28). This provides a finer/more subtle indication of episodic memory impairments of the participants and may have led to the differences with the PAQUID study. Only later follow up with validation through knowledge of progression can the comparison of relative performance be known – it may be that over-diagnosis is occurring.

The instability of the clinical diagnosis led to the emergence of the algorithmic approach to diagnose dementia in cohort studies. The comparison of dementia incidence ten years apart in PAQUID and 3C has shown that the type of diagnosis used can lead to mixed results and have an influence on conclusions about secular trends (17). Only the algorithmic diagnosis showed a decrease in the incidence of dementia with the trends stable for clinical diagnosis. Similar observations have been made in the comparison of dementia prevalence twenty years apart in the PAQUID and AMI studies (29). In the Framingham study, the authors have reviewed a second time each case diagnosed before 2001 to apply up to date criteria (8); however, the same indicators are needed to control for evolution. In the Health and Retirement Study, an algorithmic approach based on cognitive deficit assessed with a 27-point scale has also been used (14, 30). These results provide further evidence to support the use of approaches that are less prone to secular changes in diagnostic thresholds when evaluating time trends and computing projections. When comparing cases diagnosed by either the clinical or the CDA diagnosis in the two French populations, it appeared that cases diagnosed by purely clinical diagnosis were more educated and had a higher MMSE score at diagnosis than the cases diagnosed by the algorithm only, thus diagnosing people earlier in the disease course than the algorithm (or indeed over diagnosis). The CDA items and cutpoints were mapped to the dementia syndrome criteria. In 2015, the major change between the DSM-IV and the latest edition, the DSM-V, heralded the “end” of the word dementia with substitution of “Major

Neurocognitive Disorder" where the loss of independent functioning remains an important criterion. Algorithms have become even more relevant as these are highly compatible with this approach.

The AGECAT algorithm was validated according to the DSM III-R criteria and prevalence and incidence estimates and time trends have already been published for CFAS I and II (16, 18). One difficulty in CFAS I was the two-phase design where a majority of individuals had not undergone the assessment process, although sampling and assessment was across the cognitive spectrum. The estimations show that the CFAS CDA prevalence is slightly higher for CFAS I, and for CFAS II lower when compared with the prevalence found in the published paper where study design has been accommodated by a Bayesian missing data model of the AGECAT diagnosis with inverse probability weighting has been used. For CFAS I, the incidence estimates using the CDA were much higher than the incidence rates found with the AGECAT and Bayesian procedure but slightly lower for CFAS II. Using the CDA approach thus showed an even more marked reduction in incidence of dementia between CFAS I and II than has been published. The results also showed a significant decline in women, not found with the AGECAT. This could be explained by the fact that disability in women has improved between the two generations and these measures of disability were not directly part of the AGECAT algorithm unlike the CDA algorithm (31).

To conclude, secular trends analyses of dementia are important and have attracted considerable attention. Investigating the best ways to provide the most accurate estimations is critical. Such estimations are used to predict future dementia worldwide. It is therefore essential to employ a stable diagnosis over time and studies. We provide here a simple and easy to use algorithmic approach that can be applied to most pre-existing cohorts. Further studies exploring secular trends of dementia in multiple cohorts could stabilise/standardise their methods over time by using this approach.

Table 1: Descriptive data on cohorts

	PAQUID	CFAS I	3C	CFAS II
Inclusion date	1988-1989	1990-1993	1999-2000	2008-2011
Number of participants				
-total population	3777	7635	2104	7762
-subpopulation[1]	-	1459	-	-
Age at baseline: mean (SD)				
-total population	75.5 (6.9)	75.8 (7.1)	74.6 (5.1)	75.7 (7.3)
-subpopulation[1]	-	77.4 (7.9)	-	-
Gender (Women): n (%)				
-total population	2200 (58.3)	4594 (60.1)	1288 (61.2)	4228 (54.5)
-subpopulation[1]	-	(921 (63.6)	-	-
Low educational level: n (%)				
-total population	2980 (78.9)	5532 (74.1)	872 (41.5)	2045 (26.8)
-subpopulation[1]	-	1065 (79.3)	-	-
MMSE score at baseline: mean (SD)				
-total population	25.6 (3.7)	24.8 (6.1)	27.2 (2.4)	26.8 (3.5)
-subpopulation[1]	-	20.9 (7.4)	-	-

[1]: subjects with assessment by AGECAT algorithm diagnosis
Low educational level: less than 10 years of study

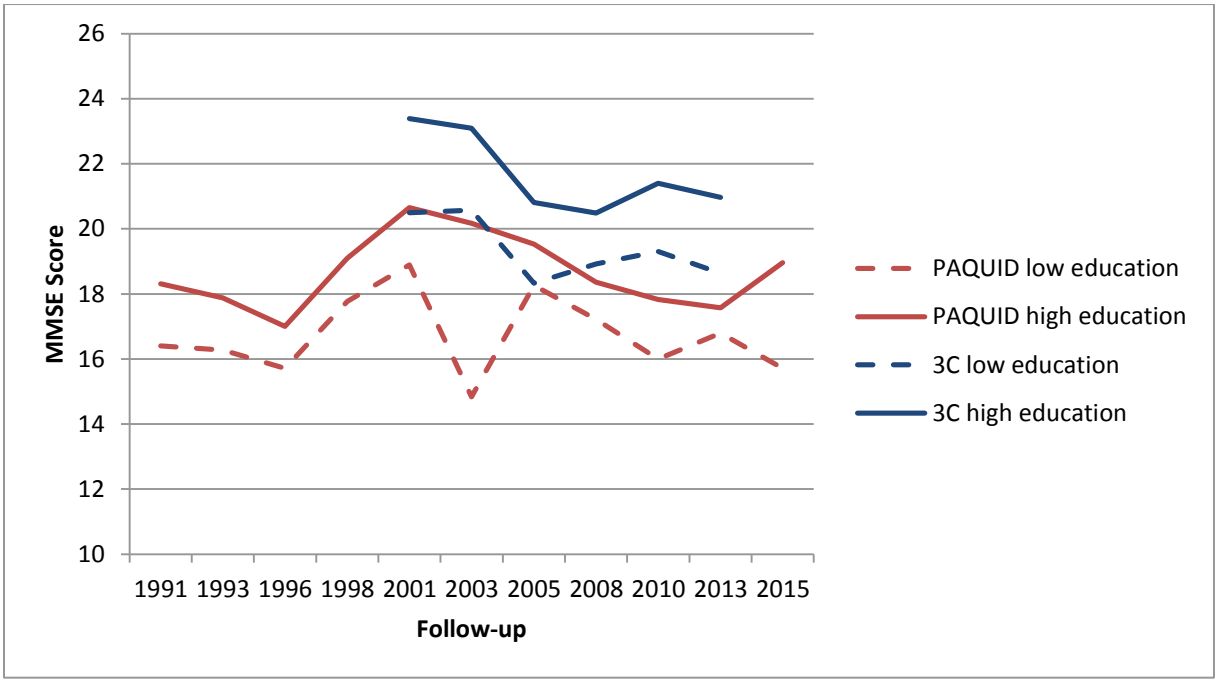


Figure 1: MMSE (mean) at time of study clinical diagnosis (incident) across time in 3C-Bordeaux and PAQUID.

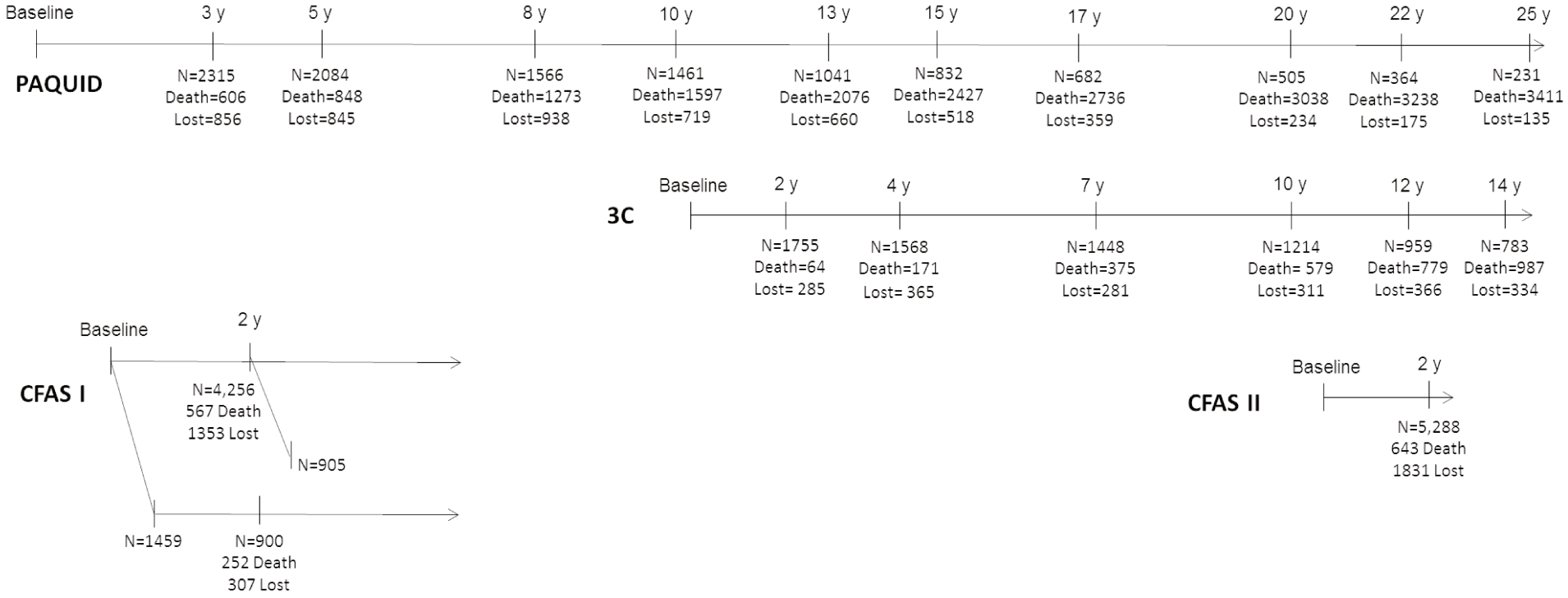
Table 2: Characteristics of participants according to clinical or algorithmic diagnostic method in the first 10 years of follow-up in PAQUID and 3C-Bordeaux, n=545.

Diagnostic type	Clinical = 1 Algorithm = 0 N=156	Clinical = 0 Algorithm = 1 N=389
3C/PAQUID % (n)	60.9 (95)	24.2 (94)
Women % (n)	60.3 (94)	72.7 (283)
Low education % (n)	21.1 (33)	57.8 (225)
Diagnosis Rosow disability % (n)	90.2 (138)	98.2 (376)
Diagnosis Katz disability % (n)	13.1 (20)	29.7 (114)
Diagnosis age mean (s.d.)	83.4 (5.5)	83.5 (6.2)
Diagnosis MMSE mean (s.d.)	23.5 (3.0)	19.9 (4.0)

Diagnosis type =0: no dementia; =1: dementia

Table 3: Incidence rates in CFAS I and CFAS II by age and gender, defined using CDA and weighted for non-response and population selection.

/1000 PY	CFAS I		CFAS II	
	Rate	95% CI	Rate	95% CI
Men				
65-69	8.5	6.6 – 11.0	4.1	3.2 – 5.3
70-74	11.4	9.0 – 14.4	5.5	4.3 – 6.9
75-79	19.5	15.8 – 24.0	9.4	7.6 – 11.5
80-84	53.0	44.4 – 63.4	25.5	21.5 – 30.2
85 +	106.9	88.7 – 128.7	51.3	43.4 – 60.8
Women				
65-69	12.8	10.1 – 16.2	6.1	4.8 – 7.8
70-74	17.1	13.7 – 21.3	8.2	6.6 – 10.3
75-79	29.3	24.4 – 35.3	14.1	11.6 – 17.1
80-84	79.7	68.9 – 92.2	38.3	33.0 – 44.4
85 +	160.7	139.0 – 185.7	77.2	67.5 – 88.3



Supplementary figure: Flow chart presenting the follow-up for the four cohorts used in the study, with number of subjects seen at each follow-up, cumulative death and lost to follow-up. ╲ : Individuals selected for assessment of dementia in CFAS I.

References

1. Hofman A, Rocca WA, Brayne C, Breteler MM, Clarke M, Cooper B, et al. The prevalence of dementia in Europe: a collaborative study of 1980-1990 findings. Eurodem Prevalence Research Group. International journal of epidemiology. 1991;20(3):736-48.
2. Launer LJ, Andersen K, Dewey ME, Letenneur L, Ott A, Amaducci LA, et al. Rates and risk factors for dementia and Alzheimer's disease: results from EURODEM pooled analyses. EURODEM Incidence Research Group and Work Groups. European Studies of Dementia. Neurology. 1999;52(1):78-84.
3. Brayne C, Stephan BC, Matthews FE. A European perspective on population studies of dementia. Alzheimers Dement. 2011;7(1):3-9.
4. Erkinjuntti T, Ostbye T, Steenhuis R, Hachinski V. The effect of different diagnostic criteria on the prevalence of dementia. N Engl J Med. 1997;337(23):1667-74.
5. Wu Y-T, Lee H-Y, Norton S, Chen C, Chen H, He C, et al. Prevalence studies of dementia in mainland china, Hong Kong and taiwan: a systematic review and meta-analysis. PloS one. 2013;8(6).
6. Qiu C, von Strauss E, Bäckman L, Winblad B, Fratiglioni L. Twenty-year changes in dementia occurrence suggest decreasing incidence in central Stockholm, Sweden. Neurology. 2013;80(20):1888-94.
7. Schrijvers EMC, Verhaaren BFJ, Koudstaal PJ, Hofman A, Ikram MA, Breteler MMB. Is dementia incidence declining?: Trends in dementia incidence since 1990 in the Rotterdam Study. Neurology. 2012;78(19):1456-63.
8. Satizabal CL, Beiser AS, Chouraki V, Chene G, Dufouil C, Seshadri S. Incidence of Dementia over Three Decades in the Framingham Heart Study. N Engl J Med. 2016;374(6):523-32.
9. Lobo A, Saz P, Marcos G, Dia JL, De-la-Camara C, Ventura T, et al. Prevalence of dementia in a southern European population in two different time periods: the ZARADEMP Project. Acta psychiatrica Scandinavica. 2007;116(4):299-307.
10. Rocca WA, Petersen RC, Knopman DS, Hebert LE, Evans DA, Hall KS, et al. Trends in the incidence and prevalence of Alzheimer's disease, dementia, and cognitive impairment in the United States. Alzheimers Dement. 2011;7(1):80-93.
11. Doblhammer G, Fink A, Zylla S, Willekens F. Compression or expansion of dementia in Germany? An observational study of short-term trends in incidence and death rates of dementia between 2006/07 and 2009/10 based on German health insurance data. Alzheimer's research & therapy. 2015;7(1):66.
12. Doblhammer G, Fink A, Fritze T. Short-term trends in dementia prevalence in Germany between the years 2007 and 2009. Alzheimers Dement. 2015;11(3):291-9.
13. van Bussel EF, Richard E, Arts DL, Nooyens AC, Coloma PM, de Waal MW, et al. Dementia incidence trend over 1992-2014 in the Netherlands: Analysis of primary care data. PLoS medicine. 2017;14(3):e1002235.
14. Langa KM, Larson EB, Crimmins EM, Faul JD, Levine DA, Kabeto MU, et al. A Comparison of the Prevalence of Dementia in the United States in 2000 and 2012. JAMA Intern Med. 2017;177(1):51-8.
15. American Psychiatric Association. (2000). Diagnostic and statistical manual of mental disorders (4th ed., text rev.).Author. Washington, DC.
16. Matthews FE, Arthur A, Barnes LE, Bond J, Jagger C, Robinson L, et al. A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II. Lancet. 2013;382(9902):1405-12.
17. Grasset L, Brayne C, Joly P, Jacqmin-Gadda H, Peres K, Foubert-Samier A, et al. Trends in dementia incidence: Evolution over a 10-year period in France. Alzheimer's & Dementia. 2016;12(3):272-80.

18. Matthews FE, Stephan BC, Robinson L, Jagger C, Barnes LE, Arthur A, et al. A two decade dementia incidence comparison from the Cognitive Function and Ageing Studies I and II. Nature communications. 2016;7:11398.
19. Will new diagnostic criteria for diabetes mellitus change phenotype of patients with diabetes? Reanalysis of European epidemiological data. DECODE Study Group on behalf of the European Diabetes Epidemiology Study Group. Bmj. 1998;317(7155):371-5.
20. Copeland JR, Dewey ME, Griffiths-Jones HM. A computerized psychiatric diagnostic system and case nomenclature for elderly subjects: GMS and AGECAT. Psychological medicine. 1986;16(1):89-99.
21. Copeland JR, Dewey ME, Griffiths-Jones HM. Dementia and depression in elderly persons: AGECAT compared with DSM III and pervasive illness. International journal of geriatric psychiatry. 1990;5:45-51.
22. Cognitive function and dementia in six areas of England and Wales: the distribution of MMSE and prevalence of GMS organicity level in the MRC CFA Study. The Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). Psychological medicine. 1998;28(2):319-35.
23. 3C Study Group. Vascular factors and risk of dementia: design of the Three-City Study and baseline characteristics of the study population. Neuroepidemiology. 2003;22(6):316-25.
24. Dartigues JF, Gagnon M, Letenneur L, Barberger-Gateau P, Commenges D, Evaldre M, et al. Principal lifetime occupation and cognitive impairment in a French elderly cohort (Paquid). Am J Epidemiol. 1992;135(9):981-8.
25. Copeland JR, Dewey ME, Henderson AS, Kay DW, Neal CD, Harrison MA, et al. The Geriatric Mental State (GMS) used in the community: replication studies of the computerized diagnosis AGECAT. Psychological medicine. 1988;18(1):219-23.
26. Launer LJ. Counting dementia: There is no one "best" way. Alzheimers Dement. 2011;7(1):10-4.
27. Grimmer T, Beringer S, Kehl V, Alexopoulos P, Busche A, Forstl H, et al. Trends of patient referral to a memory clinic and towards earlier diagnosis from 1985-2009. International psychogeriatrics / IPA. 2015;27(12):1939-44.
28. Grober E, Buschke H. Genuine memory deficits in dementia. Developmental neuropsychology. 1987;3(1):13-36.
29. Peres K, Brayne C, Matharan F, Grasset L, Helmer C, Letenneur L, et al. Trends in Prevalence of Dementia in French Farmers from Two Epidemiological Cohorts. J Am Geriatr Soc. 2017;65(2):415-20.
30. Crimmins EM, Kim JK, Langa KM, Weir DR. Assessment of cognition using surveys and neuropsychological assessment: the Health and Retirement Study and the Aging, Demographics, and Memory Study. The journals of gerontology Series B, Psychological sciences and social sciences. 2011;66 Suppl 1:i162-71.
31. Pérès K, Edjolo A, Dartigues JF, Barberger-Gateau P. Recent Trends in Disability-Free Life Expectancy in the French Elderly: Twenty Years Follow-Up of the Paquid Cohort. Annual Review of Gerontology and Geriatrics. 2013;33(1):293-311.

4.3.4. Discussion

This work provides another evidence of the evolution of clinical dementia diagnosis over time and studies. Indeed, incident cases from the 3C-Bordeaux study were diagnosed at higher level of MMSE than the incidence cases from the PAQUID study. It seems that diagnosis can be impacted by some subjects' characteristics and by information available to make a decision. For instance, participants having a high educational level are being diagnosed at higher MMSE score than participants without diploma. Educational level was higher in 3C than in PAQUID, because of the improvement of education that has occurred over the last century. Furthermore, some cognitive tests such as the Free and Cued Selective Reminding Test (FCSRT) evidenced more subtle cognitive impairment, more related to preclinical stage of AD (228). The FCSRT test has not been assessed in PAQUID whereas it has been in 3C. This could lead to the identification of milder cases of dementia than in studies with less cognitive test available. Thus, this, combined to the higher education level, could explain the difference between PAQUID and 3C in this work. This diagnosis instability needs to be accounted for when studying secular trends, which often requires comparison of different studies at different times.

When applying the CDA algorithm to the CFAS I and II data, we were also able to evidence a decrease in prevalence and incidence of dementia. This decrease was even larger with the CDA than with the AGECAT, corroborating the decrease. However, estimates were not the same than the ones published based on the AGECAT algorithm. Prevalence estimates were higher with the CDA algorithm in CFAS I and lower in CFAS II. Incidence rates were much higher with the CDA approach for CFAS I and a bit lower with the CDA for CFAS II. Women and individuals of older ages from CFAS I had higher incidence rates with the CDA approach than with the AGECAT algorithm. The AGECAT algorithm does not take disability into account unlike the CDA, and contains items about clinical opinion from the interviewers. Exempt of clinical opinion, the CDA could thus be more replicable in different context to assess secular trends.

4.4. Secular trends of mortality and life expectancy according to dementia status

4.4.1. Introduction

The decrease of dementia incidence is of good promise for health of the elderly. It is also of interest to investigate the evolution of mortality and whether it differs between individuals with and without dementia. Another relevant indicator for public health is the life expectancy without dementia, combining directly mortality and health data. Indeed, dementia is a costly disease, and life expectancy free of dementia or with dementia could help estimate dementia management needs and costs. From a more individual perspective, duration of life with dementia is also interesting. It is therefore important to look at the evolution of these indicators over time and whether different trajectories are observed through different populations (gender, educational level …). Increasing life expectancy does not in itself mean a healthier population. An increase in total life expectancy may be accompanied by increase in life expectancy without dementia but also with dementia. The most optimistic scenario is a compression of morbidity where the increase in life expectancy is only composed of extra years free of dementia. This means that we would live longer, but longer in a healthy state and shorter in a diseased state. However, the increase in life expectancy can also be associated with extra years with dementia, named the expansion of morbidity, where we would live longer but also longer in a diseased state. To nuance these scenarios, a dynamic equilibrium theory has been build where we would live longer in a healthy state but the same time in a diseased state. There would be a delayed entry in disease. More lately, an alternative scenario has emerged: unhealthy years may increase but the proportion of life spent healthily is increasing or decreasing, resulting either in a relative compression or relative expansion.

Health expectancies were developed to bring a quality-of-life dimension to life expectancy. In the literature, a high number of studies are focused on disability-free life expectancy. However, only few studies have investigated secular trends of dementia-free life expectancy. This work thus aimed at evaluating the evolution of mortality, life expectancy and duration of life with dementia.

4.4.2. Methods

The two populations compared in this study are the same as in the first paper investigating trends in dementia incidence. We thus analysed data from participants 10 years apart from the same areas of the PAQUID (**the 1990's population**, n=1,342) and the 3C studies (**the 2000's population**, n=1,996). In this work, only the algorithmic diagnosis has been used which definition was a MMSE score <24 (or a missing MMSE score for "cognitive reason") AND a 4 IADL score ≥2.

The same illness-death model was applied to provide mortality, life expectancies and duration of life with dementia estimates. Results were thus presented globally and by gender and education level for ages 70, 75, 80, 85, and 90 years old.

4.4.3. Article

Secular trends of mortality and Dementia-Free Life Expectancy over a 10-year period in France.

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Abstract

Introduction: Whether the increase of life expectancy is associated to greater years of life spent without dementia has been poorly investigated. The aims of this paper were to investigate the evolution of mortality and life expectancy according to dementia status in two French populations ten years apart.

Methods: Two different populations of subjects aged 65 years or older included in 1988–1989 (n=1342) and 1999–2000 (n=1996) and initially not demented were followed up over 10 years. Dementia was assessed using an algorithmic approach. Multi-states illness-death models were used to compare mortality with and without dementia, and to provide total life expectancy (LE) and Dementia Free Life Expectancy (DemFLE), as well as duration of life with dementia.

Results: Mortality without dementia has decreased among men and women between the two populations (HR= 0.63 (0.49-0.81) for men and HR=0.67 (0.50-0.90) for women), whereas mortality with dementia has decreased for women only (HR=0.59 (0.41-0.87)). Total LE and DemFLE has increased between the 90's and the 2000's population (total LE at age 75: + 2.4 years; DemFLE at age 75: + 2.2 years), as well as duration of life with dementia (+ 0.6 years at age 75). The proportion of life spent healthy has slightly increased; yet, not for all ages, gender and educational level.

Discussion: The improvement of DemFLE is promising. However, as duration of life with dementia has also increased, efforts to delay dementia onset should be reinforced.

Introduction

In most high-income countries worldwide, a regular increase in life expectancy (LE) at age 60 by around two years per decade has been evidenced (1). According to WHO, worldwide average life expectancy at age 60 years was 21.5 years for women and 18.5 for men in 2012, whereas it was 19.7 and 16.6 years for women and men respectively in 1990 (2). Life expectancy is expected to keep increasing in several countries up to 2030 (3). The major risk factor for dementia being age, the number of persons at risk of becoming demented is thus expected to rise. Indeed, the forecasted number of dementia cases worldwide has been estimated at 74.7 million in 2030 and 131.5 in 2050 (4). The high burden of dementia impacting not only the patients but their families and societies, it is therefore critical to explore any evolution of life expectancies. If the increase of global life expectancy is known, the increase of life expectancy according to dementia status has been poorly investigated. Yet, the quality of life became as important as the number of remaining years to live and a real progress in life expectancy should be associated with an increase of years spent in a healthy state without disease. Three scenarios can apply. First, an overall increase in LE associated with extra years of life spent in good health (without dementia) is referred to as a compression of morbidity (5). Then, if the extra years of LE are spent in poor health (with dementia), it is defined as expansion of morbidity (Kramer M 1980). Alternately, unhealthy years with dementia can increase but the proportion of life spent healthily is increasing or decreasing, resulting either in a relative compression or relative expansion (6). Finally, morbidity can increase at a similar rate to LE but not severity, which is known as “dynamic equilibrium” (7).

Nevertheless, several studies have shown decreasing trends of prevalence and incidence of dementia over the last three decades (8-15). However, only few papers have investigated changes over time in mortality and/or survival among people free of dementia and with dementia (10, 16, 17). Life expectancies are related to both mortality and incidence or prevalence of dementia. Studies investigating secular trends of life expectancies are lacking to evidence which scenario could be accurate.

In a previous paper, we published the decrease of dementia incidence, found in women between two French populations 10 years apart (12). In this work, we aimed at investigating within the same population whether the improvement of mortality is common between participants with or without dementia, and which factors could be related to these evolutions. Moreover, we established life expectancies and duration of life with dementia.

Methods

1) Study population

This study is based on two prospective population-based cohorts in the Bordeaux area of France (PAQUID and Three-City). Participants aged 65 and over living in the community were randomly chosen from the electoral rolls for both cohorts.

The Personnes Agées Quid (PAQUID) cohort was formed in 1988–1989 with a representative sample of 3,777 participants living at home in the departments of Gironde and Dordogne. The selection was stratified by sex, age and size of urban unit. For this paper, only participants from the Urban Community of Bordeaux (n=1,469) have been selected from PAQUID. The Three-City (3C) cohort started in 1999 and recruited 2,104 participants from the Urban Community of Bordeaux, within 10 districts. For both cohorts, a standardized questionnaire assessing socio-demographic, medical, cognitive, and functional data was administered by trained neuropsychologists during face-to-face interviews, at baseline and at each follow-up (3, 5, 8 and 10 years for PAQUID and 2, 4, 7 and 10 for 3C) (supplementary figure 1). Participants were followed-up even if they moved to a care home. At each follow-up vital status was systematically recorded for all the participants. Full details of the studies have been described elsewhere (18, 19).

Thus, 1,469 subjects from PAQUID (named 1990's population in the following, baseline screening response rate 60%) and 2,104 from 3C (named 2000's population, baseline screening response rate 39%) were available. After exclusion of prevalent dementia cases using an algorithmic diagnosis and missing values for adjustment factors (12), the study population was thus comprised of 1342 participants for the 1990's population and 1996 participants for the 2000's population.

2) Diagnosis of dementia

To diagnose dementia consistently between generations, an algorithmic approach has been used (ref papier 1). The algorithmic diagnosis was based on cognitive and functional assessments, using the Mini Mental State Examination (MMSE) (20) and the 4 Instrumental Activities of Daily Living (IADL) (ability to use the telephone, transportation, responsibility for medications and ability to manage its budget). For each activity, participants were considered disabled for the first level of disability; thus the score range from 0 for a subject

completely unimpaired to 4 for a person dependent for the four activities. Considering the old age of the participants and the associated high proportion of subjects restricted in the activity of transport, we considered restriction in activities from at least two restricted activities out of the four (21). The algorithmic diagnosis of dementia was then defined by a MMSE score <24 (or a missing MMSE score for "cognitive reason") AND a 4 IADL score ≥2.

3) Baseline Characteristics

Several risk factors were used for adjustment in statistical models. First, sociodemographic factors such as gender and educational level. In adjustment for mortality ratios, a three level variable was used: validated primary school level or short secondary school level, long secondary school level or more, vs. no diploma. Then, vascular-related factors were considered: history of stroke as well as treatment with antihypertensive drugs, lipid-lowering drugs, and anti-diabetic drugs as proxy for vascular risk factors. Data on treatments were collected using a standardized questionnaire as well as visual inspection of the participant's medicine packs.

4) Statistical analyses

The two populations were compared in terms of sociodemographic and health factors, as well as for cognitive and functional abilities at baseline.

Analyses comparing both populations have been established with an Illness-Death model. This multi-state model describes the pathway from a healthy state to an absorbing state (death) either directly or through a demented state (figure) (ref). A semi-parametric approach using M-Splines was used to provide transition intensities and interval censoring was accounted for. We have estimated mortality hazard ratios according to dementia status by fitting models separately for men and women, pooling the two populations with the population as a binary adjustment factor. To investigate in what extent risk factors explained the evolutions of mortality risk, additional adjustment were tested: 1) educational level; 2) vascular risk factors and 3) both educational level and vascular risk factors. The SmoothHazard package also estimates transition probabilities, cumulative event probabilities and life expectancies and we have fitted separated model for the two populations and adjusted on sex and educational level (two highest levels combined to compare participants with or without diploma). The following predictive parameters were computed: 1) the probability of being alive without dementia according to age; 2) the probability of being alive with

dementia; 3) the probability of dying; 4) the total life expectancy (LE); 5) the life expectancy free of dementia (DemFLE) alongside with the % of total life expectancy without dementia; and 6) the duration of life/survival with dementia. Probabilities correspond to the probability to be in a given state at a given age for participants being in state 0 at the beginning (at age 66 in the following results). Life expectancy without dementia at a given age was defined as the average number of years a participant who attained that age without dementia was expected to live free of dementia. Life expectancy with dementia at a given age can be defined as the average number of years a participant who attained that age without dementia was expected to live with dementia. It is the difference between the total life expectancy and the DemFLE. It has to be differentiated from the survival with dementia, corresponding to the average number of years an individual with dementia is expected to live. Both indicators have different interests, life expectancy with dementia being more relevant from a Public Health point of view and survival with dementia more relevant from a clinical point of view and for the patient himself.

Results

The comparison of the two populations (1342 participants for the 1990's population and 1994 participants for the 2000's population) is described in table 1. The mean age at baseline did not differ between the two populations; however, the 1990's population had more participants aged 85 and more at baseline than the 2000's population. Educational level highly improved between populations. Stroke history has declined and participants from the 2000's population were more treated against hypertension and hypercholesterolemia than participants from the 1990's population. Participants from the 2000's population had better cognitive level at baseline with a higher MMSE score and were less disabled according to the 4IADL score at baseline. Mean age at time of diagnosis of algorithmic dementia over the follow-up was 79.4 (6.7) y.o. for the 1990's population and 81.4 (5.2) y.o. for the 2000's population.

Hazard ratios comparing the two populations for mortality of people with and without dementia are presented table 2. For participants dying without becoming demented, women of the second population had a lower risk than women from the first population (HR=0.67 (0.50-0.90)), and this decreased risk was even more pronounced after adjustment on educational level and vascular factors (HR=0.59 (0.43-0.81)). The risk of dying after developing dementia was also lower for women of the second population than of the first one (HR=0.59 (0.41-

0.87)). This decrease remained significant after adjustment for education but not for vascular factors (HR=0.69 (0.46-1.03)). For men, mortality without dementia was also lower in the second generation compared to the first one (HR=0.63 (0.49-0.81)), even after adjustment (HR=0.66 (0.49-0.88)). However, there were no significant differences between the two generations in mortality for men with dementia (HR=1.13 (0.64-1.98)).

Table 3 reports the total Life Expectancy (totalLE), the Dementia Free LE (DemFLE) and the percentage of life spent dementia free (%DemFLE) according to the population for different ages. Globally, total LE and DemFLE have increased between the 1990's population and the 2000's population. This increase is also found in both men and women, with and without diploma (Supplementary tables 1 and 2). However, the increase was lower after 80 years old for men and women with high education. At the age of 75 y.o., total LE has increased of 3.4 years for men without diploma and of 1.5 years for men with diploma. For women aged 70 yo, total LE has increased of 4.7 years without diploma and of 2.7 years with diploma (Figure 1). Compared with the 1990's population at age 75, Dementia Free LE (DemFLE) increased for both men with diploma (1.4 years) and without diploma (3.0 years), as well as for women with diploma (2.0 years) and without diploma (3.4 years). At this age, men and women with diploma had a longer total LE than those without diploma in the first generation; this difference was no longer observed in the second generation where only DemFLE was equal or higher among those with diploma whereas total LE was shorter (figure 1). Globally, the % of years lived free of dementia has slightly increased, but in different extent according to ages. When looking at men without diploma, % DemFLE was higher for the second population (except at age 70). However, it tended to be similar for men with high education. For women, % DemFLE tended to have increased without diploma (except at age 70) and tended to have decreased with diploma (except at age 90).

Table 4 shows the survival of participants with dementia for both populations, first globally, and then according to sex and educational level. In total, except for the youngest, survival with dementia has increased between the two populations. We found an increased survival at every age for women with (age 75: 2.7 years) and without diploma (age 75: 4.2 years). Survival was higher in women without diploma compared to women with diploma. For men without diploma, survival tended to increase between the two generations (age 75: 0.8 years) but remained similar for men with diploma (age 75: -0.1 years).

Discussion

This work has evidenced a decrease in mortality without dementia for men and women, and a decrease in mortality with dementia for women only. Both total life expectancy and dementia-free life expectancy have increased between the 90's and the 2000's. Globally, the proportion of life spent healthy without dementia has tended to slightly increase; however, %demFLE showed variations across educational level with an improvement for individuals without diploma and stability or worsening for individuals with diploma. These results seem to be in line with a relative compression of morbidity. Moreover, survival with dementia has increased between the two generations. It has mostly improved for women, which is concordant to the decrease in dementia mortality for women, but only slightly for men without diploma.

Only a few studies have investigated mortality trends according to dementia status. In line with our result, a Swedish study from Stockholm showed a significant decrease in total mortality and mortality without dementia for both sex, and a significant decrease in mortality with dementia for women only (10). However, a rural Swedish study found a significant decrease in total mortality for men only, and the decrease in mortality by dementia status was not significant (16). Sample size was however small in that latter study (between 300 and 400). Then, there is also a study using insurance data that found a stable mortality without dementia and a significant decrease in dementia mortality for women only (17). However, dementia ascertained by administrative database is highly dependent of care access, which can lead to biased trends. A US study reported an increased risk of death between generations with moderate/severe cognitive impairment (22). Explanation for the decrease in mortality has not been investigated in previously published studies. In our results, risk factors accounted for in analyses did not really explain the decrease, except for vascular treatment in mortality with dementia for women, where the decrease became non-significant.

Our findings have evidenced that the global increase in total life expectancy has also been associated with an increase in life expectancy without dementia. However, overall survival with dementia has also increased, which has not resulted in real clear improvement of proportions of life spent healthy for every individual, even if it tends to has increased in men and women with low educational level. Dementia-free life expectancy in 1989/90 has already been published by our team for nearly the same geographical area as our populations: results regarding DemFLE were similar to the ones from our 1990's population but total LE was higher (23). This difference may have different reasons: their population sample included

institutionalised participants, prevalence data was used to provide LE, and mortality from France was applied when we used mortality data from the two generations. The increase of total life expectancy in older ages has been widely documented (1, 24). A study based on the CFAS I and II participants showed an increase in life expectancy between 1991 and 2011 of 3 years for men and 2.5 years for women aged 70, with estimates of total LE in line with our results (25). However, if trends in life expectancy with and without disability have been well documented (25-28), only few studies have investigated changes in life expectancy according to dementia status between generations. A study compared life expectancy at age 65 between 2006/07 and 2009/10 and has not evidenced significant changes in total LE or DemFLE but has reported a significant decrease in LE with dementia for women, in line with our decrease in dementia mortality for women only (17). However, the time period may have been too short to evidence any trends and data are from administrative database. Another American study reported a decrease in proportion of life spent without dementia for men but an increase for women between a 1971 cohort and a 1980 cohort, related to a decrease in mortality for men only (29). Indeed, they have not shown any improvement in total LE for women but a small decrease of LE with dementia.

Survival with dementia often varies across studies from 3 to 9.3 years, differences being at least partly explained by study setting and methodology applied (30-36). When looking at duration of survival, it is important to start at the beginning of clinical sign of the symptoms and not from the time of study entry or at the beginning of reported symptoms; which could lead to an over-estimated duration of survival (30). It has been shown that patients with a longer estimated duration of symptoms at initial visit had a better prognosis (37)..

Regarding survival with dementia, we have evidenced different results according to gender and educational level. Women experienced higher life expectancies but lower proportion of life without dementia than men and higher survival with dementia. This result is in line with previous studies (23, 38). It is also interesting to note that individuals with high educational level spent higher proportions of life free of dementia than individuals with low educational level. This result has also been shown in other studies (39-42). A possible reason is that individuals with high education have better cognitive reserve and are able to cope better with brain damage. However, when they finally reach the dementia threshold, later than individuals with low educational level, neuropathology is more advanced and mortality is then higher after diagnosis (43).

The principal limit of this work is the low response rate of the 3C study, leading to the selection of healthier participants. It could have over-estimated the decrease of mortality and the differences between life expectancies. Moreover, the statistical model used for the analyses assumes risk proportionality for adjustment factors. However, to limit the loss of statistical power when computing life expectancies and probabilities, we decided to stratify analyses based on the population only and adjusted on gender and education. The SmoothHazard package does not provide life expectancy with dementia and its confidence intervals. LE with dementia was thus obtained by the difference between total LE and DemFLE.

This work has several strengths: it relied on the comparison of two large independent populations, followed for 10 years with identical design and procedures of data collection. To limit the impact of diagnosis evolution, we assessed dementia based on an algorithmic approach. The effect of several risk factors has been investigated. Furthermore, life expectancies have been calculated over a ten year period.

Investigating the quality of the extra years gained with increased life expectancy is critical. The increase of life expectancy free of dementia is thus of good promise. However, mortality with dementia has also decreased for women and thus they tend to live longer with dementia. With dementia being a great fear and leading to high costs for families and societies, a particular focus should be provided on interventions to delay dementia onset.

Table 1: Characteristics description of the two populations at baseline (N=3338)

	1990's population N=1342	2000's population N=1996	P value
Gender (Women)	815 (60.7)	1211 (60.7)	0.97
Mean age at baseline	74.3 (6.5)	74.4 (5.0)	0.69
Age at baseline			<.0001
65 – 69 y.o.	449 (33.5)	461 (23.1)	
70 – 74 y.o.	314 (23.4)	672 (33.7)	
75 – 79 y.o.	324 (24.1)	580 (29.1)	
80 – 84 y.o.	158 (11.8)	234 (11.7)	
85 – + y.o.	97 (7.2)	49 (2.4)	
Educational level			<.0001
No diploma	312 (23.2)	230 (11.5)	
Intermediate school level	825 (61.5)	1091 (54.7)	
High school level	205 (15.3)	675 (33.8)	
Stroke history	67 (5.0)	65 (3.3)	0.012
Anti-hypertensive ttt	701 (52.2)	1137 (57.0)	0.007
Anti-diabetic ttt	97 (7.2)	147 (7.4)	0.88
Lipid lowering ttt	161 (12.0)	636 (31.9)	<.0001
Mean MMSE score at baseline* (59 manquants)	26.61 (2.7)	27.39 (2.03)	<.0001
4 IADL at baseline* (6 manquants)			<.0001
0	1059 (79.0)	1724 (86.6)	
1	209 (15.6)	214 (10.7)	
2	47 (3.5)	33 (1.7)	
3	15 (1.1)	13 (0.6)	
4	11 (0.8)	7 (0.4)	

Abbreviations: MMSE, Mini Mental State Examination; 4 IADL, Instrumental Activities of Daily Living
* Missing data: MMSE (n=59); 4 IADL (n=6)

Table 2: Mortality evolution between the 1990s and the 2000s population, by sex

	Men N=1312		Women N=2026	
	HR (95% CI)	p	HR (95% CI)	p
Transition 0-2 (healthy to death)			N=	
2000's vs 1990's				
Adjusted on age	0.63 (0.49-0.81)	0.0002	0.67 (0.50-0.90)	0.008
Adjusted on age + education	0.72 (0.56-0.92)	0.01	0.67 (0.48-0.92)	0.01
Adjusted on age + vascular factors*	0.57 (0.43-0.74)	<.0001	0.61 (0.45-0.81)	0.0009
Fully adjusted†	0.66 (0.49-0.88)	0.005	0.59 (0.43-0.81)	0.0009
Transition 1-2 (dementia to death)				
2000's vs 1990's				
Adjusted on age	1.13 (0.64-1.98)	0.68	0.59 (0.41-0.87)	0.007
Adjusted on age + education	0.83 (0.49-1.42)	0.51	0.53 (0.35-0.78)	0.002
Adjusted on age + vascular factors*	1.30 (0.75-2.24)	0.34	0.69 (0.46-1.03)	0.07
Fully adjusted†	0.80 (0.45-1.43)	0.46	0.61 (0.40-0.92)	0.02

* Adjusted for BMI, stroke, antihypertensive, antidiabetic, and lipid-lowering drugs intake.
† Adjusted for education level, BMI, stroke, antihypertensive, antidiabetic and lipid-lowering drugs intake

Table 3: Total life expectancy (LE), dementia-free life expectancy (DemFLE) and proportion of life spent without dementia (%DemFLE) for selected ages according to population

	1990's population			2000's population		
	Total LE	DemFLE	% DemFLE	Total LE	DemFLE	% DemFLE
70	15.9 (15.2-16.5)	13.9 (13.2-14.4)	87.4	19.0 (18.3-19.5)	16.7 (16.0-17.1)	87.9
75	12.6 (12.0-13.2)	10.5 (9.9-11.0)	83.3	15.0 (14.4-15.6)	12.7 (12.2-13.2)	84.7
80	9.7 (9.1-10.2)	7.6 (7.1-8.1)	78.3	11.5 (10.9-12.0)	9.2 (8.7-9.6)	80.0
85	7.3 (6.7-7.9)	5.5 (5.0-6.0)	75.3	8.7 (8.1-9.3)	6.6 (6.1-7.1)	75.9
90	5.3 (4.8-6.0)	3.9 (3.4-4.5)	73.6	6.2 (5.7-6.7)	4.7 (4.2-5.2)	75.8

Table 4: Duration of life with dementia in years for selected ages according to generation, sex and education.

		Duration of life with dementia	
		1990's population	2000's population
Overall			
	70	8.2 (5.1-10.7)	7.5 (4.8-10.6)
	75	6.2 (4.6-7.9)	6.8 (5.2-8.6)
	80	4.9 (4.0-6.0)	6.2 (5.1-7.6)
	85	4.0 (3.3-4.9)	5.7 (4.7-7.0)
	90	3.3 (2.6-4.3)	4.9 (3.9-5.9)
Men without diploma			
	70	7.5 (4.5-11.3)	7.9 (4.8-12.5)
	75	5.8 (3.7-9.2)	6.4 (4.3-10.1)
	80	4.5 (3.0-8.0)	5.3 (3.6-8.7)
	85	3.6 (2.4-6.8)	4.6 (3.1-7.4)
	90	3.0 (1.9-5.6)	3.8 (2.6-6.0)
Men with diploma			
	70	5.2 (2.5-8.6)	4.9 (2.8-8.1)
	75	3.9 (2.5-6.2)	3.8 (2.7-5.5)
	80	3.0 (2.2-4.8)	3.1 (2.4-4.5)
	85	2.4 (1.7-3.9)	2.7 (1.9-4.0)
	90	1.9 (1.4-3.3)	2.3 (1.5-3.6)
Women without diploma			
	70	10.6 (6.4-13.9)	15.2 (9.8-20.5)
	75	8.5 (6.1-11.4)	12.7 (8.9-17.4)
	80	6.9 (5.2-9.7)	10.6 (7.7-14.5)
	85	5.6 (4.3-8.2)	8.6 (6.6-11.3)
	90	4.6 (3.5-6.6)	6.4 (5.3-7.9)
Women with diploma			
	70	7.6 (3.3-11.5)	10.4 (6.6-14.2)
	75	5.9 (3.8-8.4)	8.6 (6.1-11.4)
	80	4.7 (3.3-6.3)	7.2 (5.6-9.4)
	85	3.7 (2.9-5.1)	6.1 (4.8-7.7)
	90	3.0 (2.3-4.2)	4.9 (3.8-6.0)

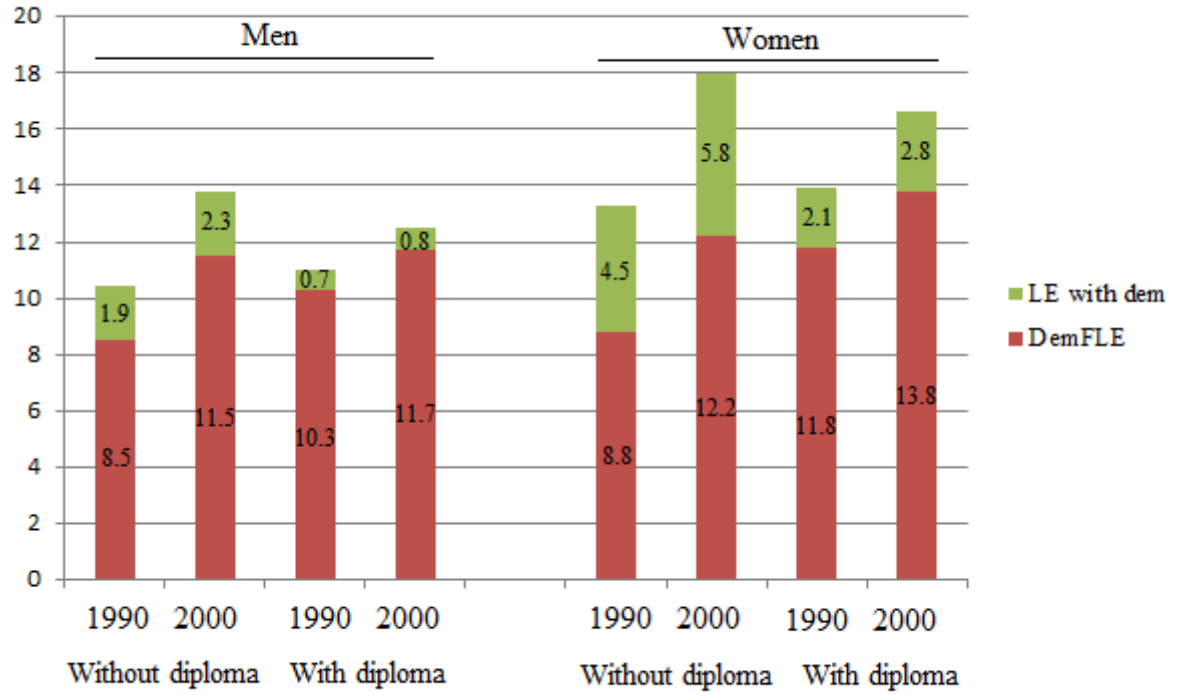

Figure 1: Life expectancy with and without dementia in years at age 75 between the two populations according to gender and educational level. (DemFLE: Dementia-Free Life Expectancy; LE with dem: Life expectancy with dementia; Total LE=DemFLE + LE with dem)

Supplementary table 1: Total life expectancy (LE), dementia-free life expectancy (DemFLE) and proportion of life spent without dementia (%DemFLE) for selected ages according to population and educational level, in men

		1990's population			2000's population		
Men without diploma		Total LE	DemFLE	% DemFLE	Total LE	DemFLE	% DemFLE
	70	13.3 (11.4-14.4)	11.5 (9.1-12.7)	86.5	17.8 (16.0-19.5)	15.4 (13.7-17.0)	86.5
	75	10.4 (9.0-11.6)	8.5 (7.3-9.6)	81.7	13.8 (12.2-15.4)	11.5 (10.0-12.9)	83.3
	80	7.9 (6.8-9.1)	6.1 (5.2-7.0)	77.2	10.4 (9.1-11.9)	8.1 (7.0-9.2)	77.9
	85	5.7 (4.9-6.8)	4.2 (3.4-5.1)	73.7	7.9 (6.9-9.0)	5.8 (4.9-6.7)	73.4
	90	4.1 (3.4-5.0)	2.9 (2.3-3.6)	70.7	5.8 (5.1-6.5)	4.2 (3.5-4.8)	72.4
Men with diploma							
	70	14.0 (12.8-14.7)	13.3 (11.6-14.1)	95.0	16.3 (15.6-17.1)	15.5 (14.7-16.2)	95.1
	75	11.0 (10.1-11.8)	10.3 (9.3-11.1)	93.6	12.5 (11.8-13.2)	11.7 (10.9-12.4)	93.6
	80	8.4 (7.6-9.1)	7.6 (6.8-8.4)	90.5	9.3 (8.7-9.9)	8.5 (7.8-9.1)	91.4
	85	6.0 (5.3-6.8)	5.1 (4.7-6.1)	90.0	6.9 (6.3-7.6)	6.2 (5.5-6.8)	89.8
	90	4.2 (3.4-5.0)	3.7 (3.0-4.5)	88.1	5.1 (4.5-5.7)	4.5 (3.9-5.0)	88.2

Supplementary table 2: Total life expectancy (LE), dementia-free life expectancy (DemFLE) and proportion of life spent without dementia (%DemFLE) for selected ages according to population and educational level, in women

		1990's population			2000's population		
Women without diploma		Total LE	DemFLE	% DemFLE	Total LE	DemFLE	% DemFLE
	70	16.9 (14.5-18.1)	12.4 (8.8-13.1)	73.4	22.3 (20.6-23.7)	16.3 (14.9-17.4)	73.1
	75	13.3 (12.0-14.7)	8.8 (7.5-9.5)	66.2	18.0 (16.5-19.2)	12.2 (11.2-13.2)	67.8
	80	10.3 (9.2-11.8)	6.0 (5.2-6.7)	58.2	14.0 (12.7-15.1)	8.6 (7.7-9.5)	61.4
	85	7.9 (6.9-9.2)	4.2 (3.5-4.8)	53.2	10.6 (9.6-11.5)	6.1 (5.3-7.0)	57.5
	90	6.0 (5.1-7.0)	3.0 (2.3-3.6)	50.0	7.5 (6.9-7.9)	4.4 (3.7-5.0)	58.7
Women with diploma							
	70	17.6 (15.7-18.4)	15.5 (12.6-16.2)	88.1	20.8 (20.0-21.5)	17.9 (17.1-18.6)	86.1
	75	13.9 (12.9-14.7)	11.8 (10.6-12.5)	84.9	16.6 (15.8-17.2)	13.8 (13.1-14.5)	83.1
	80	10.7 (10.0-11.5)	8.7 (7.8-9.5)	81.3	12.8 (12.1-13.5)	10.2 (9.5-10.8)	79.7
	85	8.1 (7.3-8.8)	6.3 (5.5-6.9)	77.8	9.7 (3.1-10.3)	7.4 (6.7-8.0)	76.3
	90	6.0 (5.2-6.8)	4.6 (3.8-5.3)	76.7	6.9 (6.4-7.3)	5.3 (4.7-5.8)	76.8

References

1. Mathers CD, Stevens GA, Boerma T, White RA, Tobias MI. Causes of international increases in older age life expectancy. Lancet. 2015;385(9967):540-8.
2. World Health Organization. World Health Statistics. Geneva. (2014) [Available from: http://apps.who.int/iris/bitstream/10665/112738/1/9789240692671_eng.pdf?ua=1.
3. Kontis V, Bennett JE, Mathers CD, Li G, Foreman K, Ezzati M. Future life expectancy in 35 industrialised countries: projections with a Bayesian model ensemble. Lancet. 2017;389(10076):1323-35.
4. Alzheimer's Disease International. World Alzheimer Report: The Global Impact of Dementia. London. 2015.
5. Fries JF. Aging, natural death, and the compression of morbidity. N Engl J Med. 1980;303(3):130-5.
6. Nusselder WJ. Compression of morbidity. In: Robine J-M, Jagger C, Mathers CD, Crimmins EM, Suzman RM, editors. Determining health expectancies. John Wiley and Sons; Chichester, UK: 2003. pp. 35 - 58
7. Manton KG. Changing concepts of morbidity and mortality in the elderly population. The Milbank Memorial Fund quarterly Health and society. 1982;60(2):183-244.
8. Matthews FE, Arthur A, Barnes LE, Bond J, Jagger C, Robinson L, et al. A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II. Lancet. 2013;382(9902):1405-12.
9. Matthews FE, Stephan BC, Robinson L, Jagger C, Barnes LE, Arthur A, et al. A two decade dementia incidence comparison from the Cognitive Function and Ageing Studies I and II. Nature communications. 2016;7:11398.
10. Qiu C, von Strauss E, Bäckman L, Winblad B, Fratiglioni L. Twenty-year changes in dementia occurrence suggest decreasing incidence in central Stockholm, Sweden. Neurology. 2013;80(20):1888-94.
11. Peres K, Brayne C, Matharan F, Grasset L, Helmer C, Letenneur L, et al. Trends in Prevalence of Dementia in French Farmers from Two Epidemiological Cohorts. J Am Geriatr Soc. 2017;65(2):415-20.
12. Grasset L, Brayne C, Joly P, Jacqmin-Gadda H, Peres K, Foubert-Samier A, et al. Trends in dementia incidence: Evolution over a 10-year period in France. Alzheimers Dement. 2016;12(3):272-80.
13. Satizabal CL, Beiser AS, Chouraki V, Chene G, Dufouil C, Seshadri S. Incidence of Dementia over Three Decades in the Framingham Heart Study. N Engl J Med. 2016;374(6):523-32.
14. Schrijvers EMC, Verhaaren BFJ, Koudstaal PJ, Hofman A, Ikram MA, Breteler MMB. Is dementia incidence declining?: Trends in dementia incidence since 1990 in the Rotterdam Study. Neurology. 2012;78(19):1456-63.
15. Wu YT, Beiser AS, Breteler MMB, Fratiglioni L, Helmer C, Hendrie HC, et al. The changing prevalence and incidence of dementia over time - current evidence. Nature reviews Neurology. 2017;13(6):327-39.
16. Wimo A, Sjolund BM, Skoldunger A, Qiu C, Klarin I, Nordberg G, et al. Cohort Effects in the Prevalence and Survival of People with Dementia in a Rural Area in Northern Sweden. Journal of Alzheimer's disease : JAD. 2016;50(2):387-96.
17. Doblhammer G, Fink A, Zylla S, Willekens F. Compression or expansion of dementia in Germany? An observational study of short-term trends in incidence and death rates of dementia between 2006/07 and 2009/10 based on German health insurance data. Alzheimer's research & therapy. 2015;7(1):66.
18. Dartigues JF, Gagnon M, Letenneur L, Barberger-Gateau P, Commenges D, Evaldre M, et al. Principal lifetime occupation and cognitive impairment in a French elderly cohort (Paquid). Am J Epidemiol. 1992;135(9):981-8.

19. 3C Study Group. Vascular factors and risk of dementia: design of the Three-City Study and baseline characteristics of the study population. Neuroepidemiology. 2003;22(6):316-25.
20. Gagnon M, Letenneur L, Dartigues JF, Commenges D, Orgogozo JM, Barberger-Gateau P, et al. Validity of the Mini-Mental State examination as a screening instrument for cognitive impairment and dementia in French elderly community residents. Neuroepidemiology. 1990;9(3):143-50.
21. Pérès K, Chrysostome V, Fabrigoule C, Orgogozo JM, Dartigues JF, Barberger-Gateau P. Restriction in complex activities of daily living in MCI: impact on outcome. Neurology. 2006;67(3):461-6.
22. Langa KM, Larson EB, Karlawish JH, Cutler DM, Kabeto MU, Kim SY, et al. Trends in the prevalence and mortality of cognitive impairment in the United States: is there evidence of a compression of cognitive morbidity? Alzheimers Dement. 2008;4(2):134-44.
23. Ritchie K, Robine JM, Letenneur L, Dartigues JF. Dementia-free life expectancy in France. Am J Public Health. 1994;84(2):232-6.
24. Oeppen J, Vaupel JW. Demography. Broken limits to life expectancy. Science (New York, NY). 2002;296(5570):1029-31.
25. Jagger C, Matthews FE, Wohland P, Fouweather T, Stephan BC, Robinson L, et al. A comparison of health expectancies over two decades in England: results of the Cognitive Function and Ageing Study I and II. Lancet. 2016;387(10020):779-86.
26. Sagardui-Villamor J, Guallar-Castillon P, Garcia-Ferruelo M, Banegas JR, Rodriguez-Artalejo F. Trends in disability and disability-free life expectancy among elderly people in Spain: 1986-1999. The journals of gerontology Series A, Biological sciences and medical sciences. 2005;60(8):1028-34.
27. Jagger C, Matthews R, Matthews F, Robinson T, Robine JM, Brayne C, et al. The burden of diseases on disability-free life expectancy in later life. The journals of gerontology Series A, Biological sciences and medical sciences. 2007;62(4):408-14.
28. Cambois E, Clavel A, Romieu I, Robine JM. Trends in disability-free life expectancy at age 65 in France: consistent and diverging partterns according to the underlying disability measure. Eur J Ageing. 2008;5:287–98.
29. Sauvaget C, Tsuji I, Haan MN, Hisamichi S. Trends in dementia-free life expectancy among elderly members of a large health maintenance organization. International journal of epidemiology. 1999;28(6):1110-8.
30. Wolfson C, Wolfson DB, Asgharian M, M'Lan CE, Ostbye T, Rockwood K, et al. A reevaluation of the duration of survival after the onset of dementia. N Engl J Med. 2001;344(15):1111-6.
31. Larson EB, Shadlen MF, Wang L, McCormick WC, Bowen JD, Teri L, et al. Survival after initial diagnosis of Alzheimer disease. Annals of internal medicine. 2004;140(7):501-9.
32. Jagger C, Clarke M, Stone A. Predictors of survival with Alzheimer's disease: a community-based study. Psychological medicine. 1995;25(1):171-7.
33. Aguero-Torres H, Fratiglioni L, Guo Z, Viitanen M, Winblad B. Prognostic factors in very old demented adults: a seven-year follow-up from a population-based survey in Stockholm. J Am Geriatr Soc. 1998;46(4):444-52.
34. van Dijk PT, Dippel DW, Habbema JD. Survival of patients with dementia. J Am Geriatr Soc. 1991;39(6):603-10.
35. Fitzpatrick AL, Kuller LH, Lopez OL, Kawas CH, Jagust W. Survival following dementia onset: Alzheimer's disease and vascular dementia. Journal of the neurological sciences. 2005;229-230:43-9.
36. Todd S, Barr S, Roberts M, Passmore AP. Survival in dementia and predictors of mortality: a review. International journal of geriatric psychiatry. 2013;28(11):1109-24.
37. Stern Y, Tang MX, Albert MS, Brandt J, Jacobs DM, Bell K, et al. Predicting time to nursing home care and death in individuals with Alzheimer disease. JAMA. 1997;277(10):806-12.
38. Dubois MF, Hebert R. Cognitive-impairment-free life expectancy for Canadian seniors. Dement Geriatr Cogn Disord. 2006;22(4):327-33.
39. Contador I, Stern Y, Bermejo-Pareja F, Sanchez-Ferro A, Benito-Leon J. Is Educational Attainment Associated with Increased Risk of Mortality in People with Dementia? A Population-based Study. Current Alzheimer research. 2017;14(5):571-6.

40. Meng X, D'Arcy C. Education and dementia in the context of the cognitive reserve hypothesis: a systematic review with meta-analyses and qualitative analyses. PloS one. 2012;7(6):e38268.
41. Tom SE, Hubbard RA, Crane PK, Haneuse SJ, Bowen J, McCormick WC, et al. Characterization of dementia and Alzheimer's disease in an older population: updated incidence and life expectancy with and without dementia. Am J Public Health. 2015;105(2):408-13.
42. Reuser M, Willekens FJ, Bonneux L. Higher education delays and shortens cognitive impairment: a multistate life table analysis of the US Health and Retirement Study. European journal of epidemiology. 2011;26(5):395-403.
43. Lievre A, Alley D, Crimmins EM. Educational differentials in life expectancy with cognitive impairment among the elderly in the United States. J Aging Health. 2008;20(4):456-77.

4.4.4. Complementary results

In addition to mortality and life expectancy, the SmoothHazard package provides different probabilities. In the following, we have investigated the probability of being alive without dementia, the probability of dying and the probability of being alive with dementia. Table 11 shows the three different probabilities for the two populations according to age. Tables 12 and 13 and figure 12 show these probabilities for both men and women respectively and according to educational level for both populations. Globally, for people healthy at age 66, the probabilities of being alive without dementia (p00) has increased and the probabilities to die (p02) have decreased between the 1990's and the 2000's population. Moreover, the probabilities of being alive with dementia (p01) for individuals without dementia at age 66 have also increased. For the probability of being alive with dementia, it increases until 85 y.o. and then decreases for the 90's population whereas it tends to decrease after 90 y.o. only for the 2000's population (except for women without diploma). This probability tends to be lower or similar for the 2000's generation compared to the 90's one, except after 80 y.o. for men and 85 y.o. for women, where the 2000's population has higher probability to remain alive without dementia than the 90's population. The probability to remain alive with dementia is higher for individuals with low educational level.

Overall, probabilities to be alive without dementia have increased and probabilities to die have decrease. For women without diploma mostly, the probability to be alive with dementia was higher in the second population after 85 y.o. This is due to a decrease in mortality more important than the decrease of dementia incidence, leading to individuals staying longer at risk of developing dementia before dying. It could also be due to a delayed onset of dementia at older ages.

Table 11: Probability (in %) to be in a given state (alive without dementia, alive with dementia and death) at different ages according to the population, for individuals healthy (without dementia) at 66 years old.

		1990's population			2000's population		
Probabilities		p00	p01	p02	p00	p01	p02
	70	89.9 (85.6-92.6)	2.2 (0.7-4.0)	7.9 (5.7-12.1)	95.6 (80.0-96.9)	2.4 (0.9-4.9)	2.0 (1.5-18.0)
	75	78.8 (73.9-82.0)	3.5 (1.9-5.2)	17.8 (15.0-22.5)	89.1 (73.7-90.7)	3.1 (1.8-5.4)	7.8 (6.6-23.3)
	80	61.9 (57.0-65.2)	7.1 (5.4-9.1)	31.0 (28.0-35.9)	77.7 (63.8-79.2)	4.9 (3.7-6.8)	17.4 (16.0-31.5)
	85	39.7 (35.3-42.7)	11.2 (9.1-13.4)	49.1 (46.0-53.6)	56.7 (46.3-58.3)	9.7 (7.7-11.3)	33.6 (31.9-45.3)
	90	18.8 (15.7-21.3)	10.0 (7.9-12.0)	71.2 (68.5-75.0)	32.5 (26.1-34.6)	13.1 (10.2-14.9)	54.4 (52.2-62.8)

p00: Probability of being alive without dementia; p01: Probability of being alive with dementia; p02: Probability of dying

Table 12: Probability (in %) to be in a given state (alive without dementia, alive with dementia and death) at different ages according to the population and educational level in men healthy (without dementia) at 66 years old.

		1990's population			2000's population		
Men with low education		p00	p01	p02	p00	p01	p02
	70	85.3 (77.7-90.5)	2.9 (1.2-7.4)	11.8 (7.4-18.1)	94.6 (88.2-96.9)	3.3 (1.0-6.2)	2.1 (1.3-7.8)
	75	69.6 (58.1-75.5)	4.3 (2.4-11.9)	26.0 (18.8-35.8)	86.7 (79.8-90.1)	4.7 (2.6-8.3)	8.6 (5.8-15.5)
	80	49.4 (37.6-56.5)	7.6 (4.2-13.6)	43.1 (35.5-54.1)	72.6 (63.3-77.9)	7.1 (4.5-10.6)	20.2 (15.5-29.0)
	85	26.4 (17.6-34.4)	9.9 (5.7-14.0)	63.7 (56.2-74.1)	48.3 (36.9-57.3)	12.0 (7.8-17.0)	39.7 (31.8-50.9)
	90	9.2 (4.7-14.7)	7.0 (3.5-12.3)	83.7 (77.1-90.0)	23.6 (14.9-31.9)	13.3 (8.0-20.2)	63.1 (53.2-73.2)
Men with high education							
	70	87.4 (82.7-91.2)	1.2 (0.5-3.2)	11.3 (7.6-16.1)	95.6 (87.3-97.1)	1.6 (0.5-3.3)	2.7 (1.8-10.6)
	75	73.6 (66.6-78.1)	1.6 (0.9-5.4)	24.7 (20.1-30.5)	84.4 (79.9-89.7)	1.9 (0.9-3.5)	10.7 (8.5-17.9)
	80	56.5 (48.8-61.3)	2.9 (1.8-5.4)	40.6 (35.0-48.2)	73.2 (66.4-76.0)	2.7 (1.8-3.9)	24.2 (21.3-31.2)
	85	36.2 (29.8-41.1)	3.8 (2.5-5.7)	59.9 (54.9-66.0)	50.0 (43.7-53.6)	4.3 (3.2-5.7)	45.6 (41.8-52.0)
	90	17.3 (13.1-21.8)	2.8 (1.7-4.6)	79.9 (75.1-84.3)	26.1 (21.2-30.3)	4.4 (3.1-6.3)	69.5 (65.1-74.3)

p00: Probability of being alive without dementia; p01: Probability of being alive with dementia; p02: Probability of dying

Table 13: Probability (in %) to be in a given state (alive without dementia, alive with dementia and death) at different ages according to the population and educational level in women healthy (without dementia) at 66 years old.

	1990's population			2000's population		
Women with low education	p00	p01	p02	p00	p01	p02
70	89.3 (81.3-92.9)	5.1 (2.2-12.8)	5.5 (3.6-9.3)	94.6 (88.7-97.3)	4.4 (1.4-9.0)	0.9 (0.6-3.8)
75	77.7 (59.8-81.5)	8.8 (5.8-22.8)	13.5 (9.6-21.3)	88.4 (82.0-91.8)	7.6 (4.3-12.4)	4.0 (2.5-8.0)
80	57.3 (41.6-62.6)	17.3 (12.7-27.5)	25.5 (21.3-35.9)	76.8 (68.5-80.9)	13.1 (9.2-18.3)	10.0 (7.4-15.6)
85	29.9 (19.9-34.5)	25.4 (18.5-32.4)	44.6 (39.8-56.0)	54.0 (45.4-59.2)	24.7 (18.8-30.4)	21.3 (17.1-29.4)
90	10.0 (5.4-13.0)	21.7 (15.0-28.1)	68.3 (62.4-77.4)	28.6 (20.3-34.3)	33.9 (25.3-42.3)	37.5 (31.0-48.8)
Women with high education						
70	92.4 (87.5-94.6)	2.3 (0.9-5.9)	5.3 (3.5-8.4)	96.4 (92.1-97.9)	2.4 (0.9-4.7)	1.2 (0.9-4.7)
75	83.7 (72.9-86.4)	3.7 (2.1-11.1)	12.6 (10.2-18.0)	91.2 (86.4-93.2)	3.7 (2.2-6.2)	5.1 (3.8-8.9)
80	69.4 (58.7-72.5)	7.3 (5.2-15.0)	23.3 (20.3-31.1)	81.5 (76.0-83.7)	6.2 (4.8-8.8)	12.3 (10.4-17.4)
85	48.0 (39.1-51.7)	11.6 (8.5-15.5)	40.4 (37.1-48.6)	62.7 (57.4-65.3)	11.7 (9.3-14.4)	25.6 (23.1-31.2)
90	25.7 (19.4-29.6)	10.9 (8.1-14.0)	63.3 (59.1-70.0)	39.5 (34.1-43.4)	16.0 (12.8-20.5)	44.5 (40.9-50.4)

p00: Probability of being alive without dementia; p01: Probability of being alive with dementia; p02: Probability of dying

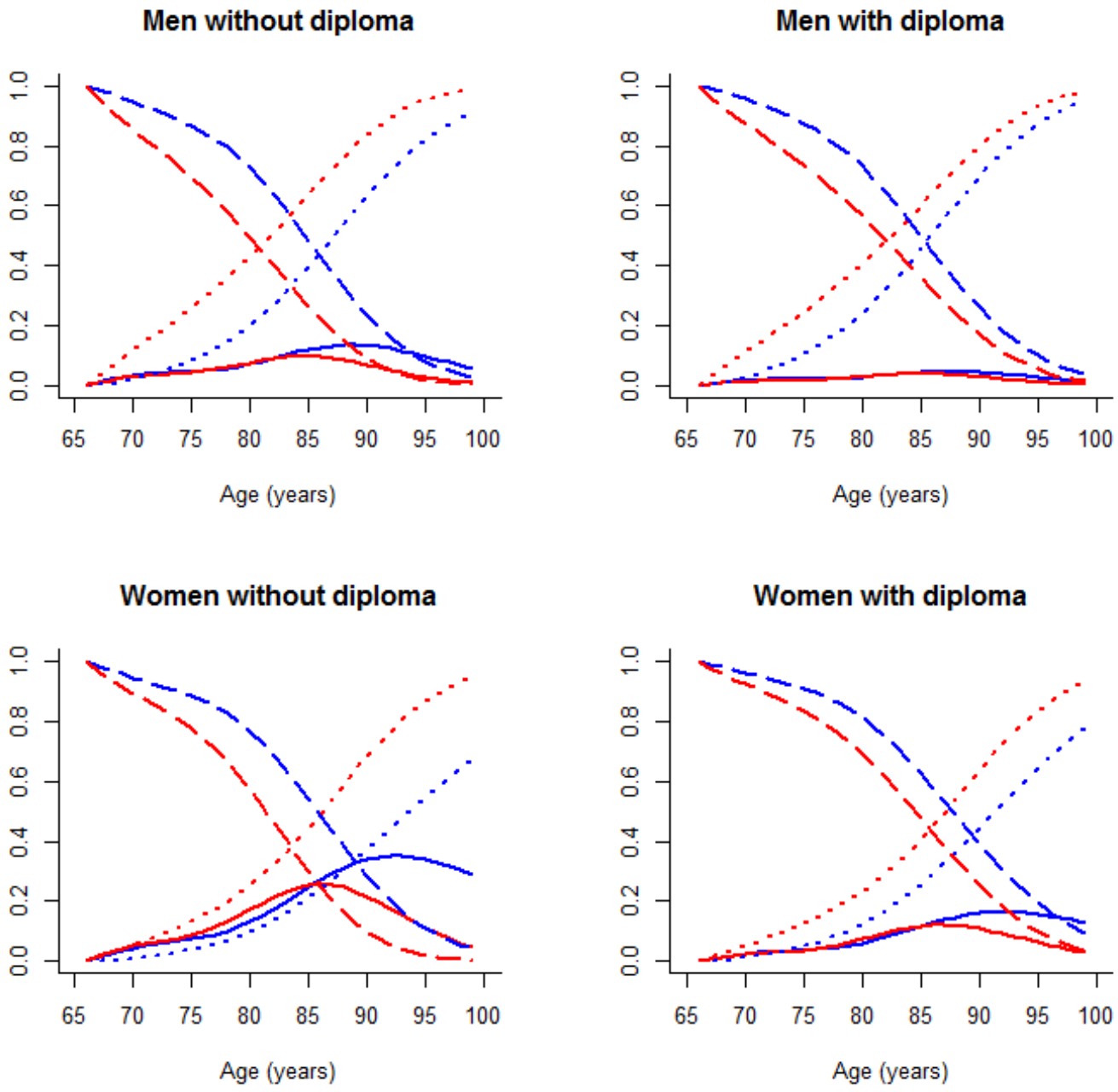

Figure 12: Probabilities of being in a given state (alive without dementia, dead, alive and demented) according to population and age, for both sex and with and without diploma. (Blue: 2000's population; red: 1990's population; continued line: alive and demented; dashed line: alive without dementia; dotted line: death)

4.4.5. Discussion

This work was motivated by the idea that, beyond the improvement of life expectancy, the quality of life of extra years gained has important implications for future medical and care requirements. Indeed, improvement of population health means more than simply delaying death or increasing life expectancy. We have evidenced that increase of total life expectancy was associated with an increase of years free of dementia but also, in a smaller extent, with an increase of years with dementia in France. Thus, the proportion of life spent healthy without dementia has tended to improve, but not clearly and not for everyone. Indeed, mortality with dementia has decreased for women and their duration of life with dementia has increased. Health expectancies have been frequently investigated but the assessment of health has been wide and trends may be highly influenced by the level of severity considered. Results in regard with expansion, compression or equilibrium of different indicators are thus mixed (229-235). However, dementia as a health indicator has been rarely investigated for trends. The decrease in dementia mortality may be linked to global improvement and advances in medicine and public health, living standards, and educational attainment. It is in itself good news even if it leads to longer survival of demented people. The major issue with dementia is that it leads to important functional impairment. However, the entire time with dementia is not spent with heavy disability. The most concerning years are the one when basic activities are impaired and an external help is needed. Indeed, these years with disability are the one bringing the highest burden for families and society. The most favourable scenario for prevention of dementia is thus to delay the onset of the disease. However, a delay in the worsening of symptoms, mostly functional ones, could also be an alternative. It would indeed conduct to a compression of life expectancy with high disability impairment but maybe also in self-perceived health.

DISCUSSION

and

CONCLUSION

5. Discussion

5.1. Principal results et consequences

During the past 30 years, dementia has been more and more highlighted as an important public health priority, on one hand because of the increase of life expectancy and the rising number of people at risk of developing the disease, and on the other hand because of the high burden related to demented people care and consequences of the disease on the patient, his family and society. Investigating secular trends of the disease, as well as the evolution of its consequences and the determinants associated seems therefore critical.

Dementia is a disease with high under-diagnosis, with only half of cases being properly diagnosed in primary care settings (14, 236). In patients with milder dementia, it is even less, with only a third of cases diagnosed (237, 238). Even with more advanced dementia, cases are still missed. Because of this under diagnosis in primary care settings, longitudinal cohort studies with active and systematic screening of dementia are critical to accurately established incidence or prevalence estimates. Some studies are still based on analysis of medical records or on healthcare administrative database. The advantage is the availability of the health outcome for everyone. They include larger populations but focus on short-term trends. The major limit is due to ascertainment bias, because of the inclusion of patients who approached medical services. Thus, differences in diagnostic practice between clinical settings cannot be fully addressed in these analyses, making interpretation of the findings challenging. Moreover, only diagnosed cases are identified and under-diagnosis could have evolved with time. Using administrative database could thus lead to wrong estimations of dementia trends. A better ascertainment and recoding of dementia in routine health records would be needed. Results based on these data are mixed with some studies reporting decreased or stable dementia prevalence or incidence (152, 153, 159, 160, 239) and others reporting increased in dementia incidence (161, 240). This emphasizes the fact that time trends should rely on population-based studies with careful assessment of dementia cases.

Our work has contributed to the growing body of evidence toward a decline of dementia risk and an improvement of global cognitive capacity for younger generations. However, because of methodological difficulties, we need to be cautious when interpreting trends results. In our work, we applied new methodologies compared to other published papers in this field to take into account some of these methodological difficulties. However, the issue regarding the

representativeness of populations compared remains unresolved. Indeed, comparison across time and studies requires comparable and unbiased sample to be generalised to the general population. Unfortunately, participation rates of the studies compared to evidence the decrease in prevalence and incidence of dementia has often differed (201). Multiple factors can influence the decision to participate or not and the characteristics of the final sample can impact estimates. A major concern is related to the nonresponse bias when reasons for study participation are associated with the factor of interest. In population-based studies, nonresponders could be individuals with more risk factors, leading thus to overestimated dementia decline (202). Drop-out during follow-up is also problematic when seeking for unbiased samples (204). Representativeness is thus a key factor to provide accurate trends and should be kept in mind when designing population-based studies.

Dementia is often associated to multiple co-morbidities due to older ages; these co-morbidities may be risk factors for the dementia pathology and/or may intervene in its diagnosis. In this context, I have also contributed to the study of the frequency of these co-morbidities associated to dementia from the 10-year follow-up of the 3C study (*Tabue-Teguo M, Grasset L, Avila-Funes JA, Genuer R, Proust-Lima C, Peres K, et al. Prevalence and Co-Occurrence of Geriatric Syndromes in People Aged 75 Years and Older in France: Results From the Bordeaux Three-city Study. J Gerontol A Biol Sci Med Sci. 2017 (Epub Ehead of Print*). Establishing a diagnosis is thus complex and more prone to clinical subjectivity than other diseases. It is sometimes difficult for general practitioners to distinguish a real degenerative pathology from the cognitive impact of sensory deficits or general illness. One of the challenges with dementia diagnosis is the lack of operational criteria to establish the diagnosis. Even if it relies on efficient test battery in more recent epidemiological studies, the degree of cognitive impairment, decline and their repercussion on the ability to perform complex tasks is left to the clinician appreciation. Ideally, additional works should be done to provide thresholds for psychometric tests above which dementia should be detected. When evaluating abilities to perform everyday life activities, the different scales available rely on patient or caregiver' statement. This subjectivity and the potential deny of symptoms by the patient and/or his caregiver can lead to an over-estimation of the patient's performances. A way to overcome this could be to use ecological activities of daily living evaluation, observing patients doing a given activity (241, 242). Such evaluations are used in some research studies or memory centres. Its implementation in primary setting is however probably more complex. Beyond clinical evaluation, the availability of biomarkers of the

pathology may modify the diagnosis. However, even if morphological imaging is recommended for the diagnosis of dementia in clinical practice, such examination is not available in every population-based cohort. Moreover, other examinations, such as cerebrospinal fluid biomarkers or imaging biomarkers are done only in specialised memory consults or in the research context. An important research focus has been made lately on early stage of dementia with better characterization of the prodromal phase. Performance to the neuropsychometric tests are not affected at the same stage in the course of the disease: some are declining early whereas others are affected in the late stages.

Indeed, in this work, we have confirmed that the clinical diagnosis has evolved over time in France and it is likely that the evolution also occurred in other countries. With substantial societal and clinical shifts in dementia awareness worldwide and among the scientific community, dementia now tends to be diagnosed earlier. The DSM criteria have changed across different updated versions. The availability of more subtle cognitive tests can also lead to earlier diagnosis. We thus evidenced that a more stable diagnostic approach is needed to provide accurate incidence and prevalence trends. Additionally, prevalence estimates have been shown to vary widely depending on diagnostic classification system used (243). As evidenced in introduction, the trends in dementia are varying across countries. In several Asian studies, an increase of dementia incidence or prevalence has often been reported, unlike American and European results. It is important to know that there has been a high improvement of basic living conditions and health of population in East Asian countries over the last hundred years. However, it has been hypothesized that methodological changes, such as diagnosis drift, could be an explanation for this increase. Indeed, there is major heterogeneity between studies and diagnostic criteria often differ (244). Training of clinicians, knowledge and attitudes to dementia in professionals has also changed over decades and affect diagnostic standards and measurement methods. Evolution of stigma of mental illness and dementia can also have impacted dementia trends. A systematic review adjusting for diagnostic criteria and age structure showed no significant variations in prevalence in China (245). Such analyses applying stable criteria such as algorithmic approach should be realized to confirm if the increase is real or linked to methodology in these populations.

The decrease in dementia incidence brings questions about healthy aging. Individuals are now living longer than the previous generations, as supported by our work on life expectancy. However, living longer is not enough anymore and quality matters as much as quantity. Indeed, unhealthy years of life are considered as high burden for individuals and society. The

main goal with life expectancy relies on the compression of morbidity, with a decrease of the time with a disease or with disability. Delaying dementia onset should lead to a decrease in time spent with dementia and thus reduce its burden. Delaying dementia symptoms and particularly the ones leading to high dependency is also an alternative. Prevention approach are thus of high interest, not only for dementia, but also for other disabling health conditions. Moreover, it appears that important inequalities in health expectancy are present among countries (246, 247) and effort to reduce inequalities should be made in the future.

The decrease in dementia prevalence and incidence was not planned and could bring a better understanding of the disease. In published studies, the decrease of dementia syndrome, and not specifically of the different aetiologies of dementia, has been investigated. However, when comparing the distribution of prevalent dementia cases at the 10-year follow-up of 3C, it is equivalent to the distribution of dementia causes from the 10-year follow-up of PAQUID (10 years apart), with a decrease of prevalence around 25% (unpublished results). This is in line with a similar decline in the different causes of dementia (AD, mixed dementia, vascular dementia or other dementias). We could hypothesise that the factors involved in this decrease, whatever they are – education, vascular, social, healthy lifestyle, improvement of care, ... – do not have an impact on the specific Alzheimer's disease pathology but a more global impact on brain, allowing to prevent the different aetiologies of dementia. Thus, these factors could together prevent an early stage of the demented process, the cerebral aging, varying from an individual to another of the same age. This cerebral aging could be considered as an at-risk stage for future development of brain pathologies, Alzheimer's disease or others. Considering this stage of cerebral aging and the impact of risk factors on it could help better understanding the development of the pathologies and the factors involved in the different stages, all along the processes.

5.2. Public health perspectives

Unfortunately, despite important research effort, no real progress has been made in the curative treatment of dementia for approximately twenty years. Indeed, several promising new agents have recently failed in Phase III clinical trials (248-251). Currently available medications for dementia and AD have relatively small effect sizes and do not clearly alter disease progression. Hopefully, the decrease in incidence and prevalence of dementia is in

favour of possible successful prevention strategies. Dementia being generally considered as a fatality in older ages, it gives promising perspective. It is therefore important to better understand the determinants explaining this decrease, in order to extend and reinforce preventive strategies. Observational studies have identified a wide range of potentially modifiable risk factors for AD and dementia, including cardiovascular risk factors, psychosocial factors and health behaviours. Some could be already involved in the decrease; others could be easy target for future prevention.

To date, only few studies have investigated the determinants of the decrease in dementia incidence or prevalence (138, 150, 155). The ones studied were mostly education and vascular factors. Despite inconclusive results in these studies as well as in ours, strong hypotheses can be assumed to explain this trend. Indeed, the prevalence of some of the risk factors highlighted in introduction has also evolved. As highlighted in several of the trends studies, educational level has highly improved between generations born in the early 1900. Worldwide, the proportion of the population without diploma also decreased from 47.2% in 1950 to 30.6% in 1980. Educational level is still improving, particularly in developing countries with a proportion of population without diploma of 30.5% in 1990 and of 17.4% in 2010 (252). This improvement has been even greater for women than for men with a gender ratio that reaches 100% in advanced countries. Leading to an increase in cognitive reserve, this is a major factor supporting the decrease in dementia incidence and in favour of a continuing decrease. Another improvement is the decrease in high blood pressure. Age-standardised prevalence of raised blood pressure has decreased globally from 1975 to 2015, from 29.5% (95% CI 24.2–35.0) to 24.1% (21.4–27.1) in men and from 26.1% (21.7–31.1) to 20.1% (17.8–22.5) in women (253). Related to hypertension, a decrease in stroke incidence has also been evidenced (254, 255). There has been strong improvement in care and management of cardiovascular risk factors, mostly with availability of treatments against hypertension (256, 257). Dementia being highly related to vascular health, it could have played a role in incidence decrease. Although these factors are not really explaining the declining trend, others could have played a role in the decrease (258). First, cognitive stimulations such as social activities or games have been evidenced as a protective factor of dementia and cognitive decline by enhancing cognitive reserve (224, 259, 260). A positive result showed that starting leisure and social activities lower the risk of dementia and individuals becoming inactive had a higher risk of dementia than individuals who remained active (261). An increase of cognitive activities over time could explain the observed

decrease. Healthy diet is also associated with dementia and healthy lifestyles such as diet have improved, potentially playing a role in the decrease of incidence. Then, even if sedentary habits may have increased, physical activities can be an interesting factor for future prevention. Finally, other less studied factors could have also been involved. Some studies have shown a link between infections and dementia (262). Indeed, reactivation of Herpes infection has been shown to increase the risk of dementia (115). A lower exposition to infections, herpes or others, together with other factors, could have contributed to the decreasing trend in dementia incidence. A reduction of these infectious diseases could be related to the improvement of global health behaviours across the 19th century with major progress in comfort, hygiene, healthcare, well-being or even mobility. These factors conducted to an improvement of global aging by promoting a safe environment (263). In addition, global health of the populations has become a major public health goal in most countries. A lot of programs aiming at reducing diseases prevalence and improving quality of life have been conducted by governments. Healthy aging has thus been a priority of the last decades (264). Even if these factors have not been assessed to explain the trends, their improvement could have been a part of the improvement of dementia risk over time. Improvement of lifestyle factors has already conducted to the decrease of other chronic conditions. For instance, the improvement of dietary habits (consumption of fresh food) and of food preservation with refrigerator has led to a decrease in risk of stomach cancer.

However, the increase of some other conditions is worrying and could reverse the trend of declining incidence of dementia. Even if hypertension has decreased, its prevalence remains high and work is still needed to control the problem (265). Indeed, studies have shown that only half of adults with hypertension have their blood pressure controlled (266). Diabetes and obesity have also worsened. First, a pooled study evidenced that global age-standardised diabetes prevalence has increased from 4.3% (2.4–7.0) in 1980 to 9.0% (7.2–11.1) in 2014 in men, and from 5.0% (2.9–7.9) to 7.9% (6.4–9.7) in women worldwide (267). Another pooled study reported that the global prevalence of diabetes mellitus in the year 2010 was 6.4% (285 million adults), and this was projected to increase to 7.7% (439 million adults) by 2030 (268). Then, mean BMI has also increased from 21.7 kg/m² (21.3-22.1) in 1975 to 24.2 (24.0-24.4) in 2014 in men and from 22.1 (21.7-22.5) to 24.4 (24.2-24.6) in women (269). This latter study also reported that prevalence of obesity increased from 3.2% (2.4-4.1) in 1975 to 10.8% (9.7-12.0) in 2014 in men and from 6.4% (5.1-7.8) to 14.9% (13.6-16.1) in women. The

global targets were established to halt the rise in the prevalence of diabetes and obesity by 2025. However, this objective seems unlikely to be attained and if post-2000 trends continue, severe obesity will surpass underweight in women (267, 269). Furthermore, wide differences are evidenced between countries. Indeed, the rise for diabetes and adiposity for instance is larger in low or middle-income countries (LMIC) than in high-income countries (HIC). These populations have lower access to care with worse primary care system and the management of diseases is not optimal. Non-communicable diseases became a high contributor to the burden of disease in these populations (270, 271), and as shown in introduction, they are expected to face a high increase of the older individuals. With a growing importance in some risk factors, individuals from LMIC could become at higher risk of developing dementia in the future decades, with a high number of cases. These countries are indeed also less prone to establish prevention strategies and the lack of resources prevents from supporting lifestyle changes or improving access to and adherence to medication. Mental and neurological disorders are often a low priority compared to infectious diseases in these countries. Strengthening health systems seems a priority to tackle non-communicable diseases in LMIC because health infrastructures and resources are often lacking (271). Moreover, research in low and middle-income countries should be developed to better understand the different social and environmental contexts. Health and social inequalities are thus a major concern, for low- and middle-income countries (272, 273), but also for populations in precarious situations within high income countries. Indeed, it has been shown that individuals with low socioeconomic status have poorer health and present more diseases (274-280). Furthermore, an association between precariousness and increased risk of dementia or greater cognitive decline has been evidenced (281). However, socio-economic inequalities in health have increased (282, 283) and substantial inequalities in healthy life years exist within EU countries (246). Moreover, health inequalities persist among the elderly (284). With widening inequalities in socio-economic status, more individuals in precarious condition are exposed to increased risk of disease and non-optimal health management. Even though important progress for health has been made, efforts should be maintained to reduce prevalence of diabetes and obesity and health inequalities (285).

Up to now however, even with results found from observational studies, evidence for a significant positive impact of interventions targeting dementia risk factors has been mixed (22, 286-290). The first trial of antihypertensive treatment for elderly people with isolated systolic hypertension (Syst-Eur trial) showed that the treatment was associated with lower

dementia incidence (291). However, a meta-analysis examining effect of hypertension treatment found no significant difference between treatment versus placebo groups, even if cognitive decline of the MMSE was lower (292, 293). Results from the Hypertension in the Very Elderly Trial (HYVET) also failed to show an improvement in dementia incidence (292). A systematic review of randomised control trial have reported that physical activity is beneficial for cognitive function in healthy older adults (294), whereas a more recent one could not evidence this improvement (295). For cognitive training, several randomised control trials have evidenced an improvement in cognitive function for cognitive intervention groups (296-299).

Dementia being a multi-factorial disease, targeting only one risk factor could not be enough to improve dementia risk or cognitive decline. Recently, some multidomain intervention trials have been conducted such as The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) study or the Multidomain Alzheimer Preventive Trial (MAPT) study. The Finger trial was a 2 year population-based multidomain randomised controlled trial done in six centres in Finland with at-risk participants aged 60 to 77 (300). The intervention consisted in nutritional counselling, physical exercise training, cognitive training, and vascular and metabolic risk factor management. They reported a significant improvement in a neuropsychological test battery, in executive functioning and processing speed but not in memory over 24 months. The MAPT trial was a 3-year randomised, placebo-controlled superiority trial with four parallel groups at 13 memory centres in France and Monaco of frail participants aged 70 years or older (301). The intervention consisted in nutritional counselling, physical exercise and cognitive training, associated or not with omega-3 supplementation. However, no differences between the placebo and the intervention groups were significant on cognitive decline. In a post-hoc analysis in which all participants who received multidomain intervention were pooled, cognitive decline was significantly improved compared to groups without the intervention.

Designing such trials bring several questions. According to a report of the National Academies of Sciences, Engineering, and Medicine on prevention of cognitive decline and dementia, the prevention research should identify individuals who are at higher risk of cognitive decline and dementia; increase participation of under-represented populations; begin more interventions at younger ages and have longer follow-up periods; use consistent cognitive outcome measures across trials to enable pooling; integrate robust cognitive outcome measures into trials with other primary purposes; include biomarkers as intermediate

outcomes; and conduct large trials designed to test the effectiveness of an intervention in broad, routine clinical practices or community settings (302). An important point is that the outcome should be chosen carefully. Investigating the risk of dementia requires longer follow-up, thus intermediate endpoint are often selected. Some cognitive tests are more prone to changes than others and; according to the test, performances are not decreasing at the same stage of the disease process. Then, the time window for action is crucial and population receiving interventions need to be selected carefully. Given that neurodegeneration may precede the onset of dementia by several decades, impact of risk factors reduction must be evaluated early enough to have impacted neurodegeneration or cerebrovascular processes. Moreover, for many factors, midlife status is associated with dementia in later life. Thus, different risk factors probably act at different times through the lifespan and at different stages and processes of the disease, the result being the development of cognitive decline and dementia status. Thus, efficient intervention needs to target the population before onset of clinical symptoms. A better understanding of the accurate time window for risk factors impact needs further researches. However, following individuals for 10 or 20 years is costly and difficultly doable. All these difficulties could prevent intervention to evidence a real benefit of the prevention of the risk factors. A growing amount of argument has yet been issued from observational studies. All these arguments, both from observational studies regarding risk factors and from current decreasing trends of dementia frequency seem sufficient to reinforce prevention without waiting for more proof from interventional studies, which design could be not the most appropriate. However, monitoring and assessment of the impact of prevention requires important human and financial support, which is crucial. An important point to keep in mind with prevention strategies is mortality. Indeed, if the factor targeted is also related to death, its prevention will lead to a decrease in mortality and thus only little changes will appear in the number of dementia cases (303). To really lower dementia prevalence, intervention should target a risk factor that is not associated with death in demented subjects, or more strongly associated with dementia than with death or when the intervention reduced only the risk of dementia.

6. Conclusion

The high global prevalence, the economic impact of dementia on families, caregivers and communities, and the associated stigma and social exclusion present a significant public health challenge. Globally, when measured in terms of morbidity and mortality, our findings support an improvement of health of older people during the last two decades. This work also highlights the need for appropriate methodology when studying an aging-related disease. Even if several studies have reported a decrease in prevalence and incidence, secular trends of dementia need further investigation. Indeed, important differences across countries have been reported and whether this decline will last is unsure. In addition, previous findings on temporal trends failed at identifying the factors explaining this decrease. Understanding the evolution and the modifiable, protective risk factors associated is yet critical. The growing body of evidence toward a decline in dementia incidence and prevalence brings hope regarding the projections of number of dementia cases in the future. Whereas dementia was once considered a fatality, it suggests that this disease is not an inevitable consequence of ageing and can be manageable. As long as efficient therapeutic treatment is lacking, research focusing on risk factors and interventions in order to prevent or even delay the onset of the disease should be a priority. Even if some studies failed to evidence a real efficacy of intervention trials targeting identified risk factors, the idea of prevention should not be withdrawn. Indeed, the hypotheses behind vascular and lifestyle factors are consistent and observational studies also provide strong evidences. Moreover, promoting healthy heart and brain lifestyles could not harm individuals, and healthy behaviours toward the entire lifespan can only help healthy aging. Thus, the benefit/risk balance appears in favour of the development of prevention. However, the implementation of preventive strategies implies to evaluate the efficacy of these strategies, requiring population-based cohorts with long follow-up and active diagnosis of dementia cases to document the trends in dementia frequency. Conducting such cohorts involving human participants is extremely complex and expensive. Funding for these studies is clearly lacking in France and in Europe. Yet it is crucial to progress in dementia research.

In summary, this thesis work has evidenced promising perspectives for the future elderly people. Further efforts will be needed to confirm and lengthen these positive trends.

Multidisciplinary research should be encouraged to apprehend the complexity of dementia in an ageing population.

7. References

1. World Health Organisation. Life expectancy. Available from: http://www.who.int/gho/mortality_burden_disease/life_tables/situation_trends_text/en/. (Accessed July 11, 2017)
2. Mathers CD, Stevens GA, Boerma T, White RA, Tobias MI. Causes of international increases in older age life expectancy. Lancet. 2015;385(9967):540-8.
3. Insee. (2016). Tableaux de l'économie françaiseInsee. 978-2-11-138704-1
4. Kontis V, Bennett JE, Mathers CD, Li G, Foreman K, Ezzati M. Future life expectancy in 35 industrialised countries: projections with a Bayesian model ensemble. Lancet. 2017;389(10076):1323-35.
5. Blanchet D, Le Gallo F. Baby-boom et allongement de la durée de vie : quelles contributions au vieillissement ? : Insee, 2013. Available from: https://www.insee.fr/fr/statistiques/1521327. (Accessed May 27, 2017)
6. Alzheimer's Disease International. World Alzheimer Report: The Global Impact of Dementia. London. 2015. Available from: http://www.alz.co.uk/research/WorldAlzheimerReport2015.pdf. (Accessed Apr 22, 2016)
7. OCDE. (2013). Panorama de la santé 2013 : Les indicateurs de l'OCDE. OCDE,. 9789264205031
8. Blanpain N, Chardon O. Projection de population à l'horizon 2060. 2010. Available from: https://www.insee.fr/fr/statistiques/1281151. (Accessed May 29, 2017)
9. Prince MJ, Wu F, Guo Y, Gutierrez Robledo LM, O'Donnell M, Sullivan R, et al. The burden of disease in older people and implications for health policy and practice. Lancet. 2015;385(9967):549-62.
10. Helmer C, Peres K, Letenneur L, Guttierez-Robledo LM, Ramaroson H, Barberger-Gateau P, et al. Dementia in subjects aged 75 years or over within the PAQUID cohort: prevalence and burden by severity. Dement Geriatr Cogn Disord. 2006;22(1):87-94.
11. World Health Organisation, Alzheimer's Disease International. Dementia: A public health priority. Geneva. World Health Organization, 2012. Report No.: 978 92 4 156445 8 Available from: http://www.who.int/mental_health/publications/dementia_report_2012/en/. (Accessed May 29, 2017)
12. Schulz R, Beach SR. Caregiving as a risk factor for mortality: the Caregiver Health Effects Study. JAMA. 1999;282(23):2215-9.
13. Schulz R, O'Brien AT, Bookwala J, Fleissner K. Psychiatric and physical morbidity effects of dementia caregiving: prevalence, correlates, and causes. The Gerontologist. 1995;35(6):771-91.
14. Helmer C, Pérès K, Pariente A, Pasquier F, Auriacombe S, Poncet M, et al. Primary and secondary care consultations in elderly demented individuals in France. Results from the Three-City Study. Dement Geriatr Cogn Disord. 2008;26(5):407-15.
15. Pimouguet C, Delva F, Le Goff M, Stern Y, Pasquier F, Berr C, et al. Survival and early recourse to care for dementia: A population based study. Alzheimers Dement. 2015;11(4):385-93.
16. Petersen RC. Mild cognitive impairment as a diagnostic entity. J Intern Med. 2004;256(3):183-94.
17. Langa KM, Foster NL, Larson EB. Mixed dementia: emerging concepts and therapeutic implications. JAMA. 2004;292(23):2901-8.
18. Bennett DA. Mixed pathologies and neural reserve: Implications of complexity for Alzheimer disease drug discovery. PLoS medicine. 2017;14(3):e1002256.
19. Mura T, Dartigues JF, Berr C. How many dementia cases in France and Europe? Alternative projections and scenarios 2010-2050. European journal of neurology. 2010;17(2):252-9.
20. Fratiglioni L, Launer LJ, Andersen K, Breteler MM, Copeland JR, Dartigues JF, et al. Incidence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology. 2000;54(11 Suppl 5):S10-5.

21. Gallez C. (2005). Rapport sur la maladie d'Alzheimer et les maladies apparentées.Assemblée nationale/Sénat. Paris.
22. Alzheimer's Disease Anti-inflammatory Prevention Trial Research G. Results of a follow-up study to the randomized Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT). Alzheimers Dement. 2013;9(6):714-23.
23. Luppa M, Luck T, Weyerer S, Konig HH, Brahler E, Riedel-Heller SG. Prediction of institutionalization in the elderly. A systematic review. Age Ageing. 2010;39(1):31-8.
24. Hajek A, Brettschneider C, Lange C, Posselt T, Wiese B, Steinmann S, et al. Longitudinal Predictors of Institutionalization in Old Age. PloS one. 2015;10(12):e0144203.
25. Fratiglioni L, Forsell Y, Aguero Torres H, Winblad B. Severity of dementia and institutionalization in the elderly: prevalence data from an urban area in Sweden. Neuroepidemiology. 1994;13(3):79-88.
26. Luppa M, Luck T, Brahler E, Konig HH, Riedel-Heller SG. Prediction of institutionalisation in dementia. A systematic review. Dement Geriatr Cogn Disord. 2008;26(1):65-78.
27. Luck T, Luppa M, Weber S, Matschinger H, Glaesmer H, Konig HH, et al. Time until institutionalization in incident dementia cases--results of the Leipzig Longitudinal Study of the Aged (LEILA 75+). Neuroepidemiology. 2008;31(2):100-8.
28. Wimo A, Guerchet M, Ali GC, Wu YT, Prina AM, Winblad B, et al. The worldwide costs of dementia 2015 and comparisons with 2010. Alzheimers Dement. 2017;13(1):1-7.
29. Aguero-Torres H, Fratiglioni L, Guo Z, Viitanen M, Winblad B. Mortality from dementia in advanced age: a 5-year follow-up study of incident dementia cases. Journal of clinical epidemiology. 1999;52(8):737-43.
30. Helmer C, Joly P, Letenneur L, Commenges D, Dartigues JF. Mortality with dementia: results from a French prospective community-based cohort. Am J Epidemiol. 2001;154(7):642-8.
31. Jagger C, Andersen K, Breteler MM, Copeland JR, Helmer C, Baldereschi M, et al. Prognosis with dementia in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology. 2000;54(11 Suppl 5):S16-20.
32. Wolfson C, Wolfson DB, Asgharian M, M'Lan CE, Ostbye T, Rockwood K, et al. A reevaluation of the duration of survival after the onset of dementia. N Engl J Med. 2001;344(15):1111-6.
33. Larson EB, Shadlen MF, Wang L, McCormick WC, Bowen JD, Teri L, et al. Survival after initial diagnosis of Alzheimer disease. Annals of internal medicine. 2004;140(7):501-9.
34. Todd S, Barr S, Roberts M, Passmore AP. Survival in dementia and predictors of mortality: a review. International journal of geriatric psychiatry. 2013;28(11):1109-24.
35. Fitzpatrick AL, Kuller LH, Lopez OL, Kawas CH, Jagust W. Survival following dementia onset: Alzheimer's disease and vascular dementia. Journal of the neurological sciences. 2005;229-230:43-9.
36. Ritchie K, Mathers C, Jorm A. Dementia-free life expectancy in Australia. Australian journal of public health. 1994;18(2):149-52.
37. Ritchie K, Robine JM, Letenneur L, Dartigues JF. Dementia-free life expectancy in France. Am J Public Health. 1994;84(2):232-6.
38. Sauvaget C, Tsuji I, Minami Y, Fukao A, Hisamichi S, Asano H, et al. Dementia-free life expectancy among elderly Japanese. Gerontology. 1997;43(3):168-75.
39. Tom SE, Hubbard RA, Crane PK, Haneuse SJ, Bowen J, McCormick WC, et al. Characterization of dementia and Alzheimer's disease in an older population: updated incidence and life expectancy with and without dementia. Am J Public Health. 2015;105(2):408-13.
40. Rizzuto D, Orsini N, Qiu C, Wang HX, Fratiglioni L. Lifestyle, social factors, and survival after age 75: population based study. Bmj. 2012;345:e5568.
41. Brodaty H, Seeher K, Gibson L. Dementia time to death: a systematic literature review on survival time and years of life lost in people with dementia. International psychogeriatrics / IPA. 2012;24(7):1034-45.
42. Winblad B, Amouyel P, Andrieu S, Ballard C, Brayne C, Brodaty H, et al. Defeating Alzheimer's disease and other dementias: a priority for European science and society. Lancet Neurol. 2016;15(5):455-532.

43. Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, et al. Global prevalence of dementia: a Delphi consensus study. Lancet. 2005;366(9503):2112-7.
44. Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. Neurology. 2013;80(19):1778-83.
45. Matthews FE, Stephan BC, Robinson L, Jagger C, Barnes LE, Arthur A, et al. A two decade dementia incidence comparison from the Cognitive Function and Ageing Studies I and II. Nature communications. 2016;7:11398.
46. Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, Salvesen GS, et al. Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. Proceedings of the National Academy of Sciences of the United States of America. 1993;90(5):1977-81.
47. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science (New York, NY). 1993;261(5123):921-3.
48. Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA. 1997;278(16):1349-56.
49. Chartier-Harlin MC, Parfitt M, Legrain S, Perez-Tur J, Brousseau T, Evans A, et al. Apolipoprotein E, epsilon 4 allele as a major risk factor for sporadic early and late-onset forms of Alzheimer's disease: analysis of the 19q13.2 chromosomal region. Human molecular genetics. 1994;3(4):569-74.
50. Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E. Alzheimer's disease. Lancet. 2011;377(9770):1019-31.
51. Lambert JC, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R, Bellenguez C, et al. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nature genetics. 2013;45(12):1452-8.
52. Hardy J, Myers A, Wavrant-De Vrieze F. Problems and solutions in the genetic analysis of late-onset Alzheimer's disease. Neuro-degenerative diseases. 2004;1(4-5):213-7.
53. Stern Y, Gurland B, Tatemichi TK, Tang MX, Wilder D, Mayeux R. Influence of education and occupation on the incidence of Alzheimer's disease. JAMA. 1994;271(13):1004-10.
54. Letenneur L, Gilleron V, Commenges D, Helmer C, Orgogozo JM, Dartigues JF. Are sex and educational level independent predictors of dementia and Alzheimer's disease? Incidence data from the PAQUID project. Journal of neurology, neurosurgery, and psychiatry. 1999;66(2):177-83.
55. Members ECC, Brayne C, Ince PG, Keage HAD, McKeith IG, Matthews FE, et al. Education, the brain and dementia: neuroprotection or compensation? Brain. 2010;133(Pt 8):2210-6.
56. Meng X, D'Arcy C. Education and dementia in the context of the cognitive reserve hypothesis: a systematic review with meta-analyses and qualitative analyses. PloS one. 2012;7(6):e38268.
57. Dartigues JF, Gagnon M, Letenneur L, Barberger-Gateau P, Commenges D, Evaldre M, et al. Principal lifetime occupation and cognitive impairment in a French elderly cohort (Paquid). Am J Epidemiol. 1992;135(9):981-8.
58. Foubert-Samier A, Catheline G, Amieva H, Dilharreguy B, Helmer C, Allard M, et al. Education, occupation, leisure activities, and brain reserve: a population-based study. Neurobiology of aging. 2012;33(2):423 e15-25.
59. Yates LA, Ziser S, Spector A, Orrell M. Cognitive leisure activities and future risk of cognitive impairment and dementia: systematic review and meta-analysis. International psychogeriatrics / IPA. 2016;28(11):1791-806.
60. Stern Y. What is cognitive reserve? Theory and research application of the reserve concept. J Int Neuropsychol Soc. 2002;8(3):448-60.
61. Valenzuela MJ. Brain reserve and the prevention of dementia. Current opinion in psychiatry. 2008;21(3):296-302.

62. Kloppenborg RP, van den Berg E, Kappelle LJ, Biessels GJ. Diabetes and other vascular risk factors for dementia: which factor matters most? A systematic review. European journal of pharmacology. 2008;585(1):97-108.
63. Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurol. 2011;10(9):819-28.
64. Hofman A, Ott A, Breteler MM, Bots ML, Slooter AJ, van Harskamp F, et al. Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study. Lancet. 1997;349(9046):151-4.
65. Launer LJ, Ross GW, Petrovitch H, Masaki K, Foley D, White LR, et al. Midlife blood pressure and dementia: the Honolulu-Asia aging study. Neurobiology of aging. 2000;21(1):49-55.
66. Kivipelto M, Helkala EL, Laakso MP, Hanninen T, Hallikainen M, Alhainen K, et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. Bmj. 2001;322(7300):1447-51.
67. Kivipelto M, Helkala EL, Hanninen T, Laakso MP, Hallikainen M, Alhainen K, et al. Midlife vascular risk factors and late-life mild cognitive impairment: A population-based study. Neurology. 2001;56(12):1683-9.
68. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. Lancet Neurol. 2005;4(8):487-99.
69. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology. 2005;64(2):277-81.
70. Kennelly SP, Lawlor BA, Kenny RA. Blood pressure and dementia - a comprehensive review. Ther Adv Neurol Disord. 2009;2(4):241-60.
71. van den Berg E, Kloppenborg RP, Kessels RP, Kappelle LJ, Biessels GJ. Type 2 diabetes mellitus, hypertension, dyslipidemia and obesity: A systematic comparison of their impact on cognition. Biochimica et biophysica acta. 2009;1792(5):470-81.
72. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med. 2003;348(13):1215-22.
73. Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. JAMA. 1997;277(10):813-7.
74. Kivipelto M, Helkala EL, Laakso MP, Hanninen T, Hallikainen M, Alhainen K, et al. Apolipoprotein E epsilon4 allele, elevated midlife total cholesterol level, and high midlife systolic blood pressure are independent risk factors for late-life Alzheimer disease. Annals of internal medicine. 2002;137(3):149-55.
75. Kivipelto M, Solomon A. Cholesterol as a risk factor for Alzheimer's disease - epidemiological evidence. Acta Neurol Scand Suppl. 2006;185:50-7.
76. Anstey KJ, Lipnicki DM, Low LF. Cholesterol as a risk factor for dementia and cognitive decline: a systematic review of prospective studies with meta-analysis. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry. 2008;16(5):343-54.
77. Reitz C, Tang MX, Luchsinger J, Mayeux R. Relation of plasma lipids to Alzheimer disease and vascular dementia. Arch Neurol. 2004;61(5):705-14.
78. Mielke MM, Zandi PP, Sjogren M, Gustafson D, Ostling S, Steen B, et al. High total cholesterol levels in late life associated with a reduced risk of dementia. Neurology. 2005;64(10):1689-95.
79. Stewart R, White LR, Xue QL, Launer LJ. Twenty-six-year change in total cholesterol levels and incident dementia: the Honolulu-Asia Aging Study. Arch Neurol. 2007;64(1):103-7.
80. Lu FP, Lin KP, Kuo HK. Diabetes and the risk of multi-system aging phenotypes: a systematic review and meta-analysis. PloS one. 2009;4(1):e4144.
81. Profenno LA, Porsteinsson AP, Faraone SV. Meta-analysis of Alzheimer's disease risk with obesity, diabetes, and related disorders. Biological psychiatry. 2010;67(6):505-12.
82. Cheng G, Huang C, Deng H, Wang H. Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. Internal medicine journal. 2012;42(5):484-91.

83. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. Lancet Neurol. 2006;5(1):64-74.
84. Yaffe K, Blackwell T, Kanaya AM, Davidowitz N, Barrett-Connor E, Krueger K. Diabetes, impaired fasting glucose, and development of cognitive impairment in older women. Neurology. 2004;63(4):658-63.
85. Beydoun MA, Beydoun HA, Wang Y. Obesity and central obesity as risk factors for incident dementia and its subtypes: a systematic review and meta-analysis. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2008;9(3):204-18.
86. Emmerzaal TL, Kiliaan AJ, Gustafson DR. 2003-2013: a decade of body mass index, Alzheimer's disease, and dementia. Journal of Alzheimer's disease : JAD. 2015;43(3):739-55.
87. Loef M, Walach H. Midlife obesity and dementia: meta-analysis and adjusted forecast of dementia prevalence in the United States and China. Obesity (Silver Spring, Md). 2013;21(1):E51-5.
88. Fitzpatrick AL, Kuller LH, Lopez OL, Diehr P, O'Meara ES, Longstreth WT, Jr., et al. Midlife and late-life obesity and the risk of dementia: cardiovascular health study. Arch Neurol. 2009;66(3):336-42.
89. Luchsinger JA, Gustafson DR. Adiposity and Alzheimer's disease. Current opinion in clinical nutrition and metabolic care. 2009;12(1):15-21.
90. Yaffe K, Kanaya A, Lindquist K, Simonsick EM, Harris T, Shorr RI, et al. The metabolic syndrome, inflammation, and risk of cognitive decline. JAMA. 2004;292(18):2237-42.
91. Barnes DE, Haight TJ, Mehta KM, Carlson MC, Kuller LH, Tager IB. Secondhand smoke, vascular disease, and dementia incidence: findings from the cardiovascular health cognition study. Am J Epidemiol. 2010;171(3):292-302.
92. Chen R, Hu Z, Zhang D, Ma Y, Wei L. Second-hand smoke and dementia. Epidemiology. 2013;24(4):623-4.
93. Anstey KJ, von Sanden C, Salim A, O'Kearney R. Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies. Am J Epidemiol. 2007;166(4):367-78.
94. Swan GE, Lessov-Schlaggar CN. The effects of tobacco smoke and nicotine on cognition and the brain. Neuropsychology review. 2007;17(3):259-73.
95. Rolland Y, Abellan van Kan G, Vellas B. Physical activity and Alzheimer's disease: from prevention to therapeutic perspectives. Journal of the American Medical Directors Association. 2008;9(6):390-405.
96. Hamer M, Chida Y. Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence. Psychological medicine. 2009;39(1):3-11.
97. de Bruijn RF, Schrijvers EM, de Groot KA, Witteman JC, Hofman A, Franco OH, et al. The association between physical activity and dementia in an elderly population: the Rotterdam Study. European journal of epidemiology. 2013;28(3):277-83.
98. Blondell SJ, Hammersley-Mather R, Veerman JL. Does physical activity prevent cognitive decline and dementia?: A systematic review and meta-analysis of longitudinal studies. BMC public health. 2014;14:510.
99. Grasset L, Joly P, Jacqmin-Gadda H, Letenneur L, Wittwer J, Amieva H, et al. Real benefit of a protective factor against dementia: Importance of controlling for death. Example of sport practice. PloS one. 2017;12(4):e0174950.
100. Samieri C, Grodstein F, Rosner BA, Kang JH, Cook NR, Manson JE, et al. Mediterranean diet and cognitive function in older age. Epidemiology. 2013;24(4):490-9.
101. Morris MC, Tangney CC, Wang Y, Sacks FM, Barnes LL, Bennett DA, et al. MIND diet slows cognitive decline with aging. Alzheimers Dement. 2015;11(9):1015-22.
102. Morris MC, Tangney CC, Wang Y, Sacks FM, Bennett DA, Aggarwal NT. MIND diet associated with reduced incidence of Alzheimer's disease. Alzheimers Dement. 2015;11(9):1007-14.
103. Scarmeas N, Stern Y, Mayeux R, Luchsinger JA. Mediterranean diet, Alzheimer disease, and vascular mediation. Arch Neurol. 2006;63(12):1709-17.
104. Scarmeas N, Stern Y, Tang MX, Mayeux R, Luchsinger JA. Mediterranean diet and risk for Alzheimer's disease. Annals of neurology. 2006;59(6):912-21.

105. Sofi F, Abbate R, Gensini GF, Casini A. Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis. The American journal of clinical nutrition. 2010;92(5):1189-96.
106. Dufouil C, Fuhrer R, Dartigues JF, Alperovitch A. Longitudinal analysis of the association between depressive symptomatology and cognitive deterioration. Am J Epidemiol. 1996;144(7):634-41.
107. Chen P, Ganguli M, Mulsant BH, DeKosky ST. The temporal relationship between depressive symptoms and dementia: a community-based prospective study. Archives of general psychiatry. 1999;56(3):261-6.
108. Heun R, Kockler M, Ptok U. Depression in Alzheimer's disease: is there a temporal relationship between the onset of depression and the onset of dementia? European psychiatry : the journal of the Association of European Psychiatrists. 2002;17(5):254-8.
109. Ganguli M, Du Y, Dodge HH, Ratcliff GG, Chang CC. Depressive symptoms and cognitive decline in late life: a prospective epidemiological study. Archives of general psychiatry. 2006;63(2):153-60.
110. Wilson RS, Hoganson GM, Rajan KB, Barnes LL, Mendes de Leon CF, Evans DA. Temporal course of depressive symptoms during the development of Alzheimer disease. Neurology. 2010;75(1):21-6.
111. Wilson RS, Barnes LL, Mendes de Leon CF, Aggarwal NT, Schneider JS, Bach J, et al. Depressive symptoms, cognitive decline, and risk of AD in older persons. Neurology. 2002;59(3):364-70.
112. Barnes DE, Yaffe K, Byers AL, McCormick M, Schaefer C, Whitmer RA. Midlife vs late-life depressive symptoms and risk of dementia: differential effects for Alzheimer disease and vascular dementia. Archives of general psychiatry. 2012;69(5):493-8.
113. Diniz BS, Butters MA, Albert SM, Dew MA, Reynolds CF, 3rd. Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. The British journal of psychiatry : the journal of mental science. 2013;202(5):329-35.
114. Alexopoulos GS. Vascular disease, depression, and dementia. J Am Geriatr Soc. 2003;51(8):1178-80.
115. Letenneur L, Peres K, Fleury H, Garrigue I, Barberger-Gateau P, Helmer C, et al. Seropositivity to herpes simplex virus antibodies and risk of Alzheimer's disease: a population-based cohort study. PloS one. 2008;3(11):e3637.
116. Roubaud Baudron C, Letenneur L, Langlais A, Buissonniere A, Megraud F, Dartigues JF, et al. Does Helicobacter pylori infection increase incidence of dementia? The Personnes Agees QUID Study. J Am Geriatr Soc. 2013;61(1):74-8.
117. Lovheim H, Gilthorpe J, Johansson A, Eriksson S, Hallmans G, Elgh F. Herpes simplex infection and the risk of Alzheimer's disease: A nested case-control study. Alzheimers Dement. 2015;11(6):587-92.
118. Wright CB, Gardener H, Dong C, Yoshita M, DeCarli C, Sacco RL, et al. Infectious Burden and Cognitive Decline in the Northern Manhattan Study. J Am Geriatr Soc. 2015;63(8):1540-5.
119. Lovheim H, Elgh F, Johansson A, Zetterberg H, Blennow K, Hallmans G, et al. Plasma concentrations of free amyloid beta cannot predict the development of Alzheimer's disease. Alzheimers Dement. 2017.
120. Baldi I, Lebailly P, Mohammed-Brahim B, Letenneur L, Dartigues JF, Brochard P. Neurodegenerative diseases and exposure to pesticides in the elderly. Am J Epidemiol. 2003;157(5):409-14.
121. Rondeau V, Jacqmin-Gadda H, Commenges D, Helmer C, Dartigues JF. Aluminum and silica in drinking water and the risk of Alzheimer's disease or cognitive decline: findings from 15-year follow-up of the PAQUID cohort. Am J Epidemiol. 2009;169(4):489-96.
122. Killin LO, Starr JM, Shiue IJ, Russ TC. Environmental risk factors for dementia: a systematic review. BMC geriatrics. 2016;16(1):175.

123. Reyes-Ortiz CA, Kuo Y-F, DiNuzzo AR, Ray LA, Raji MA, Markides KS. Near vision impairment predicts cognitive decline: data from the Hispanic Established Populations for Epidemiologic Studies of the Elderly. J Am Geriatr Soc. 2005;53(4):681-6.
124. Clemons TE, Rankin MW, McBee WL, Age-Related Eye Disease Study Research G. Cognitive impairment in the Age-Related Eye Disease Study: AREDS report no. 16. Arch Ophthalmol. 2006;124(4):537-43.
125. Rogers MAM, Langa KM. Untreated poor vision: a contributing factor to late-life dementia. Am J Epidemiol. 2010;171(6):728-35.
126. Whalley LJ, Dick FD, McNeill G. A life-course approach to the aetiology of late-onset dementias. Lancet Neurol. 2006;5(1):87-96.
127. Launer LJ. The epidemiologic study of dementia: a life-long quest? Neurobiology of aging. 2005;26(3):335-40.
128. Mortimer JA. Brain reserve and the clinical expression of Alzheimer's disease. Geriatrics. 1997;52 Suppl 2:S50-3.
129. Muller M, Sigurdsson S, Kjartansson O, Jonsson PV, Garcia M, von Bonsdorff MB, et al. Birth size and brain function 75 years later. Pediatrics. 2014;134(4):761-70.
130. Qiu C, Xu W, Fratiglioni L. Vascular and psychosocial factors in Alzheimer's disease: epidemiological evidence toward intervention. Journal of Alzheimer's disease : JAD. 2010;20(3):689-97.
131. Qiu C. Preventing Alzheimer's disease by targeting vascular risk factors: hope and gap. Journal of Alzheimer's disease : JAD. 2012;32(3):721-31.
132. Tolppanen AM, Solomon A, Soininen H, Kivipelto M. Midlife vascular risk factors and Alzheimer's disease: evidence from epidemiological studies. Journal of Alzheimer's disease : JAD. 2012;32(3):531-40.
133. Gottesman RF, Schneider AL, Zhou Y, Coresh J, Green E, Gupta N, et al. Association Between Midlife Vascular Risk Factors and Estimated Brain Amyloid Deposition. JAMA. 2017;317(14):1443-50.
134. Samieri C, Sun Q, Townsend MK, Chiuve SE, Okereke OI, Willett WC, et al. The association between dietary patterns at midlife and health in aging: an observational study. Annals of internal medicine. 2013;159(9):584-91.
135. Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. Alzheimers Dement. 2015;11(6):718-26.
136. Brookmeyer R, Gray S, Kawas C. Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. Am J Public Health. 1998;88(9):1337-42.
137. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. Lancet Neurol. 2014;13(8):788-94.
138. de Bruijn RF, Bos MJ, Portegies ML, Hofman A, Franco OH, Koudstaal PJ, et al. The potential for prevention of dementia across two decades: the prospective, population-based Rotterdam Study. BMC medicine. 2015;13:132.
139. Williams JW, Plassman BL, Burke J, Benjamin S. Preventing Alzheimer’s disease and cognitive decline. 2010. Available from: (Accessed
140. Larson EB, Yaffe K, Langa KM. New insights into the dementia epidemic. N Engl J Med. 2013;369(24):2275-7.
141. Wu YT, Beiser AS, Breteler MMB, Fratiglioni L, Helmer C, Hendrie HC, et al. The changing prevalence and incidence of dementia over time - current evidence. Nature reviews Neurology. 2017;13(6):327-39.
142. Prince M, Ali GC, Guerchet M, Prina AM, Albanese E, Wu YT. Recent global trends in the prevalence and incidence of dementia, and survival with dementia. Alzheimer's research & therapy. 2016;8(1):23.
143. Qiu C, von Strauss E, Bäckman L, Winblad B, Fratiglioni L. Twenty-year changes in dementia occurrence suggest decreasing incidence in central Stockholm, Sweden. Neurology. 2013;80(20):1888-94.

144. Wiberg P, Waern M, Billstedt E, Ostling S, Skoog I. Secular trends in the prevalence of dementia and depression in Swedish septuagenarians 1976-2006. Psychological medicine. 2013;43(12):2627-34.
145. Wimo A, Sjolund BM, Skoldunger A, Qiu C, Klarin I, Nordberg G, et al. Cohort Effects in the Prevalence and Survival of People with Dementia in a Rural Area in Northern Sweden. Journal of Alzheimer's disease : JAD. 2016;50(2):387-96.
146. Matthews FE, Arthur A, Barnes LE, Bond J, Jagger C, Robinson L, et al. A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II. Lancet. 2013;382(9902):1405-12.
147. Lobo A, Saz P, Marcos G, Dia JL, De-la-Camara C, Ventura T, et al. Prevalence of dementia in a southern European population in two different time periods: the ZARADEMP Project. Acta psychiatrica Scandinavica. 2007;116(4):299-307.
148. Peres K, Brayne C, Matharan F, Grasset L, Helmer C, Letenneur L, et al. Trends in Prevalence of Dementia in French Farmers from Two Epidemiological Cohorts. J Am Geriatr Soc. 2017;65(2):415-20.
149. Hall KS, Gao S, Baiyewu O, Lane KA, Gureje O, Shen J, et al. Prevalence rates for dementia and Alzheimer's disease in African Americans: 1992 versus 2001. Alzheimers Dement. 2009;5(3):227-33.
150. Langa KM, Larson EB, Crimmins EM, Faul JD, Levine DA, Kabeto MU, et al. A Comparison of the Prevalence of Dementia in the United States in 2000 and 2012. JAMA Intern Med. 2017;177(1):51-8.
151. Langa KM, Larson EB, Karlawish JH, Cutler DM, Kabeto MU, Kim SY, et al. Trends in the prevalence and mortality of cognitive impairment in the United States: is there evidence of a compression of cognitive morbidity? Alzheimers Dement. 2008;4(2):134-44.
152. Doblhammer G, Fink A, Fritze T. Short-term trends in dementia prevalence in Germany between the years 2007 and 2009. Alzheimers Dement. 2015;11(3):291-9.
153. Manton KC, Gu XL, Ukraintseva SV. Declining prevalence of dementia in the U.S. elderly population. Adv Gerontol. 2005;16:30-7.
154. Rocca WA, Petersen RC, Knopman DS, Hebert LE, Evans DA, Hall KS, et al. Trends in the incidence and prevalence of Alzheimer's disease, dementia, and cognitive impairment in the United States. Alzheimers Dement. 2011;7(1):80-93.
155. Satizabal CL, Beiser AS, Chouraki V, Chene G, Dufouil C, Seshadri S. Incidence of Dementia over Three Decades in the Framingham Heart Study. N Engl J Med. 2016;374(6):523-32.
156. Gao S, Ogunniyi A, Hall KS, Baiyewu O, Unverzagt FW, Lane KA, et al. Dementia incidence declined in African-Americans but not in Yoruba. Alzheimers Dement. 2016;12(3):244-51.
157. Schrijvers EMC, Verhaaren BFJ, Koudstaal PJ, Hofman A, Ikram MA, Breteler MMB. Is dementia incidence declining?: Trends in dementia incidence since 1990 in the Rotterdam Study. Neurology. 2012;78(19):1456-63.
158. Hebert LE, Bienias JL, Aggarwal NT, Wilson RS, Bennett DA, Shah RC, et al. Change in risk of Alzheimer disease over time. Neurology. 2010;75(9):786-91.
159. Doblhammer G, Fink A, Zylla S, Willekens F. Compression or expansion of dementia in Germany? An observational study of short-term trends in incidence and death rates of dementia between 2006/07 and 2009/10 based on German health insurance data. Alzheimer's research & therapy. 2015;7(1):66.
160. Sposato LA, Kapral MK, Fang J, Gill SS, Hackam DG, Cipriano LE, et al. Declining Incidence of Stroke and Dementia: Coincidence or Prevention Opportunity? JAMA neurology. 2015;72(12):1529-31.
161. Ukraintseva S, Sloan F, Arbeev K, Yashin A. Increasing rates of dementia at time of declining mortality from stroke. Stroke. 2006;37(5):1155-9.
162. Chan KY, Wang W, Wu JJ, Liu L, Theodoratou E, Car J, et al. Epidemiology of Alzheimer's disease and other forms of dementia in China, 1990-2010: a systematic review and analysis. Lancet. 2013;381(9882):2016-23.

163. Dong MJ, Peng B, Lin XT, Zhao J, Zhou YR, Wang RH. The prevalence of dementia in the People's Republic of China: a systematic analysis of 1980-2004 studies. Age Ageing. 2007;36(6):619-24.
164. Zhang Y, Xu Y, Nie H, Lei T, Wu Y, Zhang L, et al. Prevalence of dementia and major dementia subtypes in the Chinese populations: a meta-analysis of dementia prevalence surveys, 1980-2010. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia. 2012;19(10):1333-7.
165. Yu R, Chau PH, McGhee SM, Cheung WL, Chan KC, Cheung SH, et al. Trends in prevalence and mortality of dementia in elderly Hong Kong population: projections, disease burden, and implications for long-term care. International journal of Alzheimer's disease. 2012;2012:406852.
166. Dodge HH, Buracchio TJ, Fisher GG, Kiyohara Y, Meguro K, Tanizaki Y, et al. Trends in the prevalence of dementia in Japan. International journal of Alzheimer's disease. 2012;2012:956354.
167. Okamura H, Ishii S, Ishii T, Eboshida A. Prevalence of dementia in Japan: a systematic review. Dement Geriatr Cogn Disord. 2013;36(1-2):111-8.
168. Li S, Yan F, Li G, Chen C, Zhang W, Liu J, et al. Is the dementia rate increasing in Beijing? Prevalence and incidence of dementia 10 years later in an urban elderly population. Acta psychiatrica Scandinavica. 2007;115(1):73-9.
169. Sekita A, Ninomiya T, Tanizaki Y, Doi Y, Hata J, Yonemoto K, et al. Trends in prevalence of Alzheimer's disease and vascular dementia in a Japanese community: the Hisayama Study. Acta psychiatrica Scandinavica. 2010;122(4):319-25.
170. Ohara T, Hata J, Yoshida D, Mukai N, Nagata M, Iwaki T, et al. Trends in dementia prevalence, incidence, and survival rate in a Japanese community. Neurology. 2017;88(20):1925-32.
171. Steenland K, MacNeil J, Vega I, Levey A. Recent trends in Alzheimer disease mortality in the United States, 1999 to 2004. Alzheimer disease and associated disorders. 2009;23(2):165-70.
172. Sauvaget C, Tsuji I, Haan MN, Hisamichi S. Trends in dementia-free life expectancy among elderly members of a large health maintenance organization. International journal of epidemiology. 1999;28(6):1110-8.
173. Bordone V, Scherbov S, Steiber N. Smarter ever day: The deceleration of population ageing in terms of cognition. Intelligence. 2015;52:90-6.
174. Steiber N. Population Aging at Cross-Roads: Diverging Secular Trends in Average Cognitive Functioning and Physical Health in the Older Population of Germany. PloS one. 2015;10(8):e0136583.
175. Christensen K, Thinggaard M, Oksuzyan A, Steenstrup T, Andersen-Ranberg K, Jeune B, et al. Physical and cognitive functioning of people older than 90 years: a comparison of two Danish cohorts born 10 years apart. Lancet. 2013;382(9903):1507-13.
176. de Rotrou J, Wu YH, Mabire JB, Moulin F, de Jong LW, Rigaud AS, et al. Does cognitive function increase over time in the healthy elderly? PloS one. 2013;8(11):e78646.
177. Llewellyn DJ, Matthews FE. Increasing levels of semantic verbal fluency in elderly English adults. Neuropsychology, development, and cognition Section B, Aging, neuropsychology and cognition. 2009;16(4):433-45.
178. Sacuiu S, Gustafson D, Sjogren M, Guo X, Ostling S, Johansson B, et al. Secular changes in cognitive predictors of dementia and mortality in 70-year-olds. Neurology. 2010;75(9):779-85.
179. Dodge HH, Zhu J, Lee CW, Chang CC, Ganguli M. Cohort effects in age-associated cognitive trajectories. The journals of gerontology Series A, Biological sciences and medical sciences. 2014;69(6):687-94.
180. Dodge HH, Zhu J, Hughes TF, Snitz BE, Chang CH, Jacobsen EP, et al. Cohort effects in verbal memory function and practice effects: a population-based study. International psychogeriatrics / IPA. 2017;29(1):137-48.
181. Gerstorf D, Ram N, Hoppmann C, Willis SL, Schaie KW. Cohort differences in cognitive aging and terminal decline in the Seattle Longitudinal Study. Developmental psychology. 2011;47(4):1026-41.

182. Finkel D, Reynolds CA, McArdle JJ, Pedersen NL. Cohort differences in trajectories of cognitive aging. The journals of gerontology Series B, Psychological sciences and social sciences. 2007;62(5):P286-94.
183. Zelinski EM, Kennison RF. Not your parents' test scores: cohort reduces psychometric aging effects. Psychol Aging. 2007;22(3):546-57.
184. Karlsson P, Thorvaldsson V, Skoog I, Gudmundsson P, Johansson B. Birth cohort differences in fluid cognition in old age: comparisons of trends in levels and change trajectories over 30 years in three population-based samples. Psychol Aging. 2015;30(1):83-94.
185. Brailean A, Huisman M, Prince M, Prina AM, Deeg DJ, Comijs H. Cohort Differences in Cognitive Aging in the Longitudinal Aging Study Amsterdam. The journals of gerontology Series B, Psychological sciences and social sciences. 2016.
186. Crimmins EM. Trends in the health of the elderly. Annu Rev Public Health. 2004;25:79-98.
187. Cutler DM. Declining disability among the elderly. Health Aff (Millwood). 2001;20(6):11-27.
188. Manton KG. Recent declines in chronic disability in the elderly U.S. population: risk factors and future dynamics. Annu Rev Public Health. 2008;29:91-113.
189. Jagger C, Matthews RJ, Matthews FE, Spiers NA, Nickson J, Paykel ES, et al. Cohort differences in disease and disability in the young-old: findings from the MRC Cognitive Function and Ageing Study (MRC-CFAS). BMC public health. 2007;7:156.
190. Seeman TE, Merkin SS, Crimmins EM, Karlamangla AS. Disability trends among older Americans: National Health And Nutrition Examination Surveys, 1988-1994 and 1999-2004. Am J Public Health. 2010;100(1):100-7.
191. Freedman VA, Martin LG, Schoeni RF. Recent trends in disability and functioning among older adults in the United States: a systematic review. JAMA. 2002;288(24):3137-46.
192. Heikkinen E, Kauppinen M, Rantanen T, Leinonen R, Lyyra TM, Suutama T, et al. Cohort differences in health, functioning and physical activity in the young-old Finnish population. Aging clinical and experimental research. 2011;23(2):126-34.
193. Feng Q, Zhen Z, Gu D, Wu B, Duncan PW, Purser JL. Trends in ADL and IADL disability in community-dwelling older adults in Shanghai, China, 1998-2008. The journals of gerontology Series B, Psychological sciences and social sciences. 2013;68(3):476-85.
194. Allaire SH, LaValley MP, Evans SR, O'Connor GT, Kelly-Hayes M, Meenan RF, et al. Evidence for decline in disability and improved health among persons aged 55 to 70 years: the Framingham Heart Study. Am J Public Health. 1999;89(11):1678-83.
195. Manton KG, Gu X. Changes in the prevalence of chronic disability in the United States black and nonblack population above age 65 from 1982 to 1999. Proceedings of the National Academy of Sciences of the United States of America. 2001;98(11):6354-9.
196. Manton KG, Corder L, Stallard E. Chronic disability trends in elderly United States populations: 1982-1994. Proceedings of the National Academy of Sciences of the United States of America. 1997;94(6):2593-8.
197. Crimmins EM, Saito Y, Reynolds SL. Further evidence on recent trends in the prevalence and incidence of disability among older Americans from two sources: the LSOA and the NHIS. The journals of gerontology Series B, Psychological sciences and social sciences. 1997;52(2):S59-71.
198. Peres K, Helmer C, Letenneur L, Jacqmin-Gadda H, Barberger-Gateau P. Ten-year change in disability prevalence and related factors in two generations of French elderly community dwellers: data from the PAQUID study. Aging clinical and experimental research. 2005;17(3):229-35.
199. Donald IP, Foy C, Jagger C. Trends in disability prevalence over 10 years in older people living in Gloucestershire. Age Ageing. 2010;39(3):337-42.
200. Falk H, Johansson L, Ostling S, Thogersen Agerholm K, Staun M, Host Dorfinger L, et al. Functional disability and ability 75-year-olds: a comparison of two Swedish cohorts born 30 years apart. Age Ageing. 2014;43(5):636-41.
201. Galea S, Tracy M. Participation rates in epidemiologic studies. Annals of epidemiology. 2007;17(9):643-53.

202. Launer LJ, Wind AW, Deeg DJ. Nonresponse pattern and bias in a community-based cross-sectional study of cognitive functioning among the elderly. Am J Epidemiol. 1994;139(8):803-12.
203. Little RJA, Rubin D. (1987). Statistical analysis with missing data.Wiley. New York.
204. Chatfield MD, Brayne CE, Matthews FE. A systematic literature review of attrition between waves in longitudinal studies in the elderly shows a consistent pattern of dropout between differing studies. Journal of clinical epidemiology. 2005;58(1):13-9.
205. Langa KM, Levine DA. The diagnosis and management of mild cognitive impairment: a clinical review. JAMA. 2014;312(23):2551-61.
206. Wilson RS, Beckett LA, Bienias JL, Evans DA, Bennett DA. Terminal decline in cognitive function. Neurology. 2003;60(11):1782-7.
207. 3C Study Group. Vascular factors and risk of dementia: design of the Three-City Study and baseline characteristics of the study population. Neuroepidemiology. 2003;22(6):316-25.
208. Cognitive function and dementia in six areas of England and Wales: the distribution of MMSE and prevalence of GMS organicity level in the MRC CFA Study. The Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). Psychological medicine. 1998;28(2):319-35.
209. Gagnon M, Letenneur L, Dartigues JF, Commenges D, Orgogozo JM, Barberger-Gateau P, et al. Validity of the Mini-Mental State examination as a screening instrument for cognitive impairment and dementia in French elderly community residents. Neuroepidemiology. 1990;9(3):143-50.
210. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189-98.
211. Isaacs B, Kennie AT. The Set test as an aid to the detection of dementia in old people. The British journal of psychiatry : the journal of mental science. 1973;123(575):467-70.
212. Benton A. (1965). Manuel pour l'application du test de retention visuelle. Applications cliniques et expérimentales. Deuxième édition française. Paris : Centre de Psychologie Appliquée.
213. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. The Gerontologist. 1969;9(3):179-86.
214. Barberger-Gateau P, Commenges D, Gagnon M, Letenneur L, Sauvel C, Dartigues JF. Instrumental activities of daily living as a screening tool for cognitive impairment and dementia in elderly community dwellers. J Am Geriatr Soc. 1992;40(11):1129-34.
215. Pérès K, Chrysostome V, Fabrigoule C, Orgogozo JM, Dartigues JF, Barberger-Gateau P. Restriction in complex activities of daily living in MCI: impact on outcome. Neurology. 2006;67(3):461-6.
216. Copeland JR, Dewey ME, Henderson AS, Kay DW, Neal CD, Harrison MA, et al. The Geriatric Mental State (GMS) used in the community: replication studies of the computerized diagnosis AGECAT. Psychological medicine. 1988;18(1):219-23.
217. Copeland JR, Dewey ME, Griffiths-Jones HM. Dementia and depression in elderly persons: AGECAT compared with DSM III and pervasive illness. International journal of geriatric psychiatry. 1990;5:45-51.
218. Touraine C, Helmer C, Joly P. Predictions in an illness-death model. Stat Methods Med Res. 2016;25(4):1452-70.
219. Laird NM, Ware JH. Random-effects models for longitudinal data. Biometrics. 1982;38(4):963-74.
220. Proust-Lima C, Dartigues JF, Jacqmin-Gadda H. Misuse of the linear mixed model when evaluating risk factors of cognitive decline. Am J Epidemiol. 2011;174(9):1077-88.
221. Amieva H, Mokri H, Le Goff M, Meillon C, Jacqmin-Gadda H, Foubert-Samier A, et al. Compensatory mechanisms in higher-educated subjects with Alzheimer's disease: a study of 20 years of cognitive decline. Brain. 2014;137(Pt 4):1167-75.
222. Stern Y. Cognitive reserve: implications for assessment and intervention. Folia Phoniatr Logop. 2013;65(2):49-54.
223. Higher use of psychotropic drugs among people with Alzheimer's in their nineties. Nursing standard (Royal College of Nursing (Great Britain) : 1987). 2016;31(8):17.

224. Stern Y. Cognitive reserve in ageing and Alzheimer's disease. Lancet Neurol. 2012;11(11):1006-12.
225. Stern Y. Cognitive reserve. Neuropsychologia. 2009;47(10):2015-28.
226. Flynn JR. The mean IQ of American: Massive gains 1932 to 1978. Psychological bulletin. 1984;95:29-51.
227. Grimmer T, Beringer S, Kehl V, Alexopoulos P, Busche A, Forstl H, et al. Trends of patient referral to a memory clinic and towards earlier diagnosis from 1985-2009. International psychogeriatrics / IPA. 2015;27(12):1939-44.
228. Papp KV, Rentz DM, Mormino EC, Schultz AP, Amariglio RE, Quiroz Y, et al. Cued memory decline in biomarker-defined preclinical Alzheimer disease. Neurology. 2017.
229. Jagger C, Matthews FE, Wohland P, Fouweather T, Stephan BC, Robinson L, et al. A comparison of health expectancies over two decades in England: results of the Cognitive Function and Ageing Study I and II. Lancet. 2016;387(10020):779-86.
230. Pérès K, Edjolo A, Dartigues JF, Barberger-Gateau P. Recent Trends in Disability-Free Life Expectancy in the French Elderly: Twenty Years Follow-Up of the Paquid Cohort. Annual Review of Gerontology and Geriatrics. 2013;33(1):293-311.
231. Sagardui-Villamor J, Guallar-Castillon P, Garcia-Ferruelo M, Banegas JR, Rodriguez-Artalejo F. Trends in disability and disability-free life expectancy among elderly people in Spain: 1986-1999. The journals of gerontology Series A, Biological sciences and medical sciences. 2005;60(8):1028-34.
232. Manton KG, Gu X, Lowrimore GR. Cohort changes in active life expectancy in the U.S. elderly population: experience from the 1982-2004 National Long-Term Care Survey. The journals of gerontology Series B, Psychological sciences and social sciences. 2008;63(5):S269-81.
233. Van Oyen H, Cox B, Demarest S, Deboosere P, Lorant V. Trends in health expectancy indicators in the older adult population in Belgium between 1997 and 2004. Eur J Ageing. 2008;5:137–46.
234. Jeune B, Bronnum-Hansen H. Trends in health expectancy at age 65 for various health indicators, 1987–2005, Denmark. Eur J Ageing. 2008;5:279–85.
235. Cambois E, Clavel A, Romieu I, Robine JM. Trends in disability-free life expectancy at age 65 in France: consistent and diverging partterns according to the underlying disability measure. Eur J Ageing. 2008;5:287–98.
236. Lang L, Clifford A, Wei L, Zhang D, Leung D, Augustine G, et al. Prevalence and determinants of undetected dementia in the community: a systematic literature review and a meta-analysis. BMJ open. 2017;7(2):e011146.
237. Lopponen M, Raiha I, Isoaho R, Vahlberg T, Kivela SL. Diagnosing cognitive impairment and dementia in primary health care -- a more active approach is needed. Age Ageing. 2003;32(6):606-12.
238. Bond J, Stave C, Sganga A, O'Connell B, Stanley RL. Inequalities in dementia care across Europe: key findings of the Facing Dementia Survey. Int J Clin Pract Suppl. 2005(146):8-14.
239. Kosteniuk JG, Morgan DG, O'Connell ME, Kirk A, Crossley M, Teare GF, et al. Simultaneous temporal trends in dementia incidence and prevalence, 2005-2013: a population-based retrospective cohort study in Saskatchewan, Canada. International psychogeriatrics / IPA. 2016;28(10):1643-58.
240. van Bussel EF, Richard E, Arts DL, Nooyens AC, Coloma PM, de Waal MW, et al. Dementia incidence trend over 1992-2014 in the Netherlands: Analysis of primary care data. PLoS medicine. 2017;14(3):e1002235.
241. Farina E, Fioravanti R, Pignatti R, Alberoni M, Mantovani F, Manzoni G, et al. Functional living skills assessment: a standardized measure of high-order activities of daily living in patients with dementia. European journal of physical and rehabilitation medicine. 2010;46(1):73-80.
242. Schwartz MF, Segal M, Veramonti T, Ferraro M, Buxbaum LJ. The Naturalistic Action Test: a standardised assessment for everyday action impairment. Neuropsychological rehabilitation. 2002;12:311-39.
243. Wancata J, Borjesson-Hanson A, Ostling S, Sjogren K, Skoog I. Diagnostic criteria influence dementia prevalence. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry. 2007;15(12):1034-45.

244. Wu YT, Brayne C, Matthews FE. Prevalence of dementia in East Asia: a synthetic review of time trends. International journal of geriatric psychiatry. 2015;30(8):793-801.
245. Wu YT, Lee HY, Norton S, Prina AM, Fleming J, Matthews FE, et al. Period, birth cohort and prevalence of dementia in mainland China, Hong Kong and Taiwan: a meta-analysis. International journal of geriatric psychiatry. 2014;29(12):1212-20.
246. Jagger C, Gillies C, Moscone F, Cambois E, Van Oyen H, Nusselder W, et al. Inequalities in healthy life years in the 25 countries of the European Union in 2005: a cross-national meta-regression analysis. Lancet. 2008;372(9656):2124-31.
247. Salomon JA, Wang H, Freeman MK, Vos T, Flaxman AD, Lopez AD, et al. Healthy life expectancy for 187 countries, 1990-2010: a systematic analysis for the Global Burden Disease Study 2010. Lancet. 2012;380(9859):2144-62.
248. Green RC, Schneider LS, Amato DA, Beelen AP, Wilcock G, Swabb EA, et al. Effect of tarenflurbil on cognitive decline and activities of daily living in patients with mild Alzheimer disease: a randomized controlled trial. JAMA. 2009;302(23):2557-64.
249. Doody RS, Raman R, Farlow M, Iwatsubo T, Vellas B, Joffe S, et al. A phase 3 trial of semagacestat for treatment of Alzheimer's disease. N Engl J Med. 2013;369(4):341-50.
250. Doody RS, Thomas RG, Farlow M, Iwatsubo T, Vellas B, Joffe S, et al. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. N Engl J Med. 2014;370(4):311-21.
251. Salloway S, Sperling R, Fox NC, Blennow K, Klunk W, Raskind M, et al. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. N Engl J Med. 2014;370(4):322-33.
252. Barro RJ, Lee J-W. A new data set of educational attainment in the world, 1950–2010: NBER Working Paper No. 15902. The National Bureau of Economic Research. http://www.nber.org/papers/w15902. (2010) (accessed May 29, 2017).
253. Collaboration NCDRF. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. Lancet. 2017;389(10064):37-55.
254. Koton S, Schneider AL, Rosamond WD, Shahar E, Sang Y, Gottesman RF, et al. Stroke incidence and mortality trends in US communities, 1987 to 2011. JAMA. 2014;312(3):259-68.
255. Khan NA, McAlister FA, Pilote L, Palepu A, Quan H, Hill MD, et al. Temporal trends in stroke incidence in South Asian, Chinese and white patients: A population based analysis. PloS one. 2017;12(5):e0175556.
256. Ovbiagele B, Ernstrom K, Markovic D, Raman R. Trends in antihypertensive drug prescription patterns among ambulatory stroke patients in the United States, 2000-2009. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association. 2013;22(8):e568-75.
257. Zhou M, Daubresse M, Stafford RS, Alexander GC. National trends in the ambulatory treatment of hypertension in the United States, 1997-2012. PloS one. 2015;10(3):e0119292.
258. Clare L, Wu YT, Teale JC, MacLeod C, Matthews F, Brayne C, et al. Potentially modifiable lifestyle factors, cognitive reserve, and cognitive function in later life: A cross-sectional study. PLoS medicine. 2017;14(3):e1002259.
259. Akbaraly TN, Portet F, Fustinoni S, Dartigues JF, Artero S, Rouaud O, et al. Leisure activities and the risk of dementia in the elderly: results from the Three-City Study. Neurology. 2009;73(11):854-61.
260. Dartigues JF, Foubert-Samier A, Le Goff M, Viltard M, Amieva H, Orgogozo JM, et al. Playing board games, cognitive decline and dementia: a French population-based cohort study. BMJ open. 2013;3(8):e002998.
261. Foubert-Samier A, Le Goff M, Helmer C, Peres K, Orgogozo JM, Barberger-Gateau P, et al. Change in leisure and social activities and risk of dementia in elderly cohort. The journal of nutrition, health & aging. 2014;18(10):876-82.
262. Itzhaki RF, Lathe R, Balin BJ, Ball MJ, Bearer EL, Braak H, et al. Microbes and Alzheimer's Disease. Journal of Alzheimer's disease : JAD. 2016;51(4):979-84.
263. Lunenfeld B, Stratton P. The clinical consequences of an ageing world and preventive strategies. Best Pract Res Clin Obstet Gynaecol. 2013;27(5):643-59.

264. World Health Organization. Policies and priority interventions for healthy ageing. 2012. Available from: http://www.euro.who.int/__data/assets/pdf_file/0006/161637/WHD-Policies-and-Priority-Interventions-for-Healthy-Ageing.pdf?ua=1. (Accessed May 29, 2017)
265. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet. 2005;365(9455):217-23.
266. Furberg CD, Sealey JE, Blumenfeld JD. Unsuccessfully Treated Hypertension: A Major Public Health Problem With a Potential Solution. American journal of hypertension. 2017.
267. Collaboration NCDRF. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. Lancet. 2016;387(10027):1513-30.
268. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes research and clinical practice. 2010;87(1):4-14.
269. Collaboration NCDRF. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet. 2016;387(10026):1377-96.
270. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJL. Measuring the Global Burden of Disease and Risk Factors, 1990-2001. In: Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJL, editors. Global Burden of Disease and Risk FactorsWashington (DC): 2006.
271. Miranda JJ, Kinra S, Casas JP, Davey Smith G, Ebrahim S. Non-communicable diseases in low- and middle-income countries: context, determinants and health policy. Trop Med Int Health. 2008;13(10):1225-34.
272. Hosseinpoor AR, Bergen N, Kunst A, Harper S, Guthold R, Rekve D, et al. Socioeconomic inequalities in risk factors for non communicable diseases in low-income and middle-income countries: results from the World Health Survey. BMC public health. 2012;12:912.
273. Hosseinpoor AR, Bergen N, Mendis S, Harper S, Verdes E, Kunst A, et al. Socioeconomic inequality in the prevalence of noncommunicable diseases in low- and middle-income countries: results from the World Health Survey. BMC public health. 2012;12:474.
274. McLaren L. Socioeconomic status and obesity. Epidemiologic reviews. 2007;29:29-48.
275. Mackenbach JP, Stirbu I, Roskam AJ, Schaap MM, Menvielle G, Leinsalu M, et al. Socioeconomic inequalities in health in 22 European countries. N Engl J Med. 2008;358(23):2468-81.
276. Clark AM, DesMeules M, Luo W, Duncan AS, Wielgosz A. Socioeconomic status and cardiovascular disease: risks and implications for care. Nat Rev Cardiol. 2009;6(11):712-22.
277. Link CL, McKinlay JB. Disparities in the prevalence of diabetes: is it race/ethnicity or socioeconomic status? Results from the Boston Area Community Health (BACH) survey. Ethnicity & disease. 2009;19(3):288-92.
278. Braveman PA, Cubbin C, Egerter S, Williams DR, Pamuk E. Socioeconomic disparities in health in the United States: what the patterns tell us. Am J Public Health. 2010;100 Suppl 1:S186-96.
279. Stringhini S, Dugravot A, Shipley M, Goldberg M, Zins M, Kivimaki M, et al. Health behaviours, socioeconomic status, and mortality: further analyses of the British Whitehall II and the French GAZEL prospective cohorts. PLoS medicine. 2011;8(2):e1000419.
280. Hosseinpoor AR, Stewart Williams JA, Itani L, Chatterji S. Socioeconomic inequality in domains of health: results from the World Health Surveys. BMC public health. 2012;12:198.
281. Ouvrard C, Meillon C, Dartigues JF, Avila-Funes JA, Amieva H. Psychosocioeconomic Precariousness, Cognitive Decline and Risk of Developing Dementia: A 25-Year Study. Dement Geriatr Cogn Disord. 2016;41(3-4):137-45.
282. Singh GK. Area deprivation and widening inequalities in US mortality, 1969-1998. Am J Public Health. 2003;93(7):1137-43.
283. Windenberger F, Rican S, Jougla E, Rey G. Spatiotemporal association between deprivation and mortality: trends in France during the nineties. Eur J Public Health. 2012;22(3):347-53.
284. Rueda S, Artazcoz L, Navarro V. Health inequalities among the elderly in western Europe. Journal of epidemiology and community health. 2008;62(6):492-8.
285. Mackenbach JP, Karanikolos M, McKee M. The unequal health of Europeans: successes and failures of policies. Lancet. 2013;381(9872):1125-34.

286. Martinez-Lapiscina EH, Clavero P, Toledo E, Estruch R, Salas-Salvado J, San Julian B, et al. Mediterranean diet improves cognition: the PREDIMED-NAVARRA randomised trial. Journal of neurology, neurosurgery, and psychiatry. 2013;84(12):1318-25.
287. Trompet S, van Vliet P, de Craen AJ, Jolles J, Buckley BM, Murphy MB, et al. Pravastatin and cognitive function in the elderly. Results of the PROSPER study. Journal of neurology. 2010;257(1):85-90.
288. Nilsson A, Radeborg K, Salo I, Bjorck I. Effects of supplementation with n-3 polyunsaturated fatty acids on cognitive performance and cardiometabolic risk markers in healthy 51 to 72 years old subjects: a randomized controlled cross-over study. Nutr J. 2012;11:99.
289. Yurko-Mauro K, McCarthy D, Rom D, Nelson EB, Ryan AS, Blackwell A, et al. Beneficial effects of docosahexaenoic acid on cognition in age-related cognitive decline. Alzheimers Dement. 2010;6(6):456-64.
290. Breitner JC, Baker LD, Montine TJ, Meinert CL, Lyketsos CG, Ashe KH, et al. Extended results of the Alzheimer's disease anti-inflammatory prevention trial. Alzheimers Dement. 2011;7(4):402-11.
291. Forette F, Seux ML, Staessen JA, Thijs L, Birkenhager WH, Babarskiene MR, et al. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. Lancet. 1998;352(9137):1347-51.
292. Peters R, Beckett N, Forette F, Tuomilehto J, Clarke R, Ritchie C, et al. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. Lancet Neurol. 2008;7(8):683-9.
293. McGuinness B, Todd S, Passmore P, Bullock R. Blood pressure lowering in patients without prior cerebrovascular disease for prevention of cognitive impairment and dementia. The Cochrane database of systematic reviews. 2009(4):CD004034.
294. Angevaren M, Aufdemkampe G, Verhaar HJ, Aleman A, Vanhees L. Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. The Cochrane database of systematic reviews. 2008(3):CD005381.
295. Young J, Angevaren M, Rusted J, Tabet N. Aerobic exercise to improve cognitive function in older people without known cognitive impairment. The Cochrane database of systematic reviews. 2015(4):CD005381.
296. Ball K, Berch DB, Helmers KF, Jobe JB, Leveck MD, Marsiske M, et al. Effects of cognitive training interventions with older adults: a randomized controlled trial. JAMA. 2002;288(18):2271-81.
297. Willis SL, Tennstedt SL, Marsiske M, Ball K, Elias J, Koepke KM, et al. Long-term effects of cognitive training on everyday functional outcomes in older adults. JAMA. 2006;296(23):2805-14.
298. Papp KV, Walsh SJ, Snyder PJ. Immediate and delayed effects of cognitive interventions in healthy elderly: a review of current literature and future directions. Alzheimers Dement. 2009;5(1):50-60.
299. Martin M, Clare L, Altgassen AM, Cameron MH, Zehnder F. Cognition-based interventions for healthy older people and people with mild cognitive impairment. The Cochrane database of systematic reviews. 2011(1):CD006220.
300. Ngandu T, Lehtisalo J, Solomon A, Levalahti E, Ahtiluoto S, Antikainen R, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet. 2015;385(9984):2255-63.
301. Andrieu S, Guyonnet S, Coley N, Cantet C, Bonnefoy M, Bordes S, et al. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. Lancet Neurol. 2017;16(5):377-89.
302. National Academies of Sciences E, Medicine. (2017). Preventing Cognitive Decline and Dementia: A Way Forward.The National Academies Press. Washington, DC. Leshner AI, Landis S, Stroud C, Downey A. 978-0-309-46191-7

303. Jacqmin-Gadda H, Alperovitch A, Montlahuc C, Commenges D, Leffondre K, Dufouil C, et al. 20-Year prevalence projections for dementia and impact of preventive policy about risk factors. European journal of epidemiology. 2013;28(6):493-502.

Annex 1: The Mini-Mental State Examination

En cas de réponse exacte, coder 1
En cas de réponse fausse, coder 0

1) Quel jour de la semaine sommes-nous ? /__/

2) Quelle est la date aujourd'hui ? /__/

3) En quel mois sommes-nous ? /__/

4) En quelle saison sommes-nous ? /__/

5) En quelle année sommes-nous ? /__/

6) Où sommes-nous ici ? (Quel hôpital, quelle maison de retraite, rue, lieu-dit ...) /__/

7) A quel étage sommes-nous ? /__/

8) Dans quelle ville sommes-nous ? /__/

9) Dans quel département sommes-nous ? /__/

10) Dans quel pays sommes-nous ? /__/

L'examinateur doit prononcer les mots suivants au rythme de un par seconde.

En cas de difficultés, recommencer jusqu'à 5 fois

Répétez les mots suivants : **citron, clé, ballon**

11) 1er mot cité /__/

12) 2nd mot cité /__/

13) 3ème mot cité /__/

Soustraire 7 de 100 ainsi de suite.

14) 93 /__/

15) 86 /__/

16) 79 /__/

17) 72 /__/

18) 65 /__/

Vous souvenez-vous des trois mots que vous avez répétés tout à l'heure ?

19) 1er mot cité /__/

20) 2nd mot cité /__/

21) 3ème mot cité /__/

22) Qu'est-ce-que c'est que cela (montrer un crayon) /__/

23) Qu'est-ce-que c'est que cela (montrer la montre) /__/

24) Répétez : **pas de si ni de mais** /__/

Faire exécuter au sujet les trois ordres successifs

25) **Prenez cette feuille de papier,** /__/

26) **pliez-la par le milieu, et** /__/

27) **posez-la par terre.** /__/

28) Lisez ce qui est écrit et faites l'action : **fermez les yeux** /__/

29) Ecrivez une phrase de votre choix sur cette feuille /__/

30) Copiez ce dessin sur cette feuille /__/

Score total sur 30 : /__/__/