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Longitudinal associations of objectively-assessed sedentary behaviour with cardiovascular disease and all-cause mortality among older adults

Manasa Shanta Yerramalla

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Paris Cité*

**Longitudinal associations of
objectively-assessed sedentary
behaviour with cardiovascular disease
and all-cause mortality among older
adults**

By Manasa Shanta YERRAMALLA

Thèse de doctorat de **Epidémiologie**

Dirigée par Dr Séverine Sabia

Présentée et soutenue publiquement le 13/09/2022

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Titre : Associations longitudinales entre le comportement sédentaire évalué objectivement, les maladies cardiovasculaires et la mortalité toutes causes confondues chez les personnes âgées.

Résumé : L'activité physique est un important facteur de risque modifiable et protecteur des maladies cardiovasculaires et de la mortalité toutes causes confondues. Par ailleurs, de nouvelles preuves ont montré que le comportement sédentaire (CS), comme la position assise, pouvait être néfaste pour la santé, ce qui a conduit à un récent changement d'orientation des recommandations en matière d'activité physique. En plus de pratiquer au moins deux heures et demie d'activité physique modérée à vigoureuse (APMV) par semaine, il est suggéré aux adultes de tous âges de réduire le temps passé en CS. Ces recommandations sont rarement respectées par la majorité de la population, en particulier par les personnes âgées, en partie en raison de la diminution de la capacité physiologique à réaliser une activité d'intensité plus élevée. En outre, les personnes âgées passent près de 80 % de leur temps à être sédentaires. L'activité physique d'intensité légère (APIL), telle que la promenade, pourrait être plus facile que l'APVM et pourrait potentiellement conférer certains avantages aux personnes qui ne sont pas suffisamment en forme pour pratiquer une activité physique d'intensité plus élevée. De plus, il a été suggéré que non seulement la durée totale de la sédentarité, mais aussi la manière dont elle est accumulée tout au long de la journée pourrait être importante pour les résultats de santé. Cependant, il n'y a pas suffisamment de preuves pour attester ce point. Les principaux objectifs de la thèse étaient : (i) d'examiner l'association entre la manière dont se partitionnent l'APMV, l'APIL, et le CS, mesurés de manière objective durant la période d'éveil, et le risque de maladie cardiovasculaire incidente et (ii) d'estimer l'association du temps sédentaire total et de son mode d'accumulation avec les maladies cardiovasculaires incidentes et la mortalité toutes causes confondues. Les données de la sous-étude d'accéléromètre de Whitehall II ont été utilisées. Une augmentation de la durée de l'APMV au détriment du temps passé en CS ou en APIL s'est avérée associée à une réduction du risque de maladies cardiovasculaires. Chez les personnes très sédentaires, il était préférable d'augmenter le temps passé en APMV en réduisant uniquement le CS. La réponse à l'augmentation ou à la diminution de la durée d'APMV est asymétrique : la réduction de la durée d'APMV est beaucoup plus préjudiciable au risque de maladies cardiovasculaires que les gains obtenus par l'augmentation du temps passé en APMV, surtout s'il dépasse les recommandations. Dans l'échantillon total, aucune association a été trouvée entre le temps total de sédentarité et les habitudes d'accumulation de sédentarité, d'une part, et les maladies cardiovasculaires et la mortalité toutes causes confondues, d'autre part, une fois que l'APMV a été prise en compte. Cependant, un temps de sédentarité

accru et moins fragmenté était associé à une augmentation du risque de mortalité parmi les individus les plus jeunes, indépendamment du temps passé en APMV. Les principales conclusions sont que l'APMV a un effet protecteur sur le risque de maladies cardiovasculaires chez tous les adultes âgés et qu'un pattern plus fragmenté de temps sédentaire, indépendamment de la durée passée en APMV, prévient le décès prématuré chez les personnes âgées plus jeunes.

Mots clefs : Personnes âgées ; maladies cardiovasculaires ; mortalité toutes causes ; accéléromètre ; comportement sédentaire ; activité physique d'intensité légère ; activité physique modérée à vigoureuse ; étude observationnelle ; analyse compositionnelle ; pattern d'accumulation du temps sédentaire

Title : Longitudinal associations of objectively-assessed sedentary behaviour with cardiovascular disease and all-cause mortality among older adults

Abstract : Physical activity is an important modifiable protective risk factor for cardiovascular diseases (CVD), and all-cause mortality. Emerging evidence has shown that sedentary behaviour (SB) such as sitting might be deleterious to health, leading to a recent shift in focus of physical activity guidelines from solely requiring adults of all ages to undertake at least 2 and a half hours of moderate-to-vigorous physical activity (MVPA) per week to also suggesting them to reduce time spent in SB. The MVPA recommendations are not met by the majority of the population, especially by older adults in part due to declining physiological ability to perform higher intensity activity. Also, older adults spend almost 80% of their time being sedentary. Light intensity physical activity (LIPA) such as strolling may be easier than MVPA and could potentially confer some benefits in those not fit enough to engage in physical activity at higher intensity. Additionally, it has been suggested that not just the total duration of SB, but also the manner of its accumulation throughout the day might be important for health outcomes, but there is insufficient evidence to attest this point. The main objectives of the thesis were to examine the how different compositions of objectivity-assessed MVPA, LIPA, and SB in a waking day are associated with incident CVD; and to determine the association of total sedentary time and pattern of its accumulation with incident CVD and all-cause mortality. Data from the Whitehall II accelerometer sub-study from wave 2012-2013 was used. An increase in MVPA duration at the expense of time in either SB or LIPA was found associated with lower incidence of CVD. Among highly sedentary individuals, it was better to increase MVPA by reducing SB alone. There was an asymmetrical response to the increment or decrement of MVPA duration; reducing time in MVPA was far more detrimental to CVD risk than the gains obtained from increasing MVPA, especially if it exceeded the recommended guideline. Our study did not find any associations of total sedentary time and sedentary accumulation patterns with incident CVD and all-cause mortality in the total sample once MVPA was considered. There was evidence of higher mortality risk with increased total and less interruption of prolonged SB independently from MVPA in younger older adults. Main conclusionary notes is that MVPA is cardioprotective against CVD risk among all older adults and that a more interrupted pattern of sedentary time independent of MVPA prevents premature death in younger older adults.

Keywords : Older adults ; Cardiovascular disease ; All-cause mortality ; Accelerometer ; Sedentary behaviour ; Light intensity physical activity ;

Moderate-to-vigorous physical activity ; Longitudinal cohort ; Compositional data analysis ; Sedentary accumulation pattern metrics

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LIST OF ABBREVIATIONS

ABC	Attitude Behaviour and Change
BMI	Body Mass Index
CHD	Coronary Heart Disease
CI	Confidence Interval
CVD	Cardiovascular Disease
EE	Energy Expenditure
FMD	Flow-Mediated Dilation
GLUT 4	Glucose Transporter Type 4
HF	Heart Failure
HR	Hazard Ratio
ILR	Isometric log-ratio
LDL	Low-Density Lipoprotein
LIPA	Light-Intensity Physical Activity
LPL	Lipoprotein Lipase
LVEF	Left Ventricle Ejection Fraction
MET	Metabolic Equivalent of Task
MPA	Moderate-intensity physical activity
MVPA	Moderate-to-Vigorous Physical Activity
NEAT	Non-Exercise Activity Thermogenesis
NHANES	National Health and Nutrition Examination Survey
NO	Nitrogen Oxide
PA	Physical Activity
PAEE	Physical Activity-Related Energy Expenditure
PAGA	Physical Activity Guidelines for Americans
PAL	Physical Activity Level
PURE	Prospective Urban Rural Epidemiology
RMR	Resting Metabolic Rate
RNA	Ribonucleic Acid
SB	Sedentary Behaviour
SBRN	Sedentary Behaviour Research Network
SMD	standardized mean difference
SD	Standard Deviation
TDEE	Total Daily Energy Expenditure
TEF	Thermic Effect of Food

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SCIENTIFIC PRODUCTION

Thesis Publications

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Yerramalla MS, McGregor DE, van Hees VT, Fayosse A, Dugravot A, Tabak AG, Chen M, Chastin SFM and Sabia S. Association of daily composition of physical activity and sedentary behaviour with incidence of cardiovascular disease in older adults. *International Journal of Behavioral Nutrition and Physical Activity*. 2021;18:83.

R Package Contributor

Package: GGIR Raw Accelerometer Data Analysis;

<https://cran.r-project.org/web/packages/GGIR/index.html>

Other Publications Related to Thesis

Sabia S, **Yerramalla MS** and Liu-Ambrose T. Importance of characterising sleep breaks within the 24-h movement behaviour framework. *The international journal of behavioral nutrition and physical activity*. 2022;19:3.

Chastin S, McGregor D, Palarea-Albaladejo J, Diaz KM, Hagströmer M, Hallal PC, van Hees VT, Hooker S, Howard VJ, Lee IM, von Rosen P, Sabia S, Shiroma EJ, **Yerramalla MS** and Dall P. Joint association between accelerometry-measured daily combination of time spent in physical activity, sedentary behaviour and sleep and all-cause mortality: a pooled analysis of six prospective cohorts using compositional analysis. *British journal of sports medicine*. 2021;55:1277-1285. (second last author)

Oral Communications

Yerramalla MS, McGregor DE, van Hees VT, Fayosse A, Dugravot A, Tabak AG, Chen M, Chastin SFM and Sabia S. Association of daily composition of physical activity and sedentary behaviour with incidence of cardiovascular disease in older adults.

14th European Public Health Conference. 10-12 November. Virtual Edition.2021.

Yerramalla MS, Chen M, van Hees VT, Le Cornu Q, Dugravot A and Sabia S. Association of profiles of objectively-measured physical activity and sedentary behaviour with all-cause mortality risk in older adults.

8th International conference on ambulatory monitoring of physical activity and movement. June 21-24. Keystone, Colorado, USA. 2022.

Teaching Activities

Introduction to R for Master in Public Health students at École des hautes études en santé publique (EHESP), Paris

- October-December 2021, 35 hours
- October-November 2020, 35 hours

Co-supervision

Quentin Le Cornu: Intern of Master in Public Health Research, Université Paris-Saclay (January to October 2021)

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FRENCH SUMMARY OF THE THESIS

Contexte

L'activité physique (AP) est un important facteur de risque modifiable pour les maladies cardiovasculaires et la mortalité toutes causes confondues. La directive actuelle sur l'AP recommande aux adultes de tous âges de pratiquer au moins 150 minutes par semaine d'activité physique modérée à vigoureuse (APMV). Cependant, ces recommandations ne sont pas respectées par la majorité de la population, en particulier par les personnes âgées, en partie en raison de la diminution des capacités physiques de ces dernières. Les personnes âgées passent environ deux tiers de la journée à adopter un comportement sédentaire (CS), comme rester assis pendant une période prolongée qui est de plus en plus considéré comme un facteur de risque indépendant de maladies cardiovasculaires. L'activité physique d'intensité légère (APIL), comme la promenade, pourrait être plus facile que l'APMV et pourrait potentiellement apporter certains avantages aux personnes qui ne sont pas suffisamment en forme pour pratiquer une activité physique d'une intensité plus élevée.

De nombreuses questions restent sans réponse quant à l'influence des CS sur la santé. Étant donné qu'une journée est naturellement limitée à 24 heures, on ne sait pas si le temps passé avec des CS est important en raison des effets négatifs de la sédentarité elle-même ou parce qu'il réduit le temps disponible pour des comportements plus intenses. Comme chaque journée est limitée dans le temps, l'augmentation ou la diminution du temps passé dans un comportement de mouvement modifiera le temps passé dans d'autres comportements de mouvement. La plupart des études prospectives utilisant des mesures objectives n'ont pas tenu compte de cette codépendance et ont traité les CS, l'APIL, et l'APMV comme des comportements indépendants. Les recherches épidémiologiques récentes appellent à tenir compte de la nature relative des comportements de mouvement et à utiliser des méthodes statistiques appropriées, telle que l'analyse compositionnelle des données.

Il est suggéré que non seulement la durée totale de la sédentarité, mais aussi la manière dont elle est accumulée tout au long de la journée (par exemple, en quelques longues périodes ou en plusieurs plus courtes) pourraient être des facteurs déterminants pour les résultats en

matière de santé. Des études expérimentales ont rapporté que l'interruption fréquente d'un temps de sédentarité prolongé par une activité physique améliore un large éventail de paramètres cardiovasculaires, notamment la pression artérielle et la fonction vasculaire. Il est donc nécessaire d'identifier les caractéristiques spécifiques du CS, telles que la durée totale ou la longueur des durées, qui sont préjudiciables aux maladies cardiovasculaires et à la mortalité, toutes causes confondues, bien que les preuves prospectives restent rares. De plus, la plupart des études ont mis l'accent sur les pauses sédentaires ou la durée des épisodes sédentaires comme mesures d'accumulation des habitudes.

Cependant, des concepts tels que les pauses ont été décrits comme étant des mesures brutes pour les modèles d'accumulation de quantité, limitées par leur dépendance au temps de port de l'accéléromètre et leur incapacité à fournir des informations précises sur la nature des pauses en termes de longueur ou d'intensité. L'utilisation de mesures permettant de saisir la distribution de la durée du temps sédentaire et sensibles aux changements dans le CS a récemment été recommandée.

La plupart des données sur l'association entre les multiples comportements de mouvement pendant la journée, collectivement appelés comportements de mouvement à l'éveil (CS, APIL, APMV), sont principalement basées sur des questionnaires auto-rapportés, qui sont sujets à des biais de déclaration. Ces données ont également d'autres limites comme l'incapacité de saisir les mouvements fortuits de courte période ou ceux d'intensité légère qui sont répartis sur la journée et donc moins faciles à rapporter avec précision. En effet, ces mesures sont également susceptibles d'affecter la précision des estimations des associations entre les comportements de mouvement et les résultats de santé. Les accéléromètres permettent de pallier ces problèmes en évaluant de manière objective le schéma d'activité sur un cycle de 24 heures, bien que la plupart des preuves jusqu'à présent reste de nature transversale.

Cette thèse se concentre sur les personnes âgées, les maladies cardiovasculaires et la mortalité toutes causes confondues. La part des personnes âgées dans la population mondiale devrait presque doubler entre 2015 et 2050, ce qui en fait le groupe d'âge dont la croissance sera la plus rapide dans les prochaines années. Si le vieillissement de la population peut être perçu de

façon positive, il est important de noter que les améliorations de l'espérance de vie s'accompagnent le plus souvent de périodes prolongées d'incapacité et de morbidité. Chez les personnes âgées les maladies cardiovasculaires sont la principale cause de morbidité et de décès. Compte tenu du poids de celles-ci en termes d'invalidité, de déclin fonctionnel et d'augmentation des dépenses de santé, il est crucial d'améliorer le bien-être des personnes âgées en identifiant les facteurs de risque qui peuvent être modifiés afin de prévenir leur apparition. Il est également essentiel d'évaluer l'impact des changements de mode de vie sur la mortalité car la mort est un marqueur global de la santé.

Objectifs

L'objectif principal de cette thèse est d'examiner l'association prospective entre le comportement sédentaire mesuré objectivement, les maladies cardiovasculaires et la mortalité toutes causes confondues chez les personnes âgées, tout en tenant compte de l'activité physique.

Les objectifs de la thèse sont les suivants :

1. Examiner comment différentes compositions d'APMV, APIL et CS durant la période d'éveil sont associées à l'apparition de maladies cardiovasculaires, en utilisant la régression de Cox compositionnelle.
2. Déterminer l'association entre le temps total de sédentarité et le modèle d'accumulation de ce temps, en utilisant huit indicateurs, avec les maladies cardiovasculaires et la mortalité toutes causes confondues.

Population de l'étude et méthodes

Dans l'étude de Whitehall II, une cohort prospective menée à partir de 1985-1988 chez les fonctionnaires basés à Londres, 10 308 hommes et femmes, âgés de 35 à 55 ans, ont été recrutés. Depuis le début de l'étude, les facteurs sociodémographiques, de styles de vie et de santé ont été évalués à l'aide de questionnaires et d'exams cliniques. Les évaluations de suivi ont eu lieu environ tous les 4 à 5 ans, la dernière vague ayant eu lieu en 2015-2016. Cette thèse de doctorat est basée sur les données de la sous-étude sur l'accéléromètre entreprise au cours de la vague de collecte de données de 2012-2013 pour les participants vus à la clinique de Londres et pour

ceux vivant dans les régions du Sud-Est de l'Angleterre qui ont eu un examen clinique à domicile. Les participants sans contre-indication (allergies au plastique ou au métal, voyage à l'étranger dans la semaine suivante) ont été invités à porter un accéléromètre triaxial (GENEActiv Original ; Activinsights Ltd., Kimbolton, Royaume-Uni) sur leur poignet non-dominant pendant 9 jours consécutifs sur 24 heures.

Les données ont été échantillonnées à 85,7 Hz, avec l'accélération exprimée par rapport à la gravité ($1 g = 9,81 \text{ m/seconde}^2$). Les données de l'accéléromètre ont été traitées avec le logiciel R en utilisant le paquet GGIR. Les données ont été corrigées pour tenir compte de l'erreur d'étalonnage et de la norme euclidienne des accélérations brutes moins 1, les nombres négatifs étant arrondis à zéro, ont été calculées. Les périodes de sommeil ont ensuite été détectées à l'aide d'un algorithme validé, guidé de surcroît par un journal de sommeil. Les données utilisées vont du premier réveil (jour 2) au réveil de la veille du dernier jour (jour 8), ce qui correspond à 7 jours complets. La période d'éveil a été définie comme la période entre le réveil et le début du sommeil. Les participants ont été inclus dans l'analyse s'ils avaient un temps de port quotidien $\geq 2/3$ des heures d'éveil, pendant au moins 2 jours de semaine et 2 jours de week-end. La période de non-utilisation parmi les jours valides a été corrigée sur la base d'un algorithme décrit précédemment. Le comportement de mouvement pendant la période d'éveil a été classé comme CS lorsque l'accélération moyenne sur une période de 60 secondes était inférieure à 40 milli gravité (mg), 40-99 mg pour l'APIL, et supérieure ou égale à 100 mg pour l'APVM.

Objectif 1

Une analyse compositionnelle a été utilisée pour tenir compte de la codépendance des comportements de mouvement pendant la période d'éveil. Cette méthode suppose une distribution relative des comportements de mouvement et réduit la composition en trois parties (CS, APIL, APVM) notée z , en deux variables d'exposition en les transformant en deux coordonnées log-ratio isométriques, appelées z_1 et z_2 . La première coordonnée, z_1 , représente le ratio du temps passé en CS par rapport à la moyenne géométrique de l'AP (APIL et APMV). La deuxième coordonnée, z_2 , représente le temps passé en APIL par rapport à l'APMV. Les deux coordonnées sont incorporées dans le modèle analytique en tant qu'exposition puisqu'elles

représentent ensemble la composition du mouvement durant l'éveil et ne peuvent pas être interprétées comme des entités séparées. En utilisant une rotation orthogonale, l'importance des autres composantes restantes des comportements de mouvement durant les périodes d'éveil (APIL et APMV) comparées à la moyenne géométrique des autres composantes ont également été isolées.

Les analyses ont été réalisées à l'aide d'une régression de Cox compositionnelle avec les maladies cardiovasculaires incidentes comme événement d'intérêt. L'hypothèse de risques proportionnels a été vérifiée à l'aide du test de Grambsch-Therneau. Les résultats du modèle de Cox compositionnel ont été utilisés pour extraire les rapports de risque de l'incidence des maladies cardiovasculaires en fonction de la composition des comportements de mouvement (APMV, APIL, CS) au cours de la période d'éveil. Pour ce faire, un ensemble de compositions de comportement de mouvement de référence a été défini auquel nous avons comparé les compositions dans lesquelles le temps passé dans un comportement de mouvement était supérieur de 10 (20 et 30) minutes à celui passé dans un autre comportement de mouvement au détriment du temps passé dans un autre comportement de mouvement, en gardant le temps passé dans le troisième comportement fixé au même niveau.

Objectif 2

Le modèle d'accumulation sédentaire a été mesuré à l'aide de 8 indicateurs : durée moyenne des épisodes sédentaires (5), durée des épisodes sédentaires prolongés, indice de Gini, nombre de pauses sédentaires, pauses par heure sédentaire, Alpha et probabilité de transition d'un état sédentaire à un état d'APIL ou d'APMV. Les indicateurs (temps total et mode d'accumulation) ont été calculés pour chaque jour et la moyenne sur 7 jours. Les associations non-linéaires potentielles du temps total de sédentarité et du modèle d'accumulation de sédentarité lors de la vague 2012-2013 avec le risque de maladies cardiovasculaires et de mortalité toutes causes confondues ont été testées à l'aide du test du rapport de vraisemblance comparant les modèles de régression de Cox entièrement ajustés avec un seul terme linéaire aux modèles avec des termes utilisant des splines cubiques. Lorsque les associations ont été jugées linéaires, les expositions ont été traitées comme des variables continues dans les analyses. Pour faciliter

l'interprétation et la comparabilité, les expositions ont été standardisées (moyenne = 0, écart-type = 1) en utilisant la moyenne et l'écart-type du plus grand échantillon analytique, celui dont la mortalité est l'évènement d'intérêt. Toutes les analyses ont été effectuées en utilisant la régression de Cox avec l'âge comme échelle de temps. L'hypothèse de proportionnalité a été vérifiée à l'aide du test de Schoenfeld.

Évènements d'intérêt

Les événements cardiovasculaires ont été définis comme la survenue d'une première maladie coronarienne fatale ou non-fatale, d'un accident vasculaire cérébral ou d'une insuffisance cardiaque. Les événements cardiovasculaires non mortels ont été retracés à partir de la base de données "Hospital Episode Statistics" (HES), sur la base des codes de la classification internationale des maladies. Les cas de coronaropathie et d'accident vasculaire cérébral ont également été déterminés à partir de l'enregistrement de l'électrocardiogramme de repos à 12 dérivations spécifique à l'étude Whitehall II et du questionnaire MONICA-Augsburg sur les accidents vasculaires cérébraux. Les décès, toutes causes confondues, étaient disponibles dans le registre des décès britannique ("UK Office for National Statistics Mortality Register"). Pour l'analyse des cas de maladies cardiovasculaires, les participants ont été censurés à la date de la maladie cardiovasculaire, du décès non lié à une maladie cardiovasculaire pour tenir compte des risques concurrents, ou au 31 mars 2019 (fin du suivi), selon ce qui survenait en premier. Pour la mortalité toutes causes confondues, la date de censure était soit la date du décès, soit la fin du suivi (31 mars 2019), selon ce qui survenait en premier.

Covariables

Les covariables ont été évaluées à l'aide d'un questionnaire ou lors de l'examen clinique à la vague 2012-2013 ainsi qu'avec les données des dossiers médicaux électroniques (y compris HES et Mental Health Services Data set). Les variables sociodémographiques comprenaient le sexe, l'origine ethnique, le statut marital, l'éducation, la dernière position professionnelle connue. Les facteurs de risque liés au mode de vie comprenaient la consommation d'alcool, le tabagisme et la consommation de fruits et légumes. Les facteurs de risque liés à la santé comprenaient le

diabète, l'indice de masse corporelle, l'hypertension, l'hyperlipidémie et l'indice de multimorbidité.

Résultats

Objectif 1

Parmi les 3319 participants, 299 cas de maladies cardiovasculaires ont été enregistrés au cours d'un suivi moyen (écart-type [ET]) de 6,2 (1,3) ans. Par rapport à la composition du comportement de mouvement quotidien avec APMV d'une durée recommandée de 21 min par jour (150 min/semaine), la composition avec 10 min supplémentaires d'APMV et 10 min de moins de CS a été associée à une réduction du risque de -8 % (rapport de risque [intervalle de confiance de 95 %] : 0,92 [0,87-0,99]). Une composition alliant une durée d'APMV réduite et une durée de CS plus importante était associée à une augmentation du risque de 14 % (1,14 [1,02-1,27]). Pour une durée d'APMV donnée, le risque de maladies cardiovasculaires ne différait pas en fonction des durées d'APIL et de CS.

Objectif 2

Parmi les 3321 participants, 299 cas de maladies cardiovasculaires ont été enregistrés au cours d'un suivi moyen de 6,2 (ET = 1,3) ans. Un total de 260 décès parmi 3991 participants a été enregistré au cours d'un suivi moyen (ET) de 6,4 (ET = 0,8) ans. Après ajustement pour tenir compte des facteurs de risque sociodémographiques et liés au mode de vie, une augmentation de 1 ET (100,2 minutes) du temps total de sédentarité était associée à un risque accru de 20 % de maladies cardiovasculaires (rapport de risque [intervalle de confiance à 95 %] : 1,20 [1,05-1,37]). Un temps de sédentarité plus fragmenté était associé à une réduction du risque de maladies cardiovasculaires (par exemple, 0,86 [0,76-0,97] pour une augmentation de 1-ET [6,2] des pauses par heure de sédentarité). Les associations n'étaient pas évidentes lorsque les facteurs liés à la santé et l'APMV étaient pris en compte. En ce qui concerne la mortalité toutes causes confondues, les associations avec un CS plus fragmenté (par exemple, 0,73 [0,59-0,91]

pour les pauses par heure de sédentarité) n'ont été trouvées que dans le groupe le plus jeune (< 74 ans ; p pour l'interaction avec l'âge < 0,1) indépendamment de toutes les covariables.

Conclusions

Chez les personnes âgées, il a été constaté qu'une augmentation de la durée de l'APMV au détriment du temps passé en CS ou en APIL a été associée à une plus faible incidence de maladies cardiovasculaires. L'utilisation de l'approche compositionnelle a mis en évidence l'asymétrie de la réponse à une augmentation ou à une diminution de la pratique d'une APMV. La réduction du temps consacré à la pratique d'une APMV était bien plus préjudiciable au risque de maladies cardiovasculaire que les gains obtenus par l'augmentation du temps consacré à l'APMV, surtout au-delà de la durée recommandée par jour. Il est important d'identifier les personnes qui réduisent leur temps d'APMV et de les encourager à maintenir leur temps d'APMV. Chez les personnes fortement sédentaires, il était préférable d'augmenter le temps consacré à l'APMV en réduisant le temps passé en CS plutôt qu'en APIL. Cela indique qu'une certaine quantité d'APIL est importante dans l'équilibre de la santé des maladies cardiovasculaires.

Aucune association entre le temps total de sédentarité et les modèles d'accumulation de sédentarité avec les maladies cardiovasculaires incidentes et la mortalité toutes causes confondues n'a été trouvée dans l'échantillon total une fois que l'APMV a été considérée. En outre, il y avait des preuves d'un risque plus élevé de mortalité toutes causes confondues avec une augmentation du temps sédentaire total et moins fragmenté, indépendamment de l'APMV, chez les personnes âgées les plus jeunes (< 74 ans). Si ces derniers résultats sont reproduits dans de futures études, cela soutiendrait les recommandations canadiennes actuelles sur la limitation et l'interruption de longues périodes de sédentarité. La raison pour laquelle de telles associations ne sont pas observées dans le groupe le plus âgé nécessite des recherches supplémentaires.

Forces et limites

Cette thèse présente plusieurs points forts. Nous avons utilisé des mesures objectives des comportements de mouvement, dans le cadre d'une étude prospective. Nous avons inclus des

hommes et des femmes, contrairement aux études antérieures qui ne sont basées que sur un seul sexe, et qui se concentrent exclusivement sur les personnes âgées. Nous avons utilisé une méthode innovante, la régression de Cox compositionnelle, qui tient compte de la nature relative et co-dépendante des comportements de mouvement quotidiens. En l'absence d'un indicateur de référence, nous avons utilisé un large éventail d'indicateurs, y compris ceux qui caractérisent la distribution des différentes durées de sédentarité, pour évaluer le modèle d'accumulation sédentaire. Nous avons également pris en compte un large éventail de facteurs de risque tels que les biomarqueurs de maladies cardiovasculaires, la prévalence du diabète et la multimorbidité, qui ont été mesurés via de nombreuses sources objectives, par opposition à l'auto-déclaration, telles que l'examen clinique et le couplage des dossiers médicaux avec les données hospitalières.

Il convient également de noter les limites. Un accéléromètre de poignet ne fournit pas d'informations sur la posture, ne permettant pas de différencier les positions debout et assise. Cela pourrait conduire à des erreurs de classification entre CS et APIL moins intense, ainsi que des divergences avec les estimations du temps assis rapporté par les études utilisant des accéléromètres portés à la cuisse. Cependant, les résultats des accéléromètres au poignet permettent de classer avec précision les comportements de mouvement basés sur l'intensité métabolique avec précision. L'étude Whitehall II est une cohorte professionnelle dont les participants sont en meilleure santé que la population générale mais les facteurs de risque cardiovasculaires, y compris l'AP, sont similaires à ceux de la population générale. Un ajustement a été effectué pour tenir compte d'un large éventail de facteurs de confusion, mais il est possible qu'un facteur non mesuré explique davantage l'association avec les maladies cardiovasculaires.

1 BACKGROUND

This thesis examined the prospective association of objectively-measured sedentary behaviour with incident cardiovascular disease and all-cause mortality among older adults.

Some preliminary notes on the thesis: Research using similar novel method or similar objective conducted in the year following the publication of my thesis-based articles were not elaborated in the background. Throughout this work persons aged 60 years and above were referred to as “older adults”. This is in accordance with the United Nations Committee on Economic, Social, and Cultural Rights of Older Persons, which in 1995 in favour of “older people”, rejected the label “elderly”. Descriptors such as “senior”, “aged” and “elderly” for older people have been deemed inappropriate in the context of “person-first” language in the past few years. The term “elderly” is problematic since it connotes a sense of vulnerability and dependence, which stereotypes the entire group of people. As a result, the terms “older adult/person/people” have been considered more neutral in terms of addressing preconceptions associated with this age group.

1.1 Ageing population and burden of disease

Increase in longevity over the last 200 years has seen the average human life expectancy in the industrialized countries increase from 43/45 years in 1840 to a record 78/83 years in 2015 for men and women, respectively (1, 2); with a particular expansion of those aged 60 years and over (3). The age group with the fastest growth rate globally is older adults, whose population share is projected to more than double from 962 million in 2017 to 2.1 billion by 2050 (**Figure 1**) (4). While population ageing may be seen positively, it is important to note that improvements in life expectancy are more often than not accompanied by extended periods of disability and morbidity (5). The shift to a predominantly more sedentary lifestyle coupled with energy rich-foods has led to a thermodynamic imbalance, with persistent positive energy balance i.e., when energy intake exceeds energy expenditure, associated with development of obesity and metabolic impairment, increasing risk of developing cardiovascular disease (6, 7). Among the older adults, cardiovascular disease is the leading cause of disease burden (30% of total burden)

(5), and are also responsible for 82% of deaths in this population (8). Given the burden imposed that cardiovascular disease places on older adults in terms of disability, functional decline and rising health-care expenses (9), it is crucial to improve their welfare by identifying risk factors that can be changed in order to prevent the development of cardiovascular disease. It is also essential to evaluate the impact of lifestyle changes on mortality because death is a global marker of health.

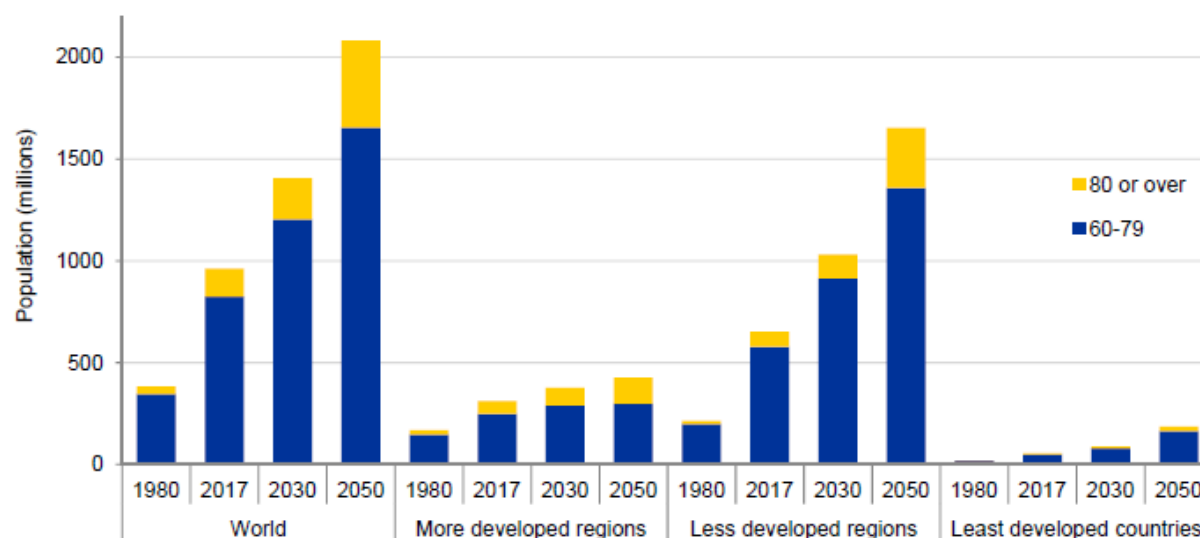


Figure 1 Number of persons aged 60-79 years and aged 80 and over for the world and development groups, 1980, 2017, 2030 and 2050. Source: United Nations (4).

1.2 Cardiovascular disease

Cardiovascular disease (CVD) includes diseases of the heart and blood vessels (10). CVD is the leading cause of death and disease burden worldwide, with the coronary heart disease contributing the highest proportion of cases, followed by stroke (11). Atherosclerosis is the leading cause of cardiovascular diseases, including myocardial infarction, heart failure, and stroke (12, 13). Atherosclerosis refers to the hardening or thickening of medium and large-sized arteries caused mainly by the accumulation of fibrofatty lesions i.e., plaque underneath the inner most layer of artery, the intima (14). Plaque build-up gradually narrows and stiffens artery walls, reducing the flow of oxygen-rich blood to the organs of the body (15, 16) (**Figure 2**).

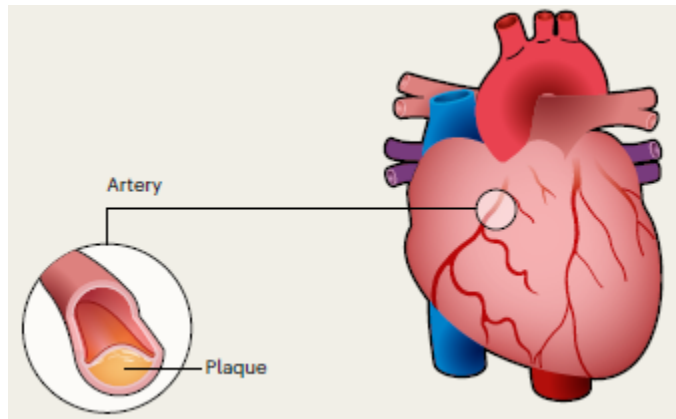


Figure 2 Illustration of plaque build-up in the artery of the heart. Source: Plackett (17).

1.2.1 Coronary heart disease

Coronary heart disease (CHD) also called ischemic heart disease or coronary artery disease is the leading cause of death worldwide, wherein atherosclerosis narrows the arteries i.e., coronary arteries, that supply the heart with blood, which can cause angina pectoris and myocardial infarction (18). Angina pectoris also known as stable angina, is the term for discomfort and pain in the chest due to tightening of heart muscle, and the most typical manifestation of CHD among women (19, 20). When the arterial lumen is at least 70% blocked by atherosclerotic plaque, angina develops (14, 21). As a result, stable angina pectoris is a condition that is typically brought on by increases in myocardial oxygen demands and is characterized by regional myocardial ischaemia brought on by insufficient coronary perfusion (22). Stable angina-related chest pain often occurs with physical exertion and is relieved by rest and/or nitro-glycerine (22, 23). In contrast, chest pain that occurs at rest usually is indicative of unstable disease, such as acute coronary syndrome that usually is caused by a coronary plaque rupture and subsequent intracoronary thrombosis formation (21, 24). The acute coronary syndrome includes unstable angina, and acute myocardial infarction (non-ST¹ segment elevation myocardial infarction and ST segment elevation myocardial infarction) (25). Myocardial infarction is the lethal manifestation of CHD, and can lead to sudden death (26).

¹ A certain area on the electrocardiogram when tracing the heart is called as ST segment.

From 1990 to 2019, there has been a decline in the global age-standardized rates for disability-adjusted life years, deaths and prevalent cases of CHD, indicating that the average increases in absolute numbers of CHD have been mainly driven by the growth of an ageing population (27). Although, in recent years, some regions, including parts of United Kingdom and the United States have seen increase in the CHD death rates, which suggest that the long-term declines in CHD due to improvements in prevention and provision of adequate health care are not occurring in these regions (27). The most common form of CHD is myocardial infarction, responsible for 15% of overall mortality (28, 29).

In the INTERHEART² study, nine modifiable risk factors accounted for over 90% of the population attributable risk for an initial acute myocardial infarction across age and sex groups worldwide (30). The nine risk factors were irregular consumption of fruits and vegetables, current or former smoking, avoidance of alcohol intake, no regular exercise, abdominal obesity, history of diabetes or hypertension, raised plasma lipids, and combined psychosocial stressors (30). Smoking and abnormal lipids were the two most important risk factors, accounting for two-thirds of the population attribution risk of an acute myocardial infarction (30).

1.2.2 Heart failure

The joint guideline of the American Heart Association and the American College of Cardiology define heart failure (HF) as “a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill or eject blood” (31, 32). In essence, it is a chronic, progressive condition in which the heart is unable to pump enough blood at a rate commensurate with systemic metabolic requirements (33). Fatigue and dyspnoea, which may restrict tolerance and cause fluid retention and/or pulmonary and/or splanchnic congestion as well as peripheral oedema, are symptoms of heart failure (34). Some patients complain predominantly of oedema, dyspnoea, or fatigue, whereas others have exercise intolerance but no indication of fluid retention (34). The term "heart failure" rather than "congestive heart failure" is recommended because some patients do not exhibit any signs

² A multicohort, standardized case-control study established to examine the importance of risk factors for coronary heart disease in 52 countries.

or symptoms of volume overload (34). There is no single clinical examination to diagnose heart failure and the clinical diagnosis is mainly based on carefully taken clinical history, physical examination, and test results (for example from an electrocardiogram, an echocardiogram) (31, 32). The clinical syndrome of heart failure mainly results from the impairment of left ventricular³ myocardial function (35), which serves as a phenotype marker for underlying pathophysiological pathways (36). Based on the left ventricle ejection fraction (LVEF), the diagnosis of heart failure can be categorised as: heart failure with reduced (LVEF \leq 40%), midrange (LVEF 40-49%) or preserved (LVEF \geq 50%) ejection fraction⁴ (37). Heart failure is most frequently brought on by coronary heart disease, which is often associated with an acute myocardial infarction or a previous myocardial infarction (35).

Heart failure is associated with poor long-term prognosis with a mean survival rate of 80-90% at year one post diagnosis, which drops to 50% at year five (38). One of the key risk factors of the growing burden of heart failure is aging (39). With over 1 million hospitalizations annually, heart failure is the leading cause of hospitalizations among older adults in the United States and Europe, which represents a significant clinical and economic burden (40). Heart failure affects less than 1% of people under the age of 40, and more than 10% of people over the age of 80, with the prevalence almost doubling each decade beyond 40 years (41). Other than coronary heart disease, the most notable risk factor to predispose HF is hypertension (42). Hypertension is the most important risk factors for HF with preserved ejection fraction (43), which is the predominant form of HF among the older adults (44). With an increase in blood pressure, cardiac myocytes are subjected to higher mechanical stress and neurohormonal stimulation, which increases the myocardial mass and causes left ventricular hypertrophy⁵, and progressing to HF even in the absence of myocardial infarction (39). According to the Framingham Heart study, individuals with blood pressure over 160/90 mmHg had a twice as high lifetime risk of developing heart failure as individuals with blood pressure under 140/90

³ Left ventricle is the main chamber of the heart and an integral part of the cardiovascular system. It is responsible for pumping oxygen into aorta, the largest artery of the body.

⁴ Percentage of blood volume ejected in each cardiac cycle and is representative of the left ventricle systolic performance (Source: Bamira and Picard, 2018).

⁵ Thickening of the heart's left pumping chamber, leading to inefficient pumping of blood.

mmHg (45). Diabetes and obesity are also thought to affect left ventricular function in the absence of coronary heart disease and hypertension (46-48).

1.2.3 Stroke

Stroke occurs when the blood supply to part of the brain is interrupted (49). The type of stroke, the area of brain that was affected, and the severity of the damage all influence the stroke's aftereffects. There are two major subtypes of stroke: ischemic and haemorrhagic. A transient ischemic attack, informally known as a "mini-stroke" or a "warning stroke", differs from the two main types of strokes in that it only temporarily blocks blood flow to the brain and does not result in permanent damage (50). Ischaemic stroke is defined as an episode of neurological dysfunction caused by the infarction⁶ of the brain, spine or retina (51). Ischemic stroke occurs when the blood supply to the brain is reduced or blocked via a blood clot (**Figure 3**). They can further be divided into 2 groups: Thrombotic stroke, caused by blood clot that develops in the blood vessel inside the brain; Embolic stroke, caused by blood clot or plaque clot that develops elsewhere in the body and then travels to one of the blood vessels in the brain through the bloodstream (51). Thrombotic stroke is caused by a blood clot that develops in the arteries supplying blood to the brain, and is usually seen in older adults, especially those with high cholesterol and atherosclerosis or diabetes (51). Haemorrhagic strokes (**Figure 3**) is caused due to the bleeding into the brain due to the bursting of the blood vessel and can be further divided into intracerebral haemorrhage and subarachnoid haemorrhage (52). Intracerebral haemorrhage occurs when the artery within brain ruptures and bleeds within the brain, while subarachnoid haemorrhage is the leakage of the blood onto the space surrounding the brain (52).

⁶ tissue death brought on by insufficient blood flow to the affected area.

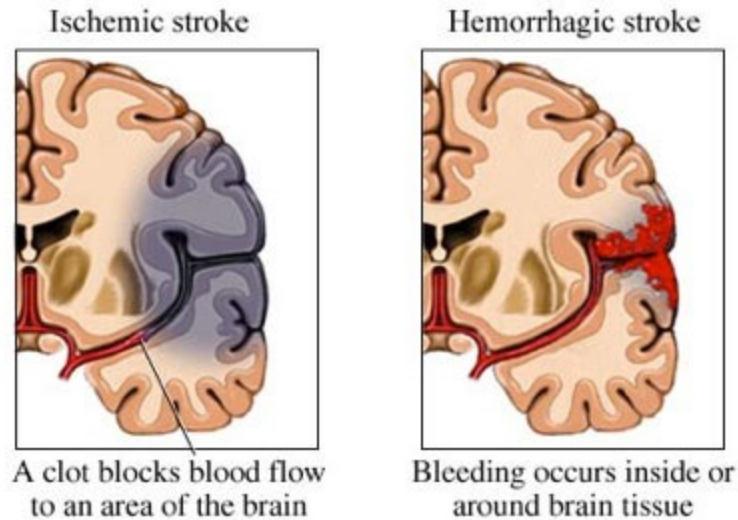


Figure 3 Difference between Ischemic and haemorrhagic brain stroke. Source: UCLA Health (53).

Stroke was the second most common cause of death, and the third-leading cause of death and disability combined in 2019 (54). Despite significant declines in age-standardized rates of stroke incidence from 1990 to 2019, there was a significant increase in the annual number of strokes and stroke-related deaths, especially among those over the age of 70 years (54). Ischemic stroke made up 62.4% of all incident stroke cases worldwide in 2019, followed by intracerebral haemorrhage (27.9%) and subarachnoid haemorrhage (9.7%) (54). With the risk of stroke rising with age, the incidence of all strokes doubling with each decade beyond the age of 45 years, and more than 70% of all strokes occurring after the age of 65 years, older age is considered to be the single most important risk factor for stroke (55, 56). The age-related change in stroke risk differs by sex; stroke incidence is higher in women than in men for persons under 30 years old, while rates are higher in men than women during midlife and older ages, and starting in the eighth decade of life, however, rates either equal by sex or higher among women (57, 58). The higher rate of stroke in younger women is reflective of pregnancy-related risks and the postpartum state, as well as other hormonal factors, such as the use of hormonal birth control (56).

According to the INTERSTROKE⁷ study's findings, five modifiable risk factors - abdominal obesity, current smoking, diet, hypertension and physical activity - accounted for 80% of the population attributable risk for all strokes (59). The Global Burden of Disease 2019 study identified high systolic blood pressure, a high body mass index, a high fasting plasma glucose, an ambient particulate matter pollution, and smoking as the five main risk factors for stroke (54). Metabolic risk factors are often more strongly associated with ischemic stroke (60), whereas haemorrhagic strokes are more strongly associated with hypertension and impaired kidney function⁸ (61, 62). In general, the majority of strokes could be avoided by controlling blood pressure, engaging in regular physical activity, eating a balanced diet, and quitting smoking (63).

1.2.4 Risk factors of cardiovascular disease

Unhealthy diet, physical inactivity, tobacco use, harmful use of alcohol, overweight and obesity, high blood lipids, raised blood pressure, and raised blood glucose have been highlighted as the leading modifiable risk factors of increased risk of CVD (64-66). The modifiable risk factors are more closely linked to human lifestyle or behavioral choices, as an unhealthy lifestyle has been shown to hasten and exacerbate the atherosclerosis process (67). The findings from the Prospective Urban Rural Epidemiology (PURE) study⁹ (68) of 155722 participants without a prior history of CVD with a median follow-up of 9.5 years (mean age = 50.2 years) show that 71% of incident CVD cases could be attributed to 10 modifiable risk factors (hypertension, high non-HDL cholesterol, household air pollution, tobacco use, poor diet, low education, abdominal obesity, diabetes, low grip strength and low physical activity), with 40% of them being attributed to metabolic risk factors, of which hypertension was the largest risk factor, contributing to 22.3% of its population-attributable fraction (69). While 75% of the deaths were attributable to modifiable risk factors, with low education accounting for largest proportion of

⁷ It is a case-control, multicentre study that aims to examine the global and regional effects of traditional and emerging risk factors associated with stroke and its major subtypes in 22 countries (Source: O'Donnell *et al.* 2010).

⁸ defined by low estimated glomerular filtration rate.

⁹ PURE is a multinational, prospective cohort study conducted in 21 countries (4 high-income, 12 middle-income, 5 low-income) using standardized protocols and centralised training. This study aimed to examine the influence of societal factors on cardiovascular and lifestyle risk factors, and chronic disease incidence (Source: Teo *et al.* 2009).

population-attributable fraction for mortality at 12.5% (69). A key aspect of the primary prevention of cardiovascular risk and ultimately death is the identification of risk factors and the estimation of future risk. For this purpose, multivariable risk prediction scores incorporating these risk factors have been developed that can be used by primary care physicians to assess the risk of developing CVD among individual patients (70). Unarguably the most widely used risk score is the Framingham Risk Score (70), a sex-specific algorithm used to predict 10-year risk of CVD for an individual. Additionally, there are country specific risk scores such as QRISK cardiovascular disease risk score for the United Kingdom (UK), developed to provide a risk estimation more appropriately calibrated to their population, with weighing for social deprivation to address health inequalities in CVD in UK (71).

Since the inception of the Framingham Heart Study in 1948, the first epidemiological study to examine the population based risk factors of CHD (72), there has been decline in the CHD mortality rates all throughout the high-income countries owing to taking preventive measures (73). However, the absolute number of CVD cases continues to grow likely due to population growth and ageing (11, 27), and also with low- and middle- income countries said to be in the midst of epidemiological transition to non-communicable diseases (74). This indicates that the threat of CVD is far from over and that there is still space for improvement. Risk factors act on several levels, with lifestyle-related risk factors influencing the upstream health factors such as the metabolic risk factors (67, 75, 76). Additionally, small changes in lifestyle are feasible and may significantly reduce the risk of CVD, making them important target for prevention (77). Sedentary behavior has in the last decade entered the debate of lifestyle-related risk factors that affect the risk of CVD and premature death with evidence indicating that even the recommended amount of physical activity does not greatly mitigate the harmful consequences of prolonged sitting (78-81). The focus of this thesis is to assess sedentary behavior as an independent lifestyle-related risk factor for CVD and all-cause mortality, irrespective of engaging in physical activity.

1.3 Physical activity, cardiovascular disease risk and mortality

The genesis of epidemiological associations between physical activity and health outcomes stems from the landmark study conducted by Morris and colleagues in 1953 (82). They concluded that double-decker bus conductors¹⁰ (i.e., physically heavier jobs; active workers) had lower rates of mortality, lower incidence and severity of coronary heart disease than bus drivers (i.e., physically lighter jobs; sedentary) (82). When postmen were compared to their sedentary colleagues, clerks and telephonists, a similar pattern emerged (82). Later, Paffenbarger and colleagues further extended the role of occupational PA in their study of San Francisco longshoremen (83, 84). They later examined the relation of leisure-based PA and exercise with heart attack in a study of 16,936 male Harvard College Alumni's aged 35-74 years using a self-reported questionnaire (85), which was responsible for the origin of several concepts of PA and exercise. In the latter study (85), physical activity was defined as the energy expended in kilocalories (kcal) while engaging in activities such as sports actively played, stairs climbed, and number of city blocks walked. Using 2000 kcal/week as a cut-off to define low and high energy categories of PA, the study indicated that physical activity, especially exercise, might be an independent protective risk factor for heart attack, with steep risk reductions in heart attack observed beyond 2500 kcal/week of PA (85).

Since then higher levels of physical activity are considered to reduce the risk of CVD by 30-50% (86). There was linear dose-response association observed for cardiovascular outcomes, with increasing duration of daily physical activity showing marked reductions in the incidence of any CVD (87, 88), including coronary heart disease (89, 90), stroke and heart failure (91, 92). As compared to being inactive¹¹, engaging in even modest levels of PA conferred protective benefit against CVD risk for middle-aged and older adults, with increase in risk reductions seen moving from lower to higher levels of PA (93). A pooled analysis of 661,137 individuals showed that individuals engaged in any leisure time activity had 20% lower mortality compared to those who did not report any PA across the age groups (94).

¹⁰Bus conductor is a person who sells tickets and collects fares on a bus, and is constantly on feet and moving throughout the journey; especially on a double decker bus wherein there are two storeys.

¹¹ In this inactive refers to having a sedentary job and engaging in no recreational activity.

The lifetime risks of CVD for poor physical activity (0 minutes per week of moderate-to-vigorous intensity PA) from ages 45 through 85 years were 52.7% and 42.4% in men and women, respectively (87). It has been observed that not just a moderate-increasing and light-stable pattern of PA from midlife to older ages were associated with reduced risk of CVD and all-cause mortality (95), implying that past PA in early life was insufficient, but a sustained active lifestyle over time was more crucial. Regardless of previous physical activity and established risk factors, older adults who increased their physical activity gained significant cardioprotective and longevity benefits (96, 97), suggesting that a primary prevention approach in later life is still worthwhile. In essence, there is unequivocal evidence that higher intensity of physical activity has a strong graded effect on CVD risk and all-cause mortality.

1.4 Defining Physical Activity and Sedentary Behaviour

Physical Activity (PA) is defined as any bodily movement produced by skeletal muscles that results in energy expenditure (98). The amount of energy expenditure doing an activity is dependent on duration, frequency and intensity (i.e., energy exerted by an individual measured as a continuous variable ranging from low to high) (98). Physical activity is measured in Metabolic equivalent of task (METs) units. Each activity is assigned a MET value to quantify the energy cost and used as a descriptive indicator of functional capacity (99). MET values are defined as the ratio of working metabolic rate to the resting metabolic rate (RMR) (100). One MET or RMR is the amount of oxygen consumed at rest, sitting quietly in a chair, approximately 3.5 ml.O₂/kg/min or 1.2 kcal/min of a person weighing 70 kg (99). So, an activity with a value 3 METs will require three times the resting metabolism (99). PA can be classified into three intensity groups (**Table 1**): light (1.6 to 2.9 METs), moderate (3.0 to 5.9 METs) and vigorous (≥ 6.0 METs) (100). Exercise is defined as planned, structured, and repetitive bodily movements done to improve or maintain one or more components of fitness, and is usually associated with activities of sports or conditioning (98). Exercise per se is a sub-category of physical activity. It is worth noting that exercise and MVPA are most often used interchangeably in epidemiological studies, although in certain contexts such as rehabilitation of person with a disease, exercise might not reach MVPA intensity.

Intensity category	Major heading	Specific activities (METs)
Light (1.6-2.9 METs)	Home activities	Ironing (1.8)
	Lawn and garden	Operating snow blower, walking (2.5)
	Walking	Walking, 2.0 miles per hour, level, slow pace, firm surface (2.8)
Moderate (3.0-5.9 METs)	Walking	Stair climbing, slow pace (4.0)
	Sports	Horseback riding, general (5.5)
Vigorous (≥ 6 METs)	Sports	Boxing, sparring (7.8)

Table 1 METs for different intensities of physical activity. Source: Ainsworth *et al* (100)

Epidemiological studies drew conclusions on the impact of sedentary living up until the turn of the century, and even into the early 2000s, by using either a weak proxy marker (e.g., sitting time) or by distinguishing it from light-intensity physical activity (101). The term “sedentary” was also used to describe low levels of PA or the absence of high intensity levels i.e., moderate-to-vigorous physical activity (MVPA), and in later instances, it referred to not being able to achieve the recommended PA guideline (102). However, SB is not the same physical inactivity but is rather a distinct construct, which is contextualised in the upcoming section. Individuals are currently classified as “physically active” if they meet the defined physical activity guidelines (103). While a person is considered as “physically inactive” if they do not engage in enough physical activity to achieve the recommended levels (104). In 2016-2017, Sedentary Behaviour Research Network (SBRN) constituted a consensus project to harmonize the definition of sedentary behaviour and its related terminology. Sedentary behaviour (stems from the latin word *sedere*, which means to sit) is any waking behaviour characterized by an energy expenditure ≤ 1.5 METs while in a sitting, lying or reclining posture (104). Example of SB include watching television, sitting and working on a computer.

Sedentary behaviour, light intensity physical and moderate-to-vigorous physical activity are collectively known as wake-time movement behaviours. Each of the movement behaviour can be

defined in terms of frequency, duration, intensity, and type of activity performed. Frequency is the number of sessions or days per week or month an activity is performed. The total duration refers to the time spent (in minutes or hours) in a specific activity for a given period (day, week, month). Intensity refers to the level of effort required to perform a specific activity, and is mainly referred in terms of METs.

1.5 Is Sedentary behaviour distinct from physical inactivity?

1.5.1 Energy Expenditure

Energy expenditure (EE) is defined as the exchange of energy required to perform biological work. Energy balance which is defined as the state achieved when the energy intake equals energy expenditure is fundamental for healthy living (105). **Figure 4** depicts the three major components of total daily energy expenditure (TDEE) (106) (107-109): (1) resting metabolic rate (RMR), which constitutes 60-75% of TDEE and is the minimum amount of energy required by body for maintenance of major bodily functions in a state of physiological and mental rest; (2) the thermic effect of food (TEF), which accounts for around 10% of TDEE is the increment in energy expenditure above metabolic rate associated with the cost of digestion, absorption and storage of nutrients following meal intake; and (3) the thermic effect of physical activity (TEA) or physical activity-related energy expenditure (PAEE), is the amount of energy expended during physical activity. Energy cost of physical activity is the most variable component of total daily energy expenditure, encompassing anything from planned exercise to spontaneous physical activity such as fidgeting, posture control, non-specific ambulatory behaviour (e.g. pacing), and activities of daily living (110, 111).

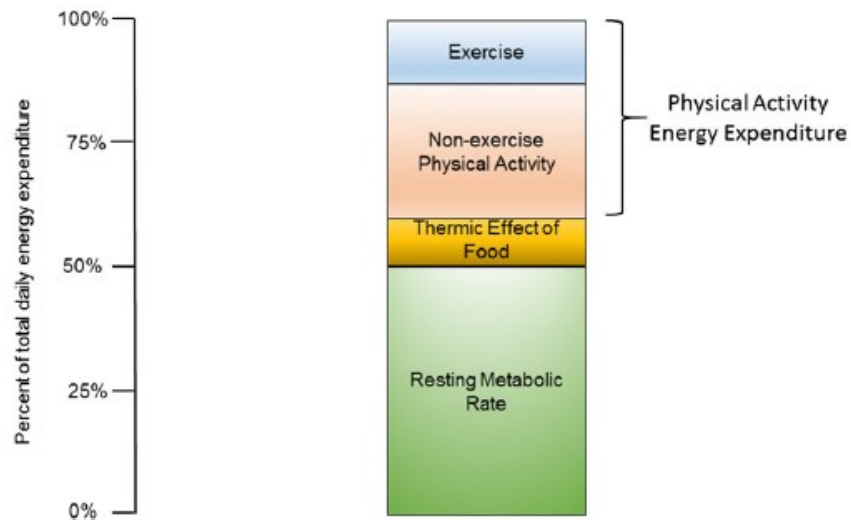


Figure 4 Components of total daily energy expenditure. Source: Melanson *et al* (112).

1.5.2 Non-exercise activity thermogenesis

The origin of SB as a separate construct of movement behaviour from physical activity can be traced back to the land work publications (113, 114) at the turn of the century, which coined the term “non-exercise activity thermogenesis” (NEAT). Levine and colleagues (113, 114) proposed that PAEE could be subdivided into exercise-related activity thermogenesis (EAT) and NEAT. EAT was defined as planned, structured, and repetitive physical activity that is done with the intent of improving health such as going to gym or doing sports (6, 113). Whereas NEAT was defined as the thermogenesis that accompanies physical activities other than exercise-related, such as activities of daily living i.e., low-intensity ambulatory movements, fidgeting, and posture maintenance (113). It has been demonstrated that NEAT mediates resistance to fat gain with overeating (113). Individuals with higher NEAT activation were able to release surplus energy from overeating, making it unavailable for fat accumulation, whereas individuals with lower NEAT activation gained weight and were more prone to develop obesity (113). NEAT was the most variable component of energy expenditure, accounting for around 15% of total daily energy expenditure in the most sedentary and up to 50% in most active individuals (115). As a result, not only the exercise component of PA, but also the occupational and domestic activities, play an essential part in body weight regulation.

The specificity principle, which states that the body's response and adaptation to a given form of exercise (stimulus) is very specific to that exercise, has been a cornerstone paradigm in exercise research (116). The low resistance associated with aerobic training, for example, will not produce the same responses as high-resistance weight training, implying that the stimulus to skeletal muscle, the cardiovascular system, and other organs will be very different. Even while exercise only accounts for a small percentage of total daily energy expenditure (**Figure 4**), it has advantages (117). In the absence of exercise, raising the resting metabolic rate by 100-200 kcal per day with drugs and hormones, for example, is unlikely to replace the unique benefits of regular exercise, such as fatigue resistance and increases in cardiac stroke volume (117). Given the acceptance of the specificity principle about exercise deficiency, the logical corollary would be that a deficiency of NEAT, which constitutes a larger proportion of total daily energy expenditure (**Figure 4**) might also cause biological problems.

Figure 5 illustrates that a brisk run of 35 miles/week or brisk walk for 5 days/week produced notably less energy expenditure and muscular contractions than the intermediate amount of NEAT for a person weighing 70 kg with a physical activity level (PAL) of 1.85¹² (118). Simply fidgeting in a chair has been demonstrated to increase energy expenditure by 20 to 30 percent as compared to sitting (119). In conclusion, we cannot simply replace the NEAT shortfall, which involves hundreds of daily muscular contractions, with a bolus of exercise a few times per week.

¹² Physical activity level or PAL is a way of expressing ones' daily physical activity as a single digit and can be used to estimate the daily energy expenditure. It is defined as an individual's total energy expenditure during a 24h period divided by his or her basal metabolic rate. PAL can also be estimated using the physical activities performed by a person day to day, with each activity assigned a number, the physical activity ratio. PAL can then be computed using a time-weighted average of physical activity ratios. Source: United Nations University (1994)

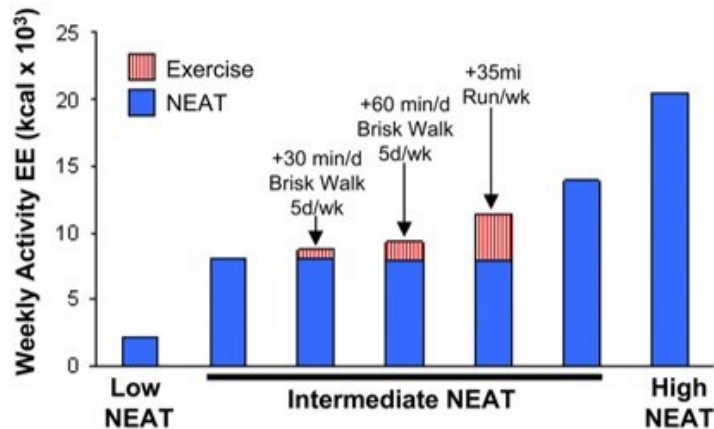


Figure 5 Comparison of weekly activity energy expenditure by undertaking exercise and NEAT. Abbreviation: EE, energy expenditure; NEAT: non-exercise activity thermogenesis; d/wk, days per week. Source: Hamilton *et al* (118).

1.5.3 Physiology of Sedentary Behaviour

Around the time of the first usage of the concept of NEAT, the first epidemiological studies investigating the relationship between deleterious effect of watching TV, as a proxy marker for sedentary behaviour, and cardiometabolic health outcomes were published (120-122). Most notable is the Nurses' Health Study (123) which explored the different domains of SB, such as sitting while watching TV, driving (these domains of SB are not included in the thesis). Later in 2004, Hamilton and colleagues (124) provided an animal-based model illustrating the role of lipoprotein lipase (LPL) regulation to underline the biological pathways of SB (formerly referred to as physical inactivity physiology) as a different class of behaviour from light-intensity physical activity (akin to NEAT) and exercise.

Lipoprotein lipase plays a vital role in the metabolism and transport of lipids. It is a multifunctional enzyme produced by tissues such as adipose tissue, cardiac and skeletal muscle, islets, and macrophages (125). It catalyses the hydrolysis of triglyceride core of circulating triglyceride-rich lipoprotein, chylomicrons, and very low-density lipoprotein (126). The catalysis produced non-esterified fatty acids and 2-monoacylglycerol is taken up for utilisation by tissues locally and processed differently; e.g. oxidised, or stored in skeletal and cardiac muscle or stored as neutral lipids in adipose tissue (125). SB appears to profoundly reduce this lipoprotein

lipase activity in skeletal muscle as compared to low-intensity ambulatory activity (akin to light-intensity physical activity) (127).

In rodent modelling of SB, hindlimb unloading¹³ in rats showed that after a delayed lag of 4 hours there is a mono-exponential decline in lipoprotein lipase activity in soleus (slow twitch oxidative fibres) and red quadriceps (mixed fibres) muscle sections relative to the ambulatory controls (128). After 12h of hindlimb unloading, restoring the contractile activity by treadmill walking at low speed for 4h period increased oxidative muscle lipoprotein lipase-activity but did not reach the levels above the ambulatory controls, though it did in white glycolytic muscles (128). Also, there was no effect on oxidative muscles when lipoprotein lipase was already high. This could be because white muscle fibres have a high recruitment threshold and are hence unlikely to be involved in regular ambulatory activities, whereas oxidative muscles have low activation threshold (129). There was a significant decrease in triglyceride-derived fatty acid uptake and heparin-release lipoprotein lipase during local sedentarity in hind limb skeletal muscle but not in heart and diaphragm, which is consistent with the established premise that tissue-specific triglyceride-uptake is determined by the amount of lipoprotein lipase activity present locally in tissues (128).

Injecting Actinomycin D¹⁴ into rodents prior to hindlimb unloading completely prevented the decrease in lipoprotein lipase-activity, although it did not have any effect on the ambulatory controls and when injected before the 4h period of restoring contractile activity did not alter rise in muscle lipoprotein lipase -activity induced by the slow treadmill walking (128). In other words, there is a lack of the effect of Actinomycin D in active muscles and a preventive effect in inactive muscles, implying that the lipoprotein lipase inhibitor gene(s) is only expressed during inactivity or that physical inactivity 'sensitizes' muscle to it (128).

In the same rodent modelling experiment, the SB induced decrease in lipoprotein lipase activity was independent of change in lipoprotein lipase mRNA concentration in solus or red quadriceps muscles after acute and prolonged intermittent sedentarity (10h/d for 11

¹³ Hindlimb unloading prevents weight-bearing activity in the hind limbs, thus providing a model to reduce contractile activity localised to the hind limbs.

¹⁴ Actinomycin D is a potent global inhibitor of transcription and has shown to raise lipoprotein lipase activity in adipose tissue without raising mRNA concentration. Source: Bey et al (2003).

continuous days) (128). This potential modulating role of lipoprotein lipase mRNA concentration could be dependent upon muscle fibre type and in turn on the intensity of activity, as there is a 2.5-fold increase in lipoprotein lipase mRNA expression in white glycolytic muscles after exercise (130, 131). This unchanged mRNA concentration is against the misconception that reduction in certain proteins during contractile activity is partly an effect of atrophy, which was not seen in rodent models (124). It has been shown that de-training healthy athletes results in decrease in muscle lipoprotein lipase that mainly occurs through post-translational mechanisms (132). Hence, the stable lipoprotein lipase mRNA concentration and the Actinomycin D results suggest that lipoprotein lipase transcription might not be required to up-regulate lipoprotein lipase -activity at the lower end of the energy expenditure continuum, instead there is a short-lived inhibitor protein for post-translational regulation of lipoprotein lipase which is induced by SB alone (**Figure 6**) (124).

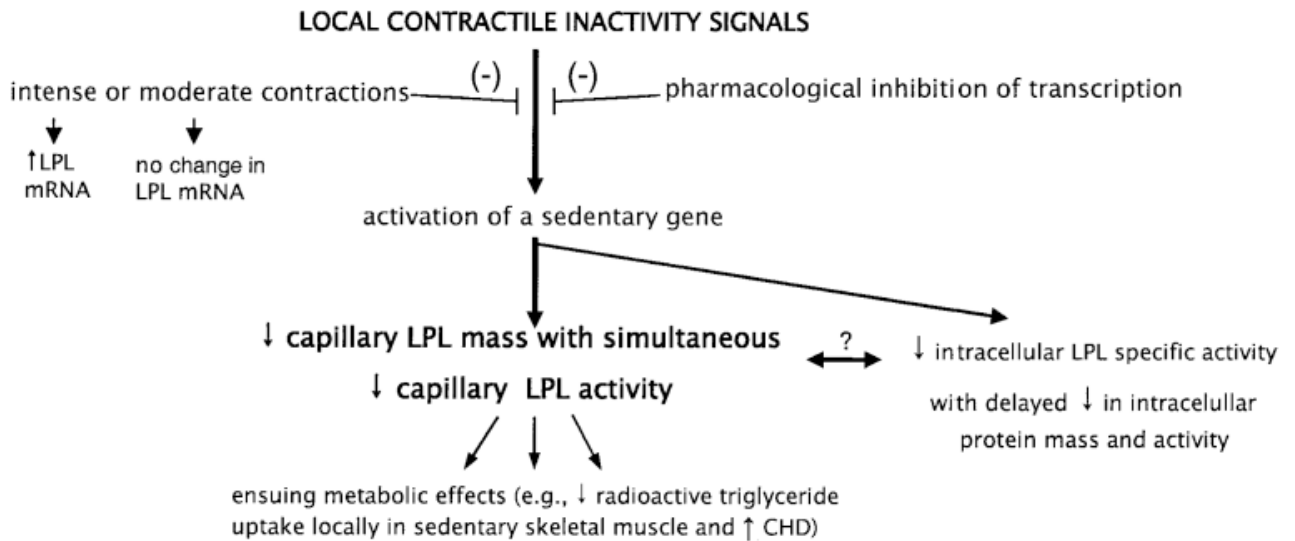


Figure 6 Potential pathways involved in decreasing LPL during contractile inactivity. Abbreviation: LPL, lipoprotein lipase; CHD, coronary heart disease. Source: Hamilton *et al* (124).

Therefore, it is suggestive that the lack of muscle contractions over the day would reduce the capacity of the body to regulate the lipids level and glucose in the blood. Also, light-intensity physical activity (LIPA) might be effective as high intensity PA in counteracting the

detrimental impact of sedentary behaviour. It is also seen that LIPA would act through different physiological processes than when exercise is performed. These physiological hypotheses that SB might act through independent mechanism is encouraging to study the association between sedentary behaviour and health outcomes.

PA has been expressed as a spectrum of energy expenditure, with vigorous intensity PA on one extreme and sedentary behaviour on the other (**Figure 7**). This continuum also depicts a range of muscle contraction intensity and frequency, and therefore energy expenditure (133). The current physical activity guidelines in general recommend undertaking at least 150 minutes per week of MVPA (134) i.e., around 2% of waking time in MVPA per day. As per this classification, sedentary behaviour and light intensity physical activity account for 98% of waking time. In addition to these guidelines, maintaining a healthy balance between time spent in SB and LIPA may be beneficial to public health (135). To put it another way, it is critical to consider all behaviours across the spectrum of energy expenditure range, not simply the least frequently practiced higher end (i.e., MVPA), even though it may yield the most benefits.

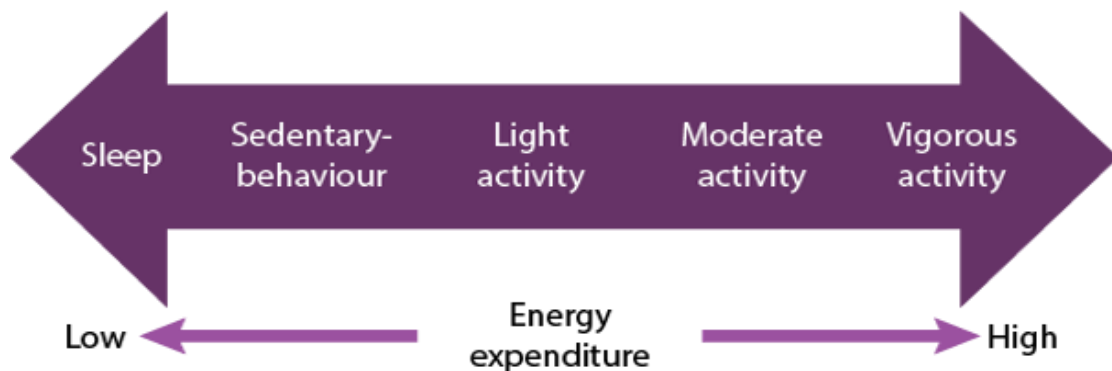


Figure 7 Energy expenditure continuum. Source: CBAC (136).

1.6 Potential biological mechanisms for sedentary behaviour induced cardiovascular disease

Although not completely understood, the physiological processes underlying the risk of prolonged sedentary behaviour, particularly sitting, with CVD are complex, span several biological systems, and interact to elevate the CVD risk (137). **Figure 8** illustrates how sedentary behaviour potentially acts across various biological systems to regulate vascular function (top

left), blood pressure (top right), blood glucose (bottom left), and cerebral blood flow (bottom right). **Vascular function:** An experimental study has previously observed that post prolonged sitting, flow-mediated dilation (FMD)¹⁵ can be reduced up to an 5% (from 22% to 17%) in absolute terms (138). A meta-analysis of experimental studies showed that acute uninterrupted sitting was significantly associated with vascular dysfunction (as indicated by decrease in FMD%) in the lower, but not the upper limbs (139). While evidence was sparse, it appeared that interrupting prolonged sitting might be protective against vascular dysfunction (139).

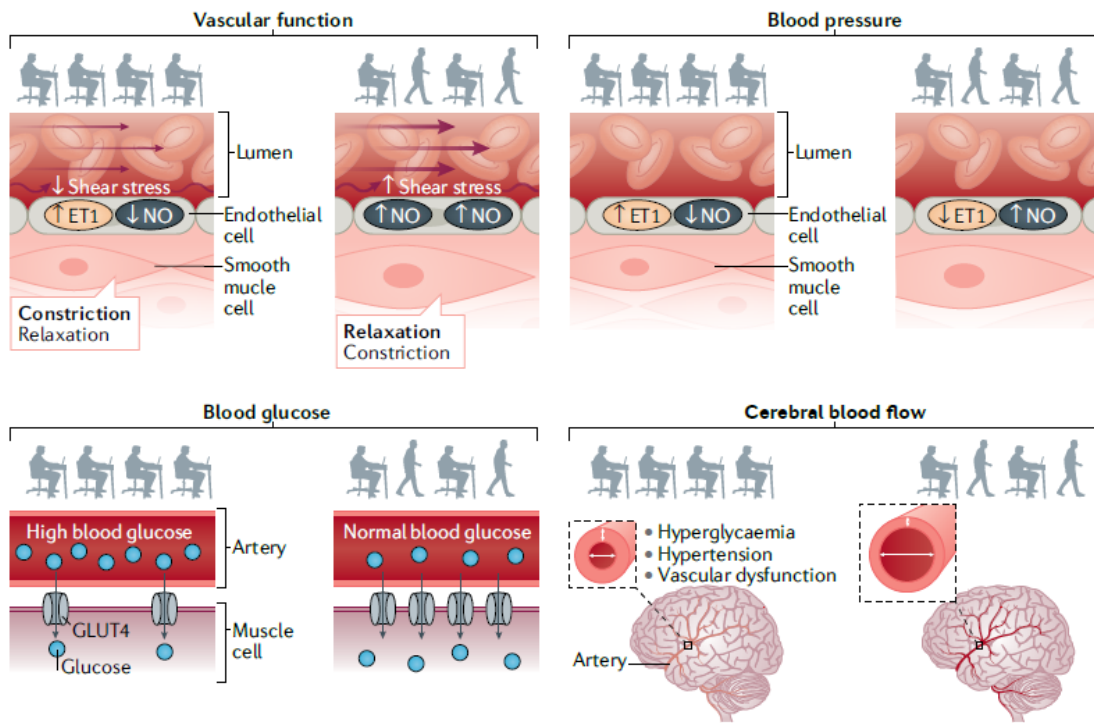


Figure 8 Potential mechanisms for sitting induced cardiovascular disease risk. Abbreviations: ET1, endothelin 1; GLUT 4, glucose transporter type 4; NO, nitric oxide. Source: Dunstan *et al* (137).

¹⁵ Flow-mediated dilation is the gold standard non-invasive method for the assessment of endothelial dysfunction (Raitakari *et al.* 2000), which is an early marker for atherosclerosis (Bonetti *et al.*, 2003; Davignon *et al.*, 2004).

A possible mechanism for sitting induced vascular dysfunction is through the reduction in blood flow and shear stress¹⁶. There is strong evidence that lowering shear stress decreases the supply of nitric oxide, a key regulator of vascular health, and leads to an overproduction of vasoconstrictors¹⁷ such as endothelin 1 (133). The lack of muscle contraction while sitting for extended period of time reduces the leg blood flow and thus shear stress in the lower extremities impairing endothelial function at the popliteal artery (140). Interventions such as fidgeting (141) or local heating of the foot (142) have shown to prevent the blood flow induced shear stress, preserving vascular function. Additionally, changes in blood viscosity (143) and an increase in muscle sympathetic nerve activity¹⁸ (144) could affect blood flow and shear stress.

Blood pressure: A recent narrative systematic review found both that breaking up prolonged sitting had short- and long-term beneficial effects on blood pressure, with walking but not standing being the most effective break strategy; although based on small number of studies using blood pressure as a secondary endpoint (145). Reductions in blood pressure with activity breaks was more pronounced in older adults or at-risk population compared to physically active health population (146). While sitting, a decrease in metabolic demand lowers the levels of vasodilator metabolites, potentially leading to vasoconstriction and increased peripheral resistance, which can raise mean arterial pressure (146). Due to the lack of relevant experimental evidence, this underlying mechanism remains largely hypothetical.

Furthermore, the sitting biomechanics itself can increase CVD risk owing to the flexion of hip and knee, and its associated “arterial bending” hindering leg blood flow and increasing peripheral vascular resistance and in turn elevating blood pressure (147). A predominantly seated posture can augment turbulent blood flow, and induce a low and oscillatory wall mean shear stress, both of which increase oxidative stress and promote atherosclerosis (133, 148). Regularly breaking up extended sitting with either simple resistance activity or light-walking

¹⁶ Shear stress or vessel wall shear stress is a physical phenomenon that is the consequence of the frictional forces generated by the blood flow on the luminal surface of the wall. Source: Roux et al (2020).

¹⁷ Vasoconstriction is the narrowing of the blood vessels resulting from the contraction of the muscles in the vessels walls. Source: Caplans’s Stroke (2009).

¹⁸ Muscle sympathetic nerve activity a vasomotor activity that governs the vascular smooth muscles distributed throughout the skeletal muscle. It plays a crucial role in regulation of arterial blood pressure and blood flow during exercise. Source: Joho (2016); Katayama et al. (2019).

breaks were effective in lowering both systolic and diastolic blood pressure in both normotensive and hypertensive populations, according to findings from pooled data of 4 randomised crossover trials (146).

Blood glucose levels: Prolonged sitting acutely raises postprandial glucose and insulin levels, resulting hyperglycaemia and insulin resistance, both of which are known to impair endothelial function and subsequently have negative effects on vasculature (149). This sitting-induced metabolic dysfunction shown to be attenuated by short breaks of physical activity (150, 151). A recent meta-analysis (152) of short-term trials showed that frequent PA breaks compared to sitting was significantly beneficial in reducing levels of glucose (standardized mean difference [SMD] = -0.54) and insulin (SMD = -0.56). Participants who were physically inactive or sedentary, as well as those who had impaired fasting glycemia or type 2 diabetes and had a higher BMI, saw stronger effects from PA breaks on glycaemic attenuation than those who were active or healthy peers (152). Furthermore, when the energy expenditure was matched, PA breaks were found to be marginally more effective for postprandial glycaemic control than a single continuous bout of PA (152).

Skeletal muscle primarily responsible for postprandial glucose disposal, achieved via muscle contraction- and insulin-mediated signalling pathways might explain the role of sitting on glucose metabolism (153). These pathways result in glucose transporter protein type 4 (GLUT 4¹⁹) transport glucose across the cell plasma membrane facilitating the uptake and removal of glucose from circulation (137, 154). A randomized clinical trial using skeletal muscle biopsy samples found that interrupting prolonged sitting with one- or three-day activity breaks consisting of either light- or moderate intensity walking reduced postprandial glucose and insulin levels compared to uninterrupted sitting for the same intervention period via an increased protein expression involved in both pathways (153). In addition, breaking up sedentary time with activity bouts led to increased skeletal muscle gene expression involved in carbohydrate metabolism which might regulate translocation of GLUT4 (155).

¹⁹ GLUT4 is part of a family of glucose transporter proteins. It is responsible for insulin-regulated glucose uptake into fat and muscle cells. Source: Stöckli et al. (2011).

The effect of breaks in PA as compared to prolonged sitting was statistically significant but small for triacylglycerols (standardized mean difference (SMD) = -0.26), while there were had moderate effects of PA breaks on insulin and glucose (152). The reasons for this could be related to the delayed activation of lipoprotein lipase following PA (156), as indicated by the fact that studies using a single day trial design found no significant effect on triacylglycerols, whereas those using two or multiple day designs did (152). Previous animal studies have indicated that prolonged muscle inactivity reduces lipoprotein lipase activity, effectively reducing muscle-mediated fatty acid uptake (137). Although human experimental research is needed to better investigate the CVD-related implications of this concept.

Cerebral blood flow: Impairments in cerebrovascular function are related to disease such as stroke and vascular dementia. Sitting-induced impairments in blood glucose (157) and blood pressure (158, 159) regulation are the likely pathways to cerebrovascular dysfunction (137). As sitting also elevates muscle sympathetic nerve activity (144), it possibly might induce cerebral vasoconstriction and thereby reduce blood flow to the cerebral region. A cross-over trial of 22 older adults (mean age = 78 years) did not find any short-term SB-induced effect on baroreflex system and cerebral autoregulation²⁰, although increases in blood pressure and cerebrovascular resistance were observed (158).

1.7 Measuring Sedentary Behaviour

The accurate measurement of movement behaviours is essential to precisely determine current levels and changes in the population, as well as to evaluate interventions targeted at modifying any of the movement behaviours. The majority of the research used to develop PA guidelines has come from subjective or direct assessments such as questionnaires, diaries/logs, and face-to-face interviews, with a self or proxy-reported questionnaire being the most common. Overall, questionnaires are simple to use, inexpensive and do not alter behaviour, making them ideal for large-scale population studies. Subjective measurements are most accurate when evaluating moderate to higher levels of PA; they are less accurate in populations such as older adults who acquire the majority of their PA from lower intensity activities, which subjective

²⁰ The combined actions of these two systems maintain cerebral blood flow.

methods struggle to assess (160-162). Moreover, self-reported methods are subject to recall and response biases (such as social desirability and inaccurate memory), and the inability to provide details on dimensions and patterns of SB (163, 164).

Objective measures of energy expenditure consist of laboratory or field based direct (e.g. room calorimetry) or indirect (e.g. ventilatory gas exchange detected by indirect calorimetry) methods (160). The direct and most precise measure of energy expenditure is called direct calorimetry, which measures the production of body heat in an individual small airtight chamber over a period of 24-hour period with a follow-up of a 10- to 12- hour fast to accurately assess resting metabolic rate (160). The indirect method of energy expenditure measures the rate of oxygen uptake and carbon dioxide production which is associated with energy transfer of substrate oxidation (160). It is conducted under pristine laboratory conditions and thus not practical for assessing activity-related energy expenditure for most activities of free-living. Although this technique is used mainly to validate the more feasible field-based measures of energy expenditure. Both the direct and indirect measures are also time, cost and technically intensive, and rather intrusive, rendering them cumbersome to use for large-scale epidemiological purpose (163). Monitor devices such as accelerometers, pedometers, inclinometers etc are more appropriate tools for objective assessment of movement behaviours per se (163, 165). Compared to using self-reported questionnaires, use of accelerometers might provide a better estimation of physical activity related energy expenditure (166, 167).

1.7.1 Relationship between self-reported and objective measures

A systematic review (163) of 148 studies involving adults did not find any clear correlation trend between self-reported and objectively measured physical activity, regardless of the type of direct measure utilized. The overall Spearman correlation (ρ) between subjectively and objectively measured PA were low-to-moderate with a mean of 0.37 (SD = 0.25) and ranged from -0.71 to 0.98²¹. PA assessed using self-reported measures were on average higher,

²¹ Negative correlations imply that self-reported estimates of the amount of PA are lower than when assessed using objective methods.

compared to using accelerometers, which was the most frequently used objective method. Mean correlations were higher in male-only studies ($\rho = 0.47$) versus female-only studies ($\rho = 0.36$), although they had similar range (males: -0.17 to 0.93; females: -0.17 to 0.95). In a review of 123 studies comparing assessment measures of SB, correlations were low-to-moderate with a mean of 0.32 (SD = 0.21), and ranged from -0.19 to 0.87²² (168). On average, self-reported studies underestimated time in SB by around 1.74 hours per day, with 72% of comparisons identifying this under-reporting. Heterogeneity was substantial ($I^2 = 99\%$) with differences in reporting of time in SB within studies going upwards of 6 hours per day.

When the independent variables are measured imprecisely, there is underestimation of effects of movement behaviour on health-related outcomes due to regression dilution bias (169). Using either subjective or objective method of measurement have reported to be associated with cardiometabolic biomarkers (170-172). However, objectively-assessed MVPA displayed more stronger associations with physiological arthrometric biomarkers against using self-reported measure (173). This might be indicative that using questionnaire as opposed to accelerometer might fail to detect true relationships with cardiometabolic disease risk factors or might underestimate the strength of the associations (174).

1.7.2 Type of Device

Accelerometers are small, portable devices that measure the body's acceleration in one or more planes of body movement (175). These devices can record second-by-second data regarding a person's frequency, duration, intensity and pattern of movement (175). In general, there are uniaxial (older generation) and triaxial (newer generation) accelerometric signals. The earlier devices, such as pedometers, were meant to track only ambulation, followed by uniaxial accelerometers, which measure acceleration in the vertical axis, and finally triaxial accelerometers, which measure acceleration in all the three axes of bodily movement (176). It has previously been shown that when comparing uniaxial accelerometer at wrist and waist level, wrist accelerometer failed to capture bodily movements contributing to physical activity

²² Negative correlations indicate that self-reported values of SB are higher while those assessed using direct methods are lower.

energy expenditure (177, 178). However, a simple summary measure derived from a triaxial accelerometer added significantly to the prediction of physical activity energy expenditure (179).

1.7.3 Choice of device placement and its validity

Research-grade accelerometers can be worn in various locations of the body, e.g., hip, waist, wrist, thigh (**Figure 9**). Because the central part of body is more immobile than the extremities, the central body is the most frequently used placement site (180). During the earlier stages of research using objective-measures of movement behaviours, the hip or waist was the preferred placement site for epidemiological and interventional studies, as it is the closest to the centre of the body and can best depict human movement (181). Waist-worn accelerometers have shown to provide valid approximation of physical activity and estimate SB (182). In the recent years there has been a shift to wrist placement with large physical activity surveillance projects worldwide using wrist placement to collect accelerometer data, for example National Health and Nutrition Examination Survey (NHANES) in the USA, UK Biobank in UK and Brazilian birth cohorts, and the Growing up in Australia Checkpoint (183). There are certain advantages to using wrist-worn accelerometers.

The device is worn for a full day, allowing researchers to collect sleep data and better characterise the day. The number of days to obtain reliable estimates of habitual physical activity using wrist-worn accelerometer ranges from 4 (30-year old adults) to 6 (middle-aged), with inclusion of weekend days strongly recommended for middle-aged group, however most studies use 7 days to represent a full week (184, 185). In a study of older adults, the majority of those who declined an invitation to participate in a 7-day accelerometer study did so because they did not want to wear the device (placement = right hip) for long periods of time (186). The number of wear-days chosen for this population thus must also consider the fact that the adherence to the usually recommended 7-day wear-time protocol might be difficult for older adults. Most of the current epidemiological studies (NHANES, Sweden Attitude Behaviour and Change (ABC) study) used the previous generation accelerometers on the hip, back or waist, attached using an elastic belt which might be discomforting to the participant and requires device removal when showering, doing water-based activities and during sleeping. Participant

might forget to reattach the device and it may affect the incompleteness of the data beyond the permitted periods of non-wear time leading to poor compliance (179).

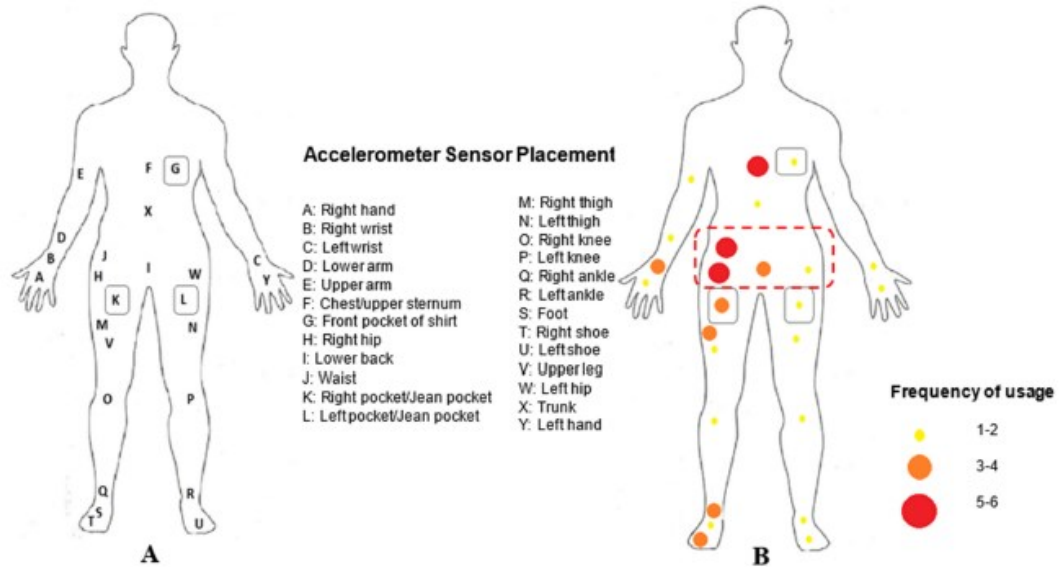


Figure 9 Different placement of accelerometers (A); Frequency of usage of different placements of accelerometer (B). Source: Allahbakshi *et al* (180)

The wrist-worn accelerometers which are compact in size, fastened like a watch, and water-proof, eliminate multiple removal of device, resulting in higher compliance rates with wear-time requirements (187). Data from NHANES (188) shows that compliance was 40%-70% in the hip-worn accelerometer study (2003-2006; wear time = 6 h/d, wear days = 6+), and 70%-80% in the wrist-worn accelerometer study (2011-2012; 21-22 h/d; 6+). Furthermore, non-wear time is computed as periods of zero activity for 20 minutes or longer when a waist-worn accelerometer is used (189-191), and excluding these periods from total waking time may lead to misclassification of movement behaviour patterns. A wrist-worn accelerometer seems to be more adapted for long-term compliance to assess SB than a hip, thigh or waist-worn accelerometer (192).

The positioning of the wrist-worn accelerometer is also important to consider, with the non-dominant hand being preferred. A dominant-wrist placement may increase an individual's time spent doing sedentary activities that require upper extremity movement, such as drawing

or writing, resulting in PA build-up when the individual is actually sedentary (175). By better differentiating SB from LIPA, which is the adjacent activity intensity to SB on the energy expenditure continuum, the placement on non-dominant wrist should help limit this misclassification of duration (193). This thesis utilises objective-data derived from a wrist worn accelerometer, GENEActiv, worn on the non-dominant wrist (**Figure 10**). A study examined the validity (187) of the non-dominant wrist-worn GENEActiv accelerometer by using posture classification for the measurement of sedentary time (i.e., sitting and lying) in adults under free living conditions, and found strong correlations between the sedentary time estimates between GENEActiv and activPAL (inclinometer) device (Pearson's $r = 0.81$), and a near perfect agreement at a group level for sedentary time during waking hours (mean difference = -3.44 min). As compared to the most frequently used accelerometer i.e., Actigraph, the posture classification of the GENEActiv has previously been shown to be superior for estimating sedentary time (194).



Figure 10 Original GENEActiv wrist worn accelerometer

1.8 Physical Activity Guideline Recommendations

In 1999 the Centres for Disease Control and Prevention, and the American College of Sports Medicine recommended that adults of all ages (≥ 18 years) should engage in at least 30 min of moderate-intensity physical activity (MPA) per day (195). Unlike its predecessors (196, 197), the 1999 recommendation was specific with respect to the amount of PA to be undertaken outside of structured exercise, and also illustrated various examples of accumulating 30 min of MPA in short bouts of everyday activity such as walking stairs instead of using elevator (195). The 2008

Physical Activity Guidelines for Americans (2008 PAGA) issued the recommendation that all adults should undertake at least 150 min (2h 30min) of MPA or 75 min (1h 15min) of VPA per week, or a combination equivalent of MVPA (198). This recommendation applied to older adults as well. In addition, they suggested to perform aerobic exercise in bouts of at least 10 min, spreading it throughout the week (198). For added benefits, adults were recommended to do muscle-strengthening activities for at least two days a week, and increase their aerobic PA up to 300 min per week (198). No recommendations were addressed specific to SB and LIPA, as most research up until that point was focussed on higher intensity PA or exercise per se. Also, almost all of the evidence used subjective measures of PA.

In the 2010's, national PA guidelines of several countries included non-quantitative recommendation for SB in terms of sitting less and breaking up prolonged sedentary time (199). The 2018 Physical Activity Guidelines for Americans (2018 PAGA) owing to the raising research interest in SB summarized evidence on its effect on health outcomes, and its relation with PA, especially higher intensity PA i.e., MVPA. It also gave a generic non-quantitative recommendation to "sit less, move more". The main PA recommendation remained the same for adults, although threshold of accumulating the MVPA target duration in bouts of 10 mins was removed. Interestingly, the Canadian guideline in 2020 used the same evidence as that of 2018 PAGA but arrived at a different conclusion. The Canadian 24-hour movement behaviour guidelines 2020 for adults of all ages recommended limiting time spent sedentary to 8 hours or less, which consists of a maximum of three hours of recreational screen time; and as much as possible breaking up extended durations of sitting (200). They were the first ones to state such quantitative limits on SB and also outlines the need to integrate physical activity, sedentary behaviour and sleep.

1.9 Adherence to PA Guideline Recommendation and prevalence of sedentary behaviour

Findings from the US based National Health and Nutrition Examination Survey (NHANES) study reveals that, based on self-reported measures, the adherence rate to the 2018 Physical Activity Guidelines for Americans for aerobic has not changed since its release in 2008, while time spent on SB has significantly increased by around an hour among adults (201, 202). There has been an

increase in SB prevalence in European Union between 2002 and 2017 from around 49.3 to 54.5% (203). A systematic review (204) showed that the time spent sedentary among older adults spent was on average 9.4 hours per day, which is equal to 65% to 80% of their waking day when measured objectively, which was twice of that estimated from self-report (mean = 5.3 h/d). From 2001 to 2016, total hours sitting per day increased significantly among adults 65 years or older (202). Using objectively-measured PA data showed 15% men and 10% woman aged 70 to 93 years met the UK recommendation of 2.5 hours of MVPA in bouts of ≥ 10 minutes (205). Another study reported that individuals over 61 years had the lowest adherence to recommendation at 11%, as compared to other age groups (206).

1.10 Total time spent in sedentary behaviour and cardiovascular disease

1.10.1 Meta-analysis and dose-response relationship between SB and CVD

Six review studies (207-212) reported on the association between sedentary behaviour and CVD, of which three (207-209) addressed the dose-response relation. A recent meta-analysis (211) has reported that higher self-reported total sitting time was associated with a 29% increased risk of incident CVD when not adjusted for physical activity; this risk estimate attenuated but remained significant at 14% (pooled HR = 1.14, 95% CI: 1.04-1.23) after adjustment for PA. A previous review by Biswas and colleagues (210) reported a similar effect size (HR = 1.14, 95% CI: 1.00-1.30), while in the study by Wilmot *et al.* the effect was stronger (RR = 2.47, 95% CI: 1.44-4.24). Grøntved *et al.* (207) observed a linear association, with a RR of 1.15 (95% CI: 1.06-1.23) for each 2 hours of television viewing per day and risk of fatal or non-fatal CVD. In contrast, a meta-analysis of 9 prospective cohort studies with 72,0425 participants (209) demonstrated a non-linear association between total sedentary time and incident CVD, with an increase in risk apparent only at duration greater than 10.04 hours per day (**Figure 11**; HR = 1.08, 95% CI: 1.00-1.14), after controlling for PA amongst other covariates. Similarly, independent of PA, a non-linear association between total SB and CVD mortality was observed, although unlike for CVD incidence the threshold above which the increased risk became significant was 6h/day (pooled RR = 1.04, 95% CI: 1.03-1.04 per h/day) (208). Patterson *et al.* (208) also reported a RR of 1.08 (95% CI: 1.05-1.12) above 4h/day for TV viewing as exposure.

Given that television viewing is a poorer measure for overall SB (213), the discrepancy between the study findings could be attributed to difference in the exposure variable.

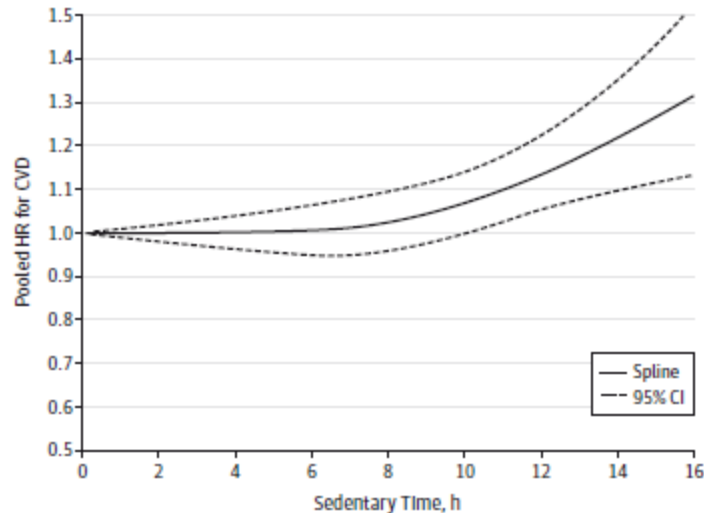


Figure 11 Continuous dose-response relation between self-reported sedentary time and incident CVD. Multivariable-adjusted model including physical activity and baseline CVD risk factors. Source: Pandey et al. (209).

Almost all of the studies included in these systematic reviews and meta-analyses used self-reported information based on a single-point measurement of SB, which is likely to understate the apparent associations. Moreover, questions to assess SB and its categorization into low and high levels for analysis varied across studies. None of the reviews focussed on older adults, that could be attributed to fewer self-reported SB studies based exclusively in this age group. Additionally, to date the main outcome of interest has been limited largely to CVD mortality with few studies examining incident CVD. Nevertheless, there are some individual studies with higher average age and outcome of incident CVD which are worth mentioning.

1.10.2 Relation between self-reported total sedentary time and cardiovascular disease in older adults

A prospective study with median follow-up of 12.2 years (214) found association between prolonged sedentary time (≥ 10 vs < 5 h/day) and incident CVD stronger among women ≥ 70 years (HR = 1.22, 95% CI: 1.09-1.36), but the same was not true for the younger women (50 to

69 years; HR = 1.08, 95% CI: 0.94-1.25). No effect modification by age was found with CVD death as an outcome in another study using the same cohort (215). Interestingly another study (216) among mid-aged women (mean age: 52.5 ± 1.5 years) also did not find any association between sitting time and incident CVD. Findings from a study (217) that included both men and women observed a slightly weaker association between TV viewing and incident CVD in older adults (HR per 1h/day = 1.04, 95% CI: 1.01-1.08) compared to those aged <60 years (HR per 1h/day = 1.10, 95% CI: 1.04-1.16). Strength of associations among older participants seem to vary depending upon whether SB is defined in terms of total sitting time or domain of sitting for instance TV viewing. Overall, findings from self-reported studies have been consistent in showing that greater SB is positively associated with risk of incident CVD risk.

1.10.3 Relation between objectively-measured total sedentary time and cardiovascular disease

Few observational studies have reported associations between objectively-assessed SB and CVD, but the findings have been inconsistent. Five studies used accelerometer-based estimates of SB, of which two reported statistically significant association between objectively-assessed total sedentary time and incident CVD (218, 219), while three did not (220-222). In all except one (222), the placement of accelerometer was hip. Bellettiere *et al.* (218) reported a multivariable (including MVPA) adjusted HR of 1.53 (95% CI: 1.09-2.14) for the upper quartile (10.3-14.1 h/day) against the lowest quartile (3.3-8.3 h/day) of total sedentary time among women with mean age of 79 ± 7 years. While in a study of all men of similar age group (221), the observed association was completely attenuated once physical functioning and high intensity PA were considered. Both positive studies deemed the shape of association as linear, with Bellettiere *et al.* (218) and Ballin *et al.* (219) reporting HRs of 1.12 (95% CI: 1.05-1.19) and 1.38 (95% CI: 1.12-1.72), respectively, for each additional 1h/day of sedentary time without adjustment for PA. Although, Dempsey *et al.* (220) observed associations with SB beyond 11 h/d alone, however this association did not remain significant on further adjustment for covariates and higher intensity PA. When using objective rather than subjective measures of SB, the

estimated associated with increased CVD risk appear to be greater on average, and in older women appear to be stronger than in older males.

1.11 Total time spent in sedentary behaviour and all-cause mortality

1.11.1 Meta-analysis and dose-response relationship between sedentary behaviour and all-cause mortality

Many meta-analyses (207, 208, 210, 212, 223-225) have previously studied the effect of sedentary behaviour on mortality, and few have examined the dose-response relationship to assess if there is a significant increase in mortality at a specific point along the daily sedentary time continuum (207, 208, 223-225). In a dose-response meta-analysis (224) of prospective studies, the association between TV viewing and all-cause mortality was J-shaped, with significant increases beyond 4 hours of daily TV viewing (RR = 1.12, 95% CI: 1.00, 1.25). Another meta-analysis found non-linear associations with an RR per h/d of 1.03 (1.01-1.04) below 3.5 hours, and higher increases above this level (RR = 1.06, 95% CI: 1.05-1.08) (208) when all studies included were adjusted for PA.

In a meta-analysis of data from 13 prospective studies (10/13 self-reported), the PA-adjusted association between total SB and mortality appeared non-linear; death risk increased more rapidly above 8 h/d of SB (RR per 1h/day: 1.04, 95% CI: 1.03-1.05) than below 8h/d (1.01, 1.00-1.01) (208). Using meta-regression techniques, Ku *et al* (226) observed a log-linear relationship between objectively-measured sedentary time and mortality in older adults, with elevated mortality risk becoming significant when sedentary time exceeded 9 hours per day. Although not all of the studies considered were focused solely on older adults and did not adjust for MVPA to determine independence, the majority of them did. A meta-analysis of prospective studies using harmonized accelerometry data (225) found a non-linear dose-response pattern in middle aged and older adults, with significantly greater risk associated with mortality reported beyond 9.5 hours per day of sedentary time, independent of MVPA (**Figure 12**). Moving from spending 7.5 to 12 hours per day of sedentary time was associated with a two-fold increase in mortality risk (225).

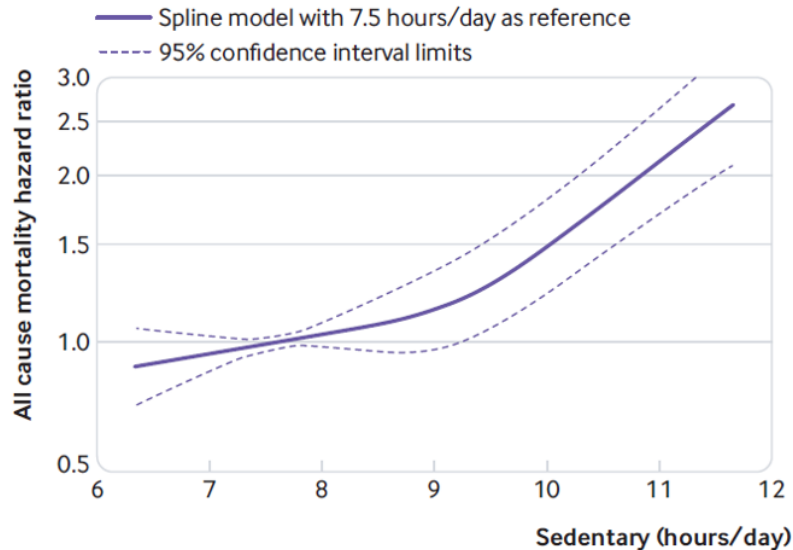


Figure 12 Continuous dose-response relation between sedentary time and incident CVD. Multivariable-adjusted model including physical activity and baseline CVD risk factors. Source: Ekelund *et al* (225).

1.11.2 Relation between total sedentary time and mortality in older adults

Based on the systematic review by Rezende *et al* (227), there were two prospective studies of moderate to high quality which assessed the association self-reported SB with all-cause mortality (228, 229). Pavey *et al* (228) found death risk in older women increased by 3% (95% CI: 1.01-1.05) for each hour per day spent sitting, after considering physical activity. During a median follow-up of 6 years, compared to participants who sat for <4 h/day, death risk significantly increased for those who sat for 8 h/d of sitting (228). Martinez-Gomez *et al* (229) showed that those sitting for less than 8 h/d had reduced risk of mortality, when compared with their counterpart in a population aged ≥ 60 years over a mean follow-up of 9 years.

Two prospective studies examined the association of objectively-measured SB with all-cause mortality exclusively in older adults (219) (230). In a sample of 1181 older men (230), those with the highest duration of SB (quartile 4; 11.2-17.6 h/day) had an increased risk of cause mortality (HR per 30 min/day = 2.73, 95% CI: 1.50-4.95) than those with the lowest SB (quartile 1; 4.9-9.3 h/day), independent of MVPA, over a median follow-up of 5 years. Among

adults aged ≥ 70 years, per 1-hour increment in SB per day was associated with 36% higher risk of mortality, during a mean follow-up of 2.7 years (219). One study did not account for MVPA or morbidity (219), while another did not adjust for any health-related risk factors (230).

1.12 Are the effects of physical activity and sedentary behaviour inter-related?

This section examines whether a particular duration of physical activity can mitigate or eliminate the deleterious effects of SB on CVD or mortality. Investigators have conducted effect modification (i.e., stratified analysis) or interaction studies to elucidate the role of physical activity in the association of SB with CVD and mortality risk.

1.12.1 CVD

Physical activity has been shown to modify the deleterious effects of sitting time, and associations with hard CVD clinical endpoints have only been observed in the least physically active, not the most physically active (214, 231). Spending more time sitting increased incident CVD risk in all physical activity categories except the most active, according to a prospective study of postmenopausal women aged ≥ 50 years, with the highest risk among physically inactive women who also reported 10 hours per day of sitting (214). The detrimental effects of sitting for more than 5 hours per day were not attenuated by accumulating the suggested PA of 150 minutes per week, corresponding to 8.4 MET-h/week of activity, but were totally attenuated by accumulating 20.5 MET-h/week, which is 2.7 times the recommended duration of PA (214, 232).

Ekelund *et al.* (233) conducted a harmonized meta-analysis of prospective cohort studies ($n=850060$; deaths= 25730) to examine the association between SB and CVD mortality stratified by quartiles of PA. Results indicated a dose-response association between levels of sitting time²³ (9%-32% higher risk; p for trend <0.001) and TV viewing (3%-59% higher risk; p for trend <0.001) with CVD mortality in the least active group (<2.5 MET-h/week, $\approx 5\text{min}/24$). There was no significant increased risk for any category of SB in the most active group (>35.5 MET-

²³ There were four levels of sitting time in hours per day (0-3.9 (ref), 4-5.9, 6-8, >8)

²⁴ Equals to spending 5min/day in moderate intensity activity.

h/week²⁵), even among those who sat or watched TV for more than 8 hour/day (vs 4 hour/day) and 5 hour/day (vs <1 hour/day), respectively. This implied that the harmful effect of SB was completely eliminated by engaging in at least 1 hour or more of moderate intensity physical activity (233). There is also protection from the negative effects of sitting for those in the intermediate moderate intensity activity groups, but only for up to 8 hour per day (233). In another study where stratification was done by MVPA groups, associations was found only in those not meeting the PA guideline (1-149 min/week of MVPA) (234).

1.12.2 All-cause mortality

In a meta-analysis of 10 prospective studies, self-reported sedentary time was significantly associated with a 49% (95% CI: 1.22-1.75) higher risk for all-cause mortality among individuals with low physical activity, but not in those with high physical activity (210). In a harmonized meta-analysis from Ekelund *et al* (235) using self-reported individual-level data of over 1 million adults (≥ 18 years), the joint associations of PA with daily sitting time on mortality was examined by deriving a variable with 16 groups, made from cross-classifying four groups of sitting time (<4, 4 to <6, 6 to 8, >8 h/day) and four groups of PA (5, 25 to 35, 50 to 65, 60 to 75 min/day of moderate-intensity physical activity (MPA)), with the combined group of lowest sitting time (<4 h/day) and highest PA (60 to 75 min/day) serving as the reference category. In the two lowest PA categories, the risk of mortality was 12-59% higher than in the reference group (235). Those sitting 4 hours or more per day had a higher mortality risk in the second most active PA group (50-65 min/day of MPA), while there was no difference in mortality rate between the sitting groups in the most active PA group (60-75 min/day of) (235). When using TV-viewing time instead of sitting time, similar results were found, though unlike sitting time, among the most active PA group, those who watched TV for ≥ 5 h/day (worst group) had a significantly increased higher risk of mortality (HR = 1.16, 95% CI: 1.05-1.28), as compared to combined group of most active PA and least TV-viewing time (<1 h/) (235). Comparatively, among the least active PA

²⁵ Equals to spending 60-75min/day in moderate intensity activity.

group, those who watched TV for ≥ 5 h/day, the risk was significantly greater (HR =1.93, 95% CI: 1.76-2.01).

In a sample of 149,077 middle-aged and older adults (234), compared with the referent group (i.e., lowest self-reported sitting (<4 h/day) and highest MVPA (≥ 420 min/week or 7 h/week), combinations of higher sitting time and lower MVPA were deleteriously associated with death risk in those engaging in less than recommended PA or no PA at all (**Figure 13**). Across the groups of physical activity recommendation, only those sitting more than 8 hours and meeting the recommended PA had a significantly increased risk of all-cause mortality, with those engaging in PA durations beyond the recommendation, completing eliminating the risks attributed by sitting ≥ 8 h/day (**Figure 13**).

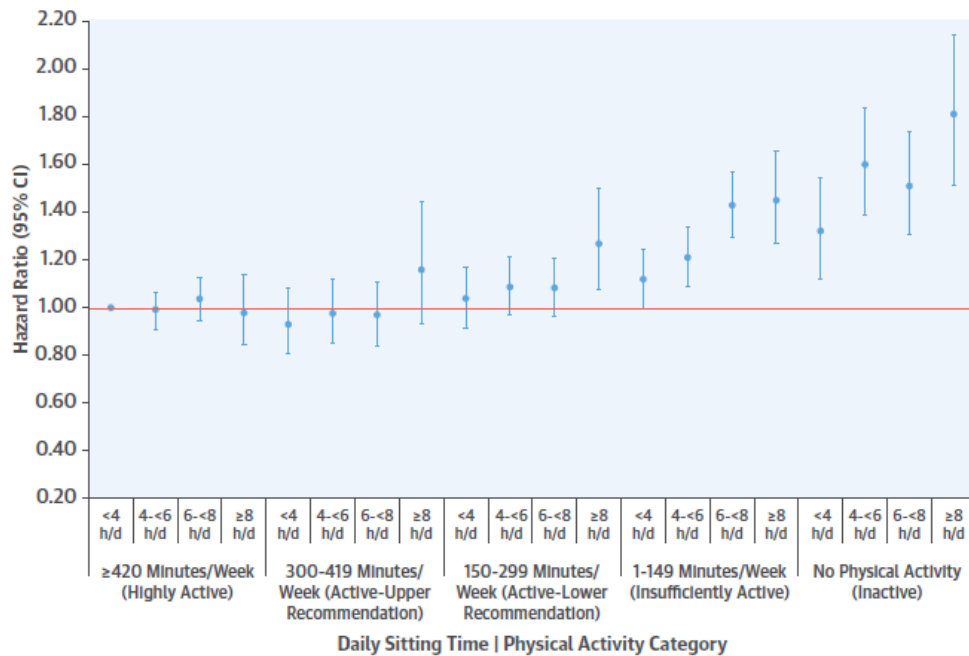


Figure 13 Joint associations of sitting time and MVPA with all-cause mortality. The reference category is those with the lowest sitting (<4 h/d) and most active (≥ 420 min/week). Source: Stamatakis *et al* (234).

In summary, the deleterious effect of SB on mortality was most pronounced among those with low physical activity, with the increased risk associated with prolonged sitting completely eliminated at PA levels beyond the recommended. Among adults, high levels of self-reported sitting time increased death risk in all but in participants who reported undertaking 60

to 75 minutes per day of moderate-intensity physical activity, which is approximately 3 times the daily recommendation of PA (21 min/day or 150 min/week of MVPA). However, this high level of PA reduces, but does not eliminate, the elevated risk associated with high TV-viewing time. Among middle-aged and older adults, the risk of mortality associated with sitting for ≥ 8 h/d was only eliminated when an individual engaged in more than 5 hours per week of MVPA.

1.13 Time-Use Epidemiology

Studies have mainly examined movement behaviours either individually or by mutually adjusting for one another movement behaviour using traditional regression approaches. This does not provide the whole picture of the impact of the energy expenditure spectrum. However, using the standard multiple regression techniques to understand the combined effect of movement behaviours is problematic as it violates the underlying assumptions of the said method. There is strong multicollinearity (positive correlation between LIPA and MVPA, negative correlation between LIPA and SB) and inherent co-dependency among the movement behaviours (236, 237). Indeed, movement behaviours have a closed structure²⁶, as time available in a waking day is finite; thus, using traditional approach would imply that time spent in one behaviour can be independent of time spent in another behaviour and is potentially infinite, which is incorrect (238). Given that the total time budget is fixed, an increase (or decrease) in time spent in one behaviour happens at the expense of other behaviours, essentially reallocating time among themselves. Thus, the amount of time spent in SB, LIPA and MVPA are considered as mutually exhaustive components of time use i.e., their sum will always constitute the whole of the waking day duration (239). In recent times, this has led to the integration of research on time spent in movement behaviours and sleep into a single unified field called “time-use epidemiology” and the variables being called “time-use data” (240). Time-use epidemiology is defined as the study of determinants, incidence distributions, and effects of health-related time-use patterns in populations and of methods for preventing unhealthy time-use patterns and achieving the optimal distribution of time for population health (240).

²⁶ Sum of all components equals the whole i.e., constant sum. Totalling of time spent in SB, LIPA and MVPA will always be 100% of the waking day duration.

Time-use behaviours carry relative rather than absolute information as they are bounded to the finite waking day duration (24hr if considering sleep as well) (241). Lately new analytical approaches including but not limited to the isotemporal substitution method and compositional data analysis have been incorporated into time-use epidemiology to overcome the aforementioned challenges to analyse time-use data and enhance the interpretation of how movement behaviours collectively relate to health outcomes.

1.13.1 Methodological considerations

Existing epidemiological evidence may underestimate the benefits of physical activity and the harms of sedentary behavior due to the associations varying depending upon the type of behavior being replaced. In the longitudinal study by Stamatakis *et al* (242), the partition model revealed that the increase of sitting time per hour/day was associated with a 3% (95% CI: 2–4%) increase in mortality risk, but when the type of activity being replaced was considered, the death risk raised to 5% (95% CI: 4–6%) and 17% (95% CI: 11–23%) for replacing sitting time with equal duration of standing and MVPA, respectively. Hence, it has been suggested that examining time-use data, which are inherently co-dependent using inappropriate statistical methods could lead to the under/overestimation of the effects of SB, LIPA, and MVPA on health outcome. The GRANADA consensus on the analytical approaches to examine the associations with objectively-assessed movement behaviors in epidemiological studies has recommended the use of compositional data transformation for co-dependent time-use data (243). The 2020 Canadian PA guideline has also emphasized the need to research the integrated effect movement behaviors on health outcomes (200). Of note, these methods refer to theoretical replacement, and not real displacement of time between movement behaviors i.e., comparing groups with different time-use compositions, and not change over the follow-up, given the lack of repeated data. This is reflected by the terminology sometimes used as “theoretical reallocation”. There is no standard terminology for describing this time exchange and earlier literature has used terms like replace, substitute, displace, and reallocate to denote the same thing.

1.13.2 Isotemporal substitution method

In 2009, Mekary and colleagues (244) first applied the use of isothermal substitution modelling in the field of physical activity, which was originally developed from nutritional epidemiology. It estimates the effect of replacing one movement behavior with another behavior for the same duration of time (244). The analytical model includes all but eliminates a single component of the movement behavior composition, given that the total day duration adjusted for in the same model represents this omitted component (244). By eliminating one movement behavior component from the model, the coefficients for the remaining components represent the consequence of substituting a given duration of included component instead of the eliminated behavior while holding the other behavior at constant (244).

1.13.2.1 CVD

Most findings using isothermal substitution are on CVD risk factors, rather than on hard CVD endpoints. A meta-analysis of cross-sectional studies using accelerometry data found that replacing 30 min per day of sedentary time with 30 min of either LIPA or MVPA results in lower WC and fasting insulin, as well as an increase in HDL-C, with additional reductions in BMI and fasting glucose when SB is replaced with MVPA for the same amount of time (245). Hamer *et al* (246) found no favorable effects of replacing SB with LIPA on HbA1c, BMI, HDL-C, or triglycerides.

Findings from the Coronary Artery Risk Development in Young Adults (CARDIA) study (247) using objective measures examined whether change in physical activity was associated with change in cardiometabolic risk factors over a 10-year period from early to late midlife. The study found a replacing a 30-minute increase in sedentary time with the same duration of MVPA resulted in significant decrease in WC, insulin, triglycerides, and an increase in HDL-C (247). This suggested that replacing the traditional increase in sedentary time with an increase in MVPA could prevent the typical deterioration in cardiometabolic health seen over time, and that it is never too late to improve cardiometabolic health, even in midlife.

There was no prospective study that had incident CVD as an endpoint using isothermal substitution method. A study (mean age = 62.8) found that reallocating 30 min of SB with both LIPA and MVPA reduced risk for CVD prevalence, but the reductions were inconsequential for

LIPA and small for MVPA (248). The 45 and Up study (234) reported replacing self-reported 1 hour per day of sitting time with either moderate or vigorous PA, but not walking associated with lower CVD mortality risk, with more pronounced replacement effect observed among those sitting more than 6 hour/day.

Some studies have suggested that replacing SB with LIPA has potential benefits for cardiometabolic health. If proven consistently, especially in prospective studies, LIPA could provide an alternative intervention strategy which is more feasible, easier to inculcate into daily life and less challenging than a more strenuous activity for enhancing cardiovascular health, especially for older adults (249). It could also be a viable option for people currently deemed active to improve their total volume of PA and so gain additional health advantages (250). With the exception of one study (234) that utilized subjective measures and did not analyze the impact of substituting LIPA with SB, there were no other prospective studies addressing hard cardiovascular outcomes. Given the cross-sectional nature of most studies, we cannot infer on how change in time spent in one or more movement behaviors at baseline effect the health outcome over time. It is also important to note that time reallocation may not necessarily reflect true temporal substitution.

1.13.2.2 All-cause mortality

In a large-scale epidemiological study of 201,129 middle-aged and older adults using self-reported measures, Stamatakis *et al* (242) reported beneficial associations on lowering mortality risk when replacing 1 hour of total sitting time with standing, walking, MVPA, and sleeping in those sleeping ≤ 7 hours per day. Results from four objectively measured prospective studies show that reallocation of 30 minutes of sedentary time with any physical activity lowered mortality risk, with stronger and sometimes more than double reductions observed when SB was replaced with MVPA (HRs ranging from 0.19 to 0.65) compared to LIPA (HRs ranging from 0.80 to 0.87) (245, 251). In the NHANES cohort (≥ 40 years) (252-254), it was found that replacing SB with LIPA or MVPA was associated with a decreased risk of death of any cause, with larger reductions in CVD mortality observed when SB was replaced with MVPA over a 6 years follow-up. In contrast, a study (255) with a smaller sample size ($n = 851$) demonstrated that replacing SB with LIPA had beneficial effect on both all-cause mortality and CVD mortality,

but replacing SB with MVPA only had a beneficial effect on CVD mortality, over a 14.2 year period, which is the longest known follow-up.

There was a lack of studies among older adults (256). According to one study with just older adults (n = 332) using subjective measurements, reallocating time in SB with MVPA was a protective factor, with mortality risk reductions of 10% to 60% for replacements of 10 and 60 minutes, respectively (257). In a study stratified by age (<65 and ≥65 years), Schmid *et al* (252) found that replacing 30 minutes of SB with LIPA lowered mortality risk in both age groups, whereas reallocating SB to MVPA was only beneficial to the older group.

1.13.3 Compositional data analysis

Even though the use of traditional isotemporal substitution analysis is widespread, it treats time-use data as absolute values, disregarding the intrinsic co-dependency of the movement behaviours (258). Chastin *et al.* (238) and Pedisic *et al.* (239) introduced compositional data analysis in 2014-2015 to deal with the relative, closed and co-dependent nature of time-use data. Each movement behaviour is considered to be a part or portion of a finite total or composition, due to which all the time-use variables are transformed into a constant sum composition usually by normalizing or rescaling them to add up to 1 (working in proportions) or 100 (percentages) (238). This property is referred to as subcompositional coherence. Also, the conclusions from analyses remain the same irrespective of the scale or in our case the time-unit utilised i.e., referred to as the scale invariance property (259). The compositional mean of time-use variables is computed using geometric mean and then transformed into isometric log-ratio (ilr) coordinates which represent the original composition in real coordinates onto the ordinary real space or a simplex (closed space) (259) (**Figure 14**). When the compositions are projected onto the simplex, the distance or the differences between compositions are well preserved due to the orthonormality property of the ilr-coordinates (259). These ilr-coordinates are included as exposures in the analysis with the first ilr-coordinate interpreted as the relative importance of one movement behaviour against the geometric mean of the remaining movement behaviours.

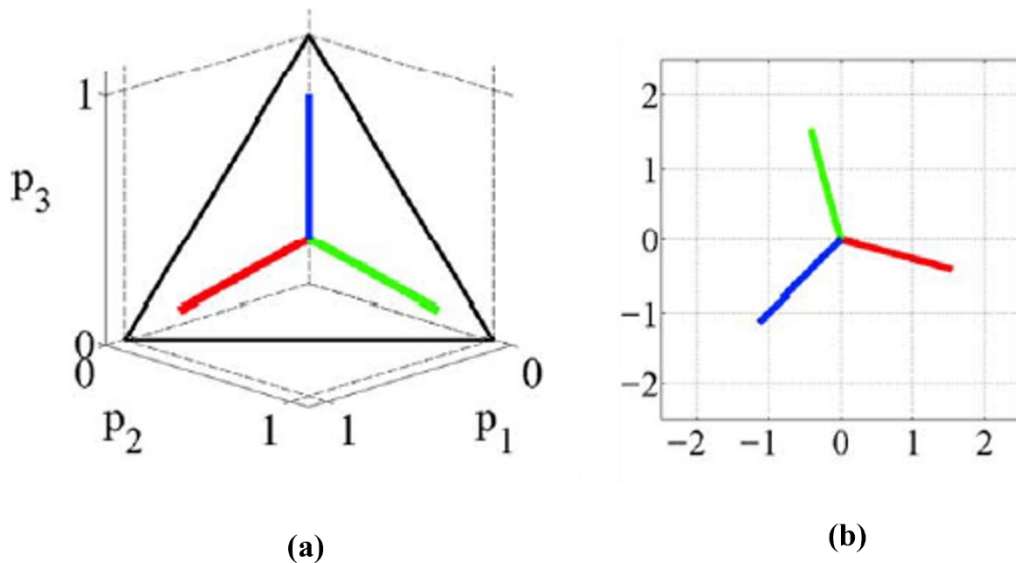


Figure 14 Demonstration of how isometric log-ratio transforms map three-part composition (P) in real coordinates in the ordinary real space (a) Vectors in the simplex space; (b) Isometric log-ratio space. Source: Andrew *et al* (260).

1.13.3.1 CVD

Few studies have investigated the relationship of the composition of movement behaviour with cardiometabolic health (238, 261-263). A recent systematic review of studies using compositional data analysis found that MVPA relative to other movement behaviours significantly lowered the risk of cardiometabolic biomarkers, while the associations for SB relative to other movement behaviours was not significant (264). The sample size for the two studies exclusively on older adults (262, 263) was quite small (122 and 366 persons), all studies were cross-sectional in design, and no study previously examined the hard CVD endpoint.

1.13.3.2 All-cause mortality

Only two studies have examined the prospective relationship between movement behaviour composition and all-cause mortality, and the findings were inconsistent (265, 266). McGregor *et al* (259) (N = 1468, deaths = 135) considered the entire 24hr by using objectively-measured wake-day movement behaviours and subjectively-assessed sleep measure and found that the proportion of time spent in SB relative to wake-day movement behaviours (LIPA and MVPA) and sleep, was not associated with mortality. While Rosen *et al* (266) (N= 851, deaths = 79)

found significantly greater risk of mortality when time spent in SB is increased relative to wake-day movement behaviours. Rosen *et al* (266) found no significant association for time spent in MVPA relative to SB and LIPA, but did find a detrimental relationship between SB relative to MVPA and death after accounting for LIPA. The quality of the evidence has been deemed as “very low quality” due to concerns regarding imprecision in measurement, attrition bias and residual confounding (264).

1.14 Pattern of Sedentary Accumulation

1.14.1 Origin of the concept of “Breaks”

As stated in section 1.8, recent physical activity guidelines have issued a generic recommendation to “break” prolonged sedentary time. The foundational evidence for the concept of “Breaks” stems from the 2008 cross-sectional seminal work by Healy and colleagues (267) based on a small sample of 168 participants from the Australian Diabetes, Obesity and Lifestyle (AusDiab) study using objective measures of movement behaviours assessed by a waist-worn accelerometer. In the study (267), increasing the number of breaks in sedentary time was favourably associated with adiposity markers, triglycerides and 2h plasma glucose, separately, after considering total sedentary time and MVPA. The investigators observed that adults who interrupt their sedentary time more frequently had a better cardiometabolic health profile than those who accrue sedentary time in prolonged uninterrupted periods.

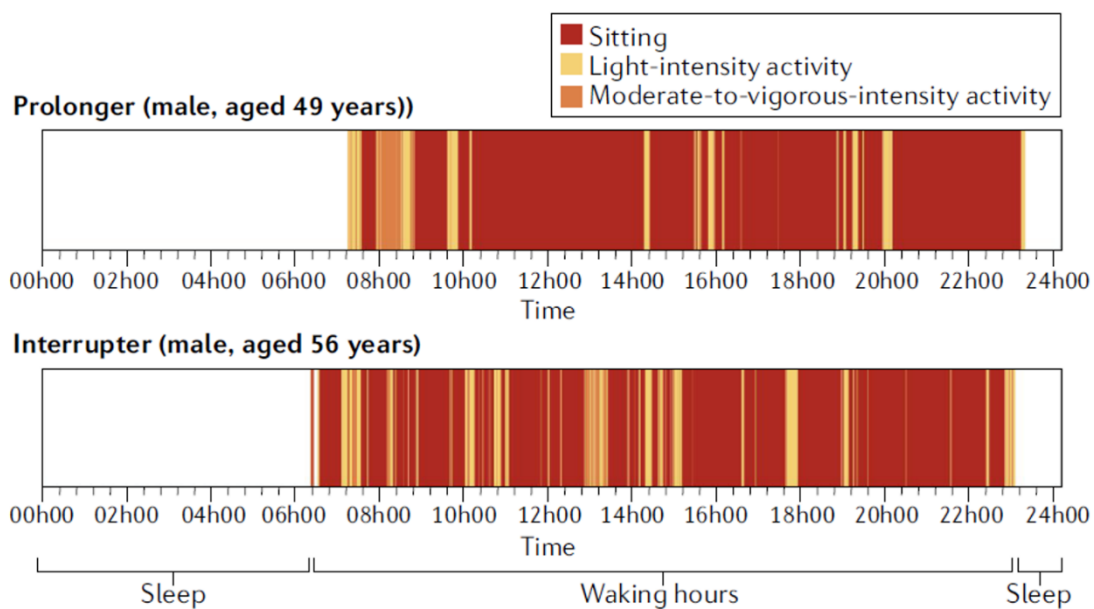


Figure 15 Visual illustration of distinct patterns of sedentary accumulation for two persons with the same duration of sedentary time in a day (a “prolonger” and a “breaker”). Source: Dunstan *et al* (137).

Figure 15 shows two participants who have the same duration of total sedentary time (~13 hours) and MVPA (~0.7 hours) but different patterning of a day, reflecting different behavioural patterns (103, 268). In **Figure 15**, on the top panel is a person who typically would sit for long periods of time i.e., the “Prolonger”; on the bottom panel is a person who typically might stand and move around more frequently during prolonged sedentary periods i.e., the “breaker” (103, 268). The relevance of examining one’s sedentary pattern in addition to total sedentary time was highlighted by this “prolonger” vs “breaker” hypothesis. It’s worth noting that a break might last as little as one minute and doesn’t always have to include exercise. Regular breaks in sedentary time, therefore, are likely to be feasible as a health intervention in a variety of situations, given that even a small amount of activity such as standing instead of sitting has been demonstrated to result in significant increase in overall energy expenditure and resistance to fat gain (113, 114).

1.14.2 Relationship of sedentary accumulation pattern with cardiometabolic risk markers

In two subsequent cross-sectional studies to Healy et al. (267) with larger sample sizes (50% male) and average age of around 46 years, independent of sedentary time and exercise, one (170) found breaking up sedentary time to be associated with lower waist circumference, higher HDL-C (for women only) and lower C-reactive protein²⁷; while the other (269) observed significant linear associations with WC, triglycerides, HDL-C, glucose, insulin and systolic blood pressure. The benefits of breaks were mostly seen with adiposity markers in those at risk of type 2 diabetes (270), with breaks in the highest compared to lowest quartile also being linked to better HDL-C in newly diagnosed type 2 diabetics (271). Overall, the associations with waist circumference were particularly consistent and clinically relevant however these could be prone to reverse causation, as studies show that adiposity markers might predict the amount of total sedentary time (272, 273) and breaks in SB (271). Also, as additional adjustment for adiposity variables attenuated the observed associations of sedentary breaks with most cardiometabolic biomarkers in majority of the studies, favourable association mainly remained

²⁷ Inflammatory biomarker

only with triglycerides and evidence remaining inconclusive for HDL-C and 2h plasma glucose (274). Of note, none of the studies on individual cardiometabolic biomarkers were exclusively focussed on older adults.

As a comparison, a meta-analysis of aggregated unadjusted data using cross-sectional studies found that increasing objectively measured sedentary time resulting in significant differences in fasting glucose, fasting insulin, triglycerides, waist circumference and HDL-C (263), whereas a review of older adults based on both subjective and objective measurements found a link consistently with metabolic syndrome and waist circumference (227).

Notwithstanding the mixed results and scarce prospective evidence, these cross-sectional studies have widely been referenced as evidence for promoting the frequent interruption of prolonged sedentary time for better cardiovascular health. Additionally, sedentary breaks are one of many ways to express the pattern of sedentary accumulation. Number of prolonged sedentary bouts of different lengths are the next most frequent used metrics to assess sedentary pattern. Van der Berg *et al.* (275) observed no or weak associations for sedentary pattern (measured as breaks, number of prolonged sedentary bout ≥ 30 min, average sedentary bout duration) with either glucose metabolism status or metabolic syndrome, independent of sedentary time and high intensity PA. On the other hand, in Huang *et al.* (276) number of breaks were associated with diabetes and HbA_{1c}²⁸, and prolonged sedentary time with HbA_{1c}, but not total sedentary time, lending support to the importance of sedentary accumulation pattern. It can also be seen that the choice of metric might play a role in explaining inconsistencies with results to some extent. This issue is further elaborated in section 1.16.4.

1.14.3 Relationship of sedentary accumulation pattern with CVD and all-cause mortality

To date, few longitudinal studies have assessed the relationship of sedentary accumulation pattern with incident CVD (218, 221) and all-cause mortality (230, 277). A study (221) among 1181 older men did not find significant associations of sedentary breaks or bouts with CVD events. In contrast, the findings from the OPACH study (218) of older women (sample size =

²⁸Glycated haemoglobin

5638, follow-up = 4.9 years) found that longer mean sedentary bout duration and total sedentary time comprised primarily of lengthy sedentary bout lengths²⁹ were detrimentally associated with CVD risk, even when MVPA was taken into account. For all-cause mortality, the REGARDS study (277) of middle-aged and older adults over a 4 year median follow-up supported the sedentary breaks hypothesis with higher number of breaks per sedentary hour found associated with a lower mortality risk, while another study (230) on older men did not find this association using the same measure over 5 years. Two of the studies used a single metric, the mean sedentary bout duration, to investigate the dose-response relationship of CVD and mortality risks. Unlike the REGARDS study (277), which found a non-linear relationship between mean sedentary bout duration and all-cause mortality, with an increased risk reported at around 10 minutes per bout, implying a threshold effect, the OPACH study (218) found a linear dose-response relationship with CVD risk using the same metric. Interestingly, when the joint associations of the two sedentary characteristics (total time and pattern) were evaluated, high total sedentary time and high sedentary bout duration together had the greatest risk for both outcomes (218, 277). These findings suggest that reducing and fragmentating sedentary time were both important although the OPACH study (218) did not provide findings adjusted for cardiovascular risk factors and MVPA. No association was found for either outcome when the sample was made up of older men.

1.14.4 Considerations on the choice of metric

There is no single gold standard indicator of sedentary accumulation pattern, with most studies using either sedentary bouts or breaks as a metric to illustrate the accrual pattern. Breaks in sedentary time is a measure of how often a person is being sedentary when total sedentary time is not considered or how often a specific duration of sedentary time is interrupted by a non-sedentary activity when accounting for the total sedentary time. However, breaks have been criticised as an imprecise metric to quantify sedentary accumulation patterns because it is prone to measurement error due their dependency on the recording period (accelerometer

²⁹Described by the metric Alpha, which assesses the distribution of sedentary bouts of different lengths.

wear time), as longer recording time might have more breaks (150); and for the inability to provide precise information on the nature of breaks in terms of length and intensity leading to misinterpretation of evidence as many equate sedentary breaks to short length of sedentary bout (150, 170).

Healy *et al* (267) in their landmark study suggested that a composite metric like breaks per sedentary hour would be more interpretable and useful in defining how time in SB is fragmented. With the exception of one (218), the majority of studies employed either sedentary breaks or length of sedentary bouts, with measures reflecting the distribution of sedentary bout duration being reported rarely, even for health outcomes other than CVD or mortality. In two intervention studies (older adults and workplace), the distribution metric was found to be the most sensitive in terms of detecting behavioural changes within and across individuals using a variety of objective measures of SB (278). While, total sedentary time and simple sedentary accumulation metrics like breaks or bouts rarely demonstrated such sensitivity to behavioural modification (278). The results from AusDiab study (279) has previously shown significant association of interrupting prolonged sitting with blood glucose using measures of sedentary accumulation based on distribution of sedentary bout duration alone. On the same line, in the Maastricht study (275) associations with glucose metabolism were observed for average sitting bout duration and number of prolonged bouts, but not with number of breaks. These findings are suggestive that the different metrics have different capabilities to detect effects and that the choice of metric to quantify sedentary accumulation pattern might be important. Moving forward in this growing research field of sedentary accumulation pattern, it is recommended to report total sedentary time, number of bouts and at least one metric characterizing the diversity of bout lengths in sedentary behaviour, as proposed by a recent review of SB measures (280).

1.15 Aims, Research Objectives and Conceptual framework

The overarching aim of this thesis is to examine the prospective association of objectively-measured sedentary behaviour with CVD and all-cause mortality among older adults while accounting for physical activity.

The objectives of the thesis are as follows:

1. Examine how different compositions of MVPA, LIPA and SB in a waking day are associated with incident CVD.
2. Determine the association of total sedentary time and pattern of its accumulation with incident CVD and all-cause mortality.

The thesis is strictly limited by the fact that, in contrast to some other earlier studies, sleep is not considered when considering the composition of movement behaviours. Since this thesis takes a behavioural approach, time spent in SB, LIPA, and MVPA is entirely up to the discretion of the individual, we chose to conduct analyses using the waking day period. The naturally process of ageing accompanied by an increase in sleep modification, which is likely controlled by underlying neurological processes (281) rather than being an individual's personal choice.

Figure 16 and **Figure 17** present a simplified conceptual framework for objective 1 and 2, respectively. Potential confounders are variables which are shown in literature to be causally associated with exposure and outcome, but not intermediate variables in the causal pathway between exposure and outcome (282). Adjusted variables are considered to be similar to the potential confounders, although whether or not they are real causes of the exposures is still debatable (depicted using dashed arrows). Both potential confounders and adjusted variables were adjusted for in the analytical models.

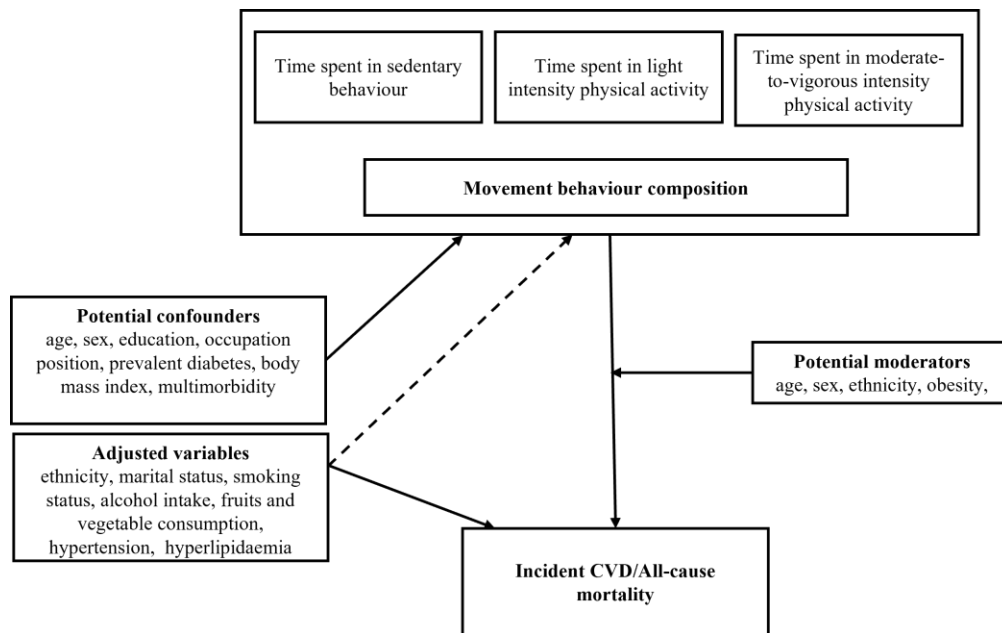


Figure 16 Conceptual framework for objective 1 of the thesis.

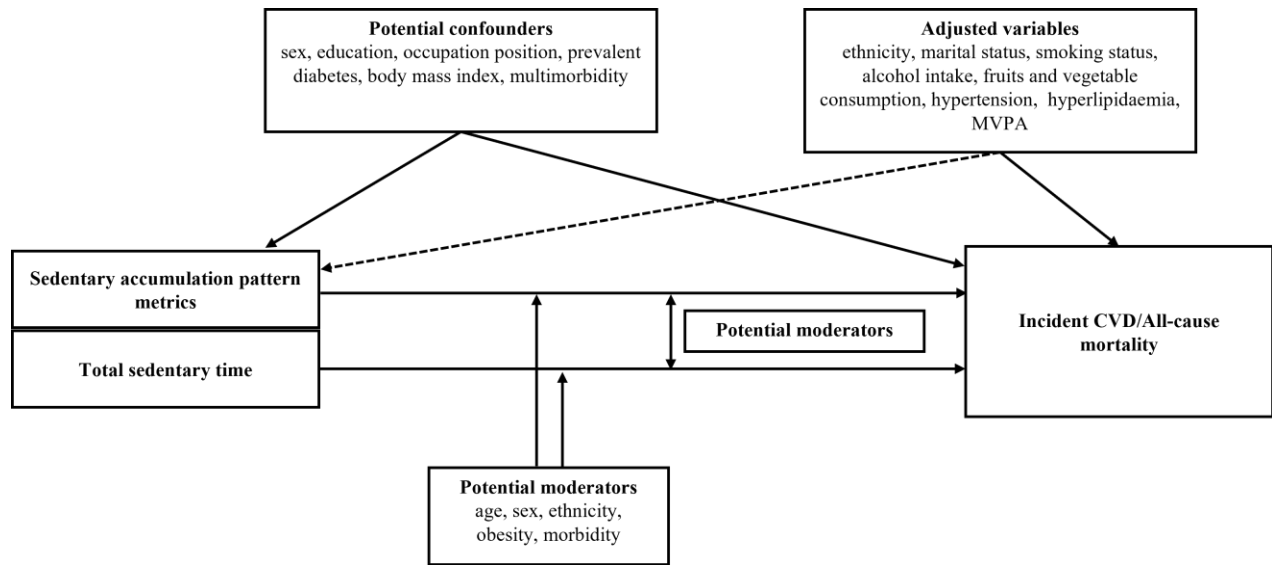


Figure 17 Conceptual framework for objective 2 of the thesis. Age was used as timescale and thus not included as part of potential confounder.

2 SAMPLE POPULATION AND MEASURES

2.1 Study population

This thesis is based on data from the Whitehall II accelerometer substudy. The Whitehall II study, also known as the “Stress and Health Study” is an ongoing prospective occupational cohort study of British civil servants set up as a successor to the original Whitehall study I (“Health Survey of Male Civil Servants aged 40 or over”) of 1960’s (283). The Whitehall I study found an inverse association between the employment grade and mortality from coronary heart disease (CHD) among the male British civil servants. This led to the creation of Whitehall II study to examine the degree and cause of social gradient, defined by employment grades in morbidity, and it also included women (284). The study was set up in 1985-88 among both male and female civil servants aged 35 to 55 years working in London offices of 20 Whitehall departments. The participants are broadly classified into three major occupational grades namely clerical and office support, middle-ranking executive, and senior administrative, with wide differences in salary across the levels. Of the 14,121 persons invited to join the study, 10,308 (73%) participants (men: 6895 (66%), women: 3413 (33%)) agreed. Since inception in 1985-88, the participants are followed-up every 2-3 years via questionnaires and every 4-5 years they are invited for clinical examination. Clinical data assessed at different phases included but were not limited to measures of anthropometry, cognitive function, mental health, physical functioning and accelerometer. The research ethics approval (reference number 85/0938) was obtained from the ethics committee of University College London, United Kingdom (UK), which was renewed at each contact with participants. Participants provided informed written consent.

2.2 Accelerometer assessed movement behaviours

The accelerometry measures were obtained at the clinical examination in 2012-13.

Participants without contraindications (i.e., allergies to plastic or metal, travelling abroad in the following week) were asked to wear a tri-axial accelerometer (GENEActiv Original; Activinsights Ltd, Kimbolton, UK) on their non-dominant wrist during 9 consecutive days over 24 hours (**Figure 10, page 49**). Data was sampled at 85.7 Hz, with acceleration expressed relative to gravity ($1 g = 9.81 \text{ m/second}^2$). Data from accelerometer was processed using GGIR package (285) and were corrected for calibration error (286) and Euclidean Norm of raw accelerations Minus 1 (ENMO) with negative numbers rounded to zero were calculated (287). Sleep periods were then detected using a validated algorithm guided by sleep log (288). Data from the first waking up (day 2) to waking up on the day before the last day (day 8) were used, corresponding to 7 full days. Waking periods were defined as periods between waking and onset of sleep. Days with daily wear time $\geq 2/3$ of waking hours was considered as valid and participants with at least 2 weekdays and 2 weekend days were included in our analyses (289). Non-wear period among valid days was corrected based on a previously reported algorithm (287).

Activity during waking hours was classified as SB when average acceleration over a 60-second epoch was < 40 milligravity (mg), 40-99 mg for LIPA and ≥ 100 mg for MVPA (290). The usual daily time spent in each activity level was calculated as the mean of time spent in each level over 7 days and for those with < 7 valid days ($n = 95$ (2.4% of all participants)), a weighted average was computed using data on weekend and week days (289). All measures sedentary accumulation pattern of were also computed for each day and averaged over the 7 days.

The 8 metrics used to measure the pattern of sedentary accumulation are as follows:

1. Mean sedentary bout duration: The total sedentary time divided by the number of sedentary bouts. This is one of the simplest and intuitive markers for prolonged and uninterrupted sedentary time, and is also referred to as the mean bout length or average bout duration. Greater value denotes that sedentary time is less fragmented (*unfavourable*).
2. Total time spent in prolonged sedentary bouts: Continuous periods of SB lasting at least 30 minutes. A higher value could correspond to a greater number of sedentary bouts with longer durations, few very long sedentary bouts or a combination of both (*unfavourable*).
3. The Gini index: A nonparametric measure for assessing variation in the length distribution of sedentary bouts (291) and ranges from 0 to 1. Closer to 0 denotes that bout lengths of all sizes contribute equally to form total sedentary time, while moving towards 1 (*unfavourable*) indicates that total sedentary time is mainly composed of a small number of longer length bouts (292).
4. Number of sedentary breaks: Also stated as the absolute number of breaks (293), is the number of interruptions (breaks) in total sedentary time (170, 267). A break is being defined as a non-sedentary bout in between two sedentary bouts (104). A higher value indicates that sedentary behaviour is more fragmented (*favourable*).
5. Breaks per sedentary hour: Number of non-sedentary breaks per sedentary hour (267, 293). Also referred to as break-rate (293) or fragmentation index (294). Larger value implies higher number of interruptions per sedentary hour (*favourable*).
6. Alpha: Known formally as the Power law scaling exponent, is a parametric measure to summarize the distribution of sedentary bout lengths (291). A higher value implies that total sedentary time is composed of a large proportion short length sedentary bouts (*favourable*). While a lower value corresponds to accumulating total sedentary time via small number of sedentary bouts which are lengthier in duration (*unfavourable*).
7. Transition probability from sedentary to LIPA or MVPA state: Defined as the proportion of total sedentary time before LIPA (or MVPA) to total sedentary time divided by mean

sedentary bout duration. Calculation of these two metrics were based on the work of Di and colleagues (292). A larger value represents frequent switching or transitioning from sedentary state to LIPA or MVPA states, respectively (*favourable*) (292).

Using retest data collected on average 26.5 (SD = 4.6) days following the initial measure, the reliability of acceleration measures was evaluated among 79 participants. There was a good test-retest reliability for all measures of movement behaviours with generally strong correlation (>0.70) between the two measures (Pearson’s *r* ranges from 0.62 to 0.82; **Table 2**).

Table 2 Test-retest reliability for all measures of movement behaviours used in this thesis (N = 79)

Measures of movement behaviours	Pearson correlation coefficient
Total time in sedentary behaviour	0.79
Total time in light intensity physical activity	0.78
Total time in moderate-to-vigorous physical activity	0.76
Mean sedentary bout duration	0.82
Total time spent in prolonged sedentary bouts (≥ 30 min)	0.79
The Gini index	0.77
Number of sedentary breaks	0.79
Breaks per sedentary hour	0.69
Alpha	0.79
Transition probability from sedentary to LIPA state	0.77
Transition probability from sedentary to MVPA state	0.62

2.3 Outcomes

CVD event was defined as the first occurrence of fatal or nonfatal CHD, stroke or heart failure. Nonfatal events were traced via record linkage to Hospital Episode Statistics (HES) database records using the participants unique National Health Services (NHS) identification number based on the International Classification of Diseases (ICD) codes for CHD (ICD-10 codes I20-I25, or procedures K40-K49, K50, K75, U19), stroke (ICD-10 codes I60-I64) and heart failure (ICD-10 code I50). Fatal CVD events were drawn from the UK national mortality registry (NHS Central

Registry). CHD and stroke cases were also determined using Whitehall II study-specific 12-lead resting electrocardiogram recording and MONICA-Augsburg stroke questionnaire, respectively (283, 295). The ascertainment of CVD events using HES has previously been validated against repeated biomedical examinations conducted in the Whitehall II cohort (295). CVD deaths were drawn from the UK Office of National Statistics death registry (NHS Central Registry). *Death* from any cause were obtained from data linkage to the UK ONS death registry.

2.4 Covariates

Numerous variables were considered as potential confounders or mediators in the association of SB with CVD and mortality. Covariates were measured by either using questionnaire or during the 2012-13 clinical examination unless otherwise noted. All clinical examinations were performed by trained nurses following standard operating protocols. When the data for covariates were missing, we used the data the previous assessment to get the most out of the data.

Sociodemographic factors

Age was calculated in years at the accelerometer measure. Sex (male, female) and ethnicity (white, non-white) were measured at the baseline phase (1985-88). Marital status was dichotomized (married/cohabitating, divorced/widowed/single). Socioeconomic status was indicated by level of education (\leq primary school, lower secondary, higher secondary school, university, higher degree; treated as a continuous variable) and occupational position. The occupational position is based on salary of the British civil service grade title were classified in three grades (296): (i) Administrative (highest status job; unified grades 1-7), (ii) Professional and Executive (middle; SEO, HEO, EO) and (iii) Clerical/Office Support (lower; clerical and “other” grades). Grades is a comprehensive measure that reflects salary, occupational status, and education.

Lifestyle factors consisted of alcohol consumption (0, 1-14 and 14 units per week to reflect the UK alcohol guidelines (297); One unit is 10ml or 8mg of pure alcohol), smoking status (current and recent ex-(less than 5 years) smokers, long-term ex-smokers, never smokers), and intake of fruits and vegetables (less than once daily, once daily, more than once daily).

Cardiometabolic risk factors

At the clinical examination, blood samples, blood pressure and anthropometric (weight, height) were taken by a trained nurse. Participants were also asked to self-report the list of any medications, tablets, tonics or pills taken in the last 14 days and whether they were prescribed by a doctor or not. The reported medications were then coded using the British National Formulary codes. Venous blood sample were taken from individuals who fasted (≥ 8 h) before undergoing a standard 75g 2h oral glucose tolerance test.

Blood was into fluoride monovette tubes and centrifuged on site within one hour. The concentration of LDL-cholesterol was calculated using Friedwald's formula. Hyperlipidaemia was defined as having LDL-cholesterol levels more than 4.1 mmol/l, or use of prescribed lipid-lowering medication. The latter measure did not distinguish statins from other lipid-lowering drugs such as fibrates, nicotine acid and its derivatives, cholesterol absorption inhibitors, or omega-3 fatty acid compounds (298).

Supine systolic and diastolic blood pressure was measured twice after 10 minutes of rest, and the mean was calculated (299). Hypertension was defined as systolic/diastolic blood pressure $\geq 140/90$ mmHg or use of antihypertensive medication.

Blood glucose was measured using the glucose oxidase method. Prevalent type 2 diabetes was defined by fasting glucose ≥ 7.0 mmol/l, or a self-reported doctor diagnosed diabetes, or use of glucose lowering medication or hospitalizations ascertained through record linkage to the HES (ICD-9 codes 250 or ICD-10 code E11).

Body weight of the participant was measured without shoes and in light clothing using Soehnle and Tanita electronic scales, and height was measured using a Stadiometer with the Frankfort plane in the horizontal position. BMI was calculated as weight in kilograms divided by the height in meters squared. BMI was categorized as < 24.9 (normal), 25-29.9 (overweight) and

≥ 30 (obese) kg/m^2 . Owing to the small number of participants, underweight older adults (BMI $< 18 \text{ kg/m}^2$) were grouped into normal BMI.

Multimorbidity index

This index was calculated as the count of specific chronic conditions which are the most common causes of mortality in high-income countries. The chronic conditions were ascertained from multiple sources: clinical examinations in the study, electronic health record linkage using NHS unique identification number, national HES database (data on inpatient and outpatient), cancer registry, the Mental Health Services Data Set (data on inpatient, outpatient and community care) and the mortality registry. The chronic conditions included in the index are as following (participants require to meet at least one criteria in the square parenthesis) (300): arthritis [self-reported longstanding illness, ICD-code codes M15-19], cancer [cancer registry with malignant cancer, ICD-10 codes C00-C97 to include prostate, colorectal, breast, lung, smoke-related, and melanoma skin cancers], chronic obstructive pulmonary diseases [ICD-10 codes J41-44], depression [usage of antidepressants, ICD-10 codes F32-33], Parkinson disease [ICD-10 code G20] and dementia [ICD-10 codes F00-03, F05.1, G30, G31]. The index additionally included CHD, stroke and heart failure as chronic conditions when the outcome was all-cause mortality. So, it ranges from 0 to 6 for analysis on CVD and from 0 to 9 for analysis on mortality.

3 OBJECTIVE 1: METHODS AND RESULTS

The first objective of the thesis was to use an innovative approach, compositional Cox regression to examine the association of time reallocation to different wake-time movement behaviours with incident CVD among older adults.

3.1 Statistical methods

Because an individual's total time available during the day is limited, increasing or lowering the amount of time spent in one movement behaviour requires reducing or increasing the amount of time spent in one or more other behaviours. Previous research has examined the relationship between these behaviours and health outcomes, particularly CVD, in isolation, and using standard regression techniques, with the underlying assumptions implying that time spent in one behaviour in the day can be independent of another behaviour in the day and that it is potentially infinite (238). However, time spent in different movement behaviours during the day are intrinsically co-dependent and finite. Compositional data analysis was used to account for the intrinsic relative scale and co-dependency of movement behaviours in a given finite waking period (238). It reduces the 3-part composition (time in SB, LIPA and MVPA) noted as z , into two exposure variables by transforming the compositional variables into two isometric log-ratio (ilr) coordinates, referred to as z_1 and z_2 . The following vector of ilr-coordinates was first constructed sequential binary partition to examine the overall importance of SB (one component of the daily composition of movement behaviour) relative to the other components (301) (Equation 1).

$$z^1 = \begin{pmatrix} z_1^1 = \sqrt{\frac{2}{3}} \ln \frac{SB}{(LIPA \cdot MVPA)^{1/2}}, \\ z_2^1 = \sqrt{\frac{1}{2}} \ln \frac{LIPA}{MVPA} \end{pmatrix} \quad (\text{Equation 1})$$

The first coordinate, z_1^1 , refers to the proportion of time spent in SB relative to the geometric average of physical activity (LIPA and MVPA). Second coordinate, z_2^1 represents the ratio of time spent in LIPA with respect to MVPA. Both ilr-coordinates are incorporated in the analytical model as

exposures since they together represent the entire wake-time movement composition and cannot be interpreted as separate entities. Using orthogonal rotation (259), the importance of the other remaining components of wake-time movement behaviours (LIPA and MVPA) compared relative to the geometric average of the remaining components were also isolated. Rotation 2 corresponding to the relative importance of LIPA was represented by ilr-coordinates z_1^2 and z_2^2 (Equation 2). Rotation 3 corresponding to the relative importance of MVPA was represented by ilr-coordinates z_1^3 and z_2^3 (Equation 3). Hence a total of six ilr-coordinates were constructed with a pair for each waking day.

$$z^2 = \begin{pmatrix} z_1^2 = \sqrt{\frac{2}{3}} \ln \frac{LIPA}{(SB \cdot MVPA)^{1/2}}, \\ z_2^2 = \sqrt{\frac{1}{2}} \ln \frac{SB}{MVPA} \end{pmatrix} \quad (\text{Equation 1})$$

$$z^3 = \begin{pmatrix} z_1^3 = \sqrt{\frac{2}{3}} \ln \frac{MVPA}{(SB \cdot LIPA)^{1/2}}, \\ z_2^3 = \sqrt{\frac{1}{2}} \ln \frac{SB}{LIPA} \end{pmatrix}$$

To make the results easier to comprehend and more intuitive, the daily time spent in SB, LIPA and MVPA were normalized to a 16-hour waking day (accounting for 8 hours of sleep \approx mean sleep duration in our cohort), which corresponded to the average duration in a waking day for our study cohort. Given the analysis of the compositional data using log-ratio approach, the zero values were imputed. MVPA had a value of zero in three records for CVD and nine records for all-cause mortality. These zeros were presumed to indicate unobserved small values, such as those arising from rounding off, falling below the level of detection or having a short observation period i.e., a result of the sampling process and not genuine zeros (302, 303). The log-ratio Expectation-Maximization (log-ratio EM) algorithm, which was implemented using the `IrEM` function in the R package *zCompositions*, used for left-censored data under a compositional approach, was used to impute the zero values of MVPA

(304). The detection level for left-censored data was set as 1 minute, below which values were treated as missing data.

Compositional Cox regression was used to analyse the data, with incident CVD as the outcome (259). The proportional hazards assumption was verified by using a Grambsch-Therneau test based on the scaled Schoenfeld residuals derived from a Cox proportional hazards model (305). For incident CVD, follow-up time started at the date of clinical examination in 2012-2013 wave and censored at the date of first CVD event (fatal or nonfatal), death caused by a cause other than CVD to take into consideration the competing risks or at the end of follow-up (31st March 2019), whichever occurred first.

Analyses were first adjusted for the waking day composition of z (z_1, z_2), sociodemographic and lifestyle risk factors. Then additionally adjusted for cardiometabolic risk factors and multimorbidity index, hereafter referred to as the health-related risk factors. The parameter estimates from the Cox Compositional regression models were used to estimate the risk associated with incidence CVD by pairwise theoretical reallocations of time between two movement behaviours while keeping the time spent in the third behaviour fixed at the reference duration. As an example, the estimated HR for a 10 min per day pairwise reallocation of time between SB and MPVA reflects the CVD risk associated with a hypothetical allocation of 10 min per day more/less to/from MVPA and remove/add the equivalent duration from/to SB, while keeping LIPA at the reference duration. This approach is also called reallocation analyses (259) or compositional isometric substitution modelling (306). Given the relative nature of compositional data, time reallocations were made in relation to a reference duration and for which several reference compositions of movement behaviours were defined.

Broadly, two set of reallocation analyses were conducted. First, we examined the importance of MVPA duration in the waking day time-use composition of an individual. To do this, three different reference compositions of movement behaviours were defined corresponding to an individual with daily MVPA duration set at: (a) 10 min, less than recommended (198); (b) 21 min, corresponds to current recommendation of 150 min per week of MVPA (307); (c) 30 min, an alternate approach to meet 150 min per week of MVPA. For these reference compositions, time spent in LIPA

and SB were set at 23 and 77%, respectively of the remaining daily waking time, based on the average proportion of each distinct movement behaviour seen in the study population.

Second set of reallocation analyses assessed the change in the risk of CVD incidence by variation in LIPA or SB duration. Two reference compositions composed of SB set at the 5th and 95th percentile, corresponding to 9 and 14 hours, respectively, and MVPA at 10 minutes. LIPA was set at the remaining duration of waking day by subtracting time spent in MVPA and SB from 16 hours. These analyses were repeated by setting MVPA at 21 minutes instead 10 minutes in the reference composition. **Table 3** presents all the reference compositions of movement behaviours.

Table 3 All reference compositions of movement behaviours

	MVPA	LIPA	SB
Less than recommended	10min	3h 39min	12h 11min
Current recommendation of 150 min per week of MVPA	21min	3h 37min	12h 2min
Alternate approach to meet 150min per week of MVPA	30min	3h 34min	11h 56min
SB set at 5 th percentile, Less than recommended MVPA	10min	6h 50min	9h
SB set at 95 th percentile, Recommended MVPA duration	10min	1h 50min	14h
SB set at 5 th percentile, less than recommended MVPA	21min	6h 39min	9h
SB set at 95 th percentile, recommended MVPA duration	21min	1h 39min	14h

Tests of effect modification were investigated by adding the multiplicative interaction terms “effect modifier* z_1 ” and “effect modifier* z_2 ” to the final adjustment model to assess whether age (<67.8 versus \geq 67.8 years (median split)), sex (men versus women), ethnicity (white versus non-white) and BMI (not obese versus obese) modified the association. As no interaction was detected, analyses for each group was not undertaken separately.

Sensitivity analysis

Further four analyses were conducted to assess the robustness of the results. First, the primary analysis was repeated by excluding participants with incident CVD events within the first 2

years of follow-up to examine the potential risk for reverse causation. Second, to examine association with incident non-fatal CVD cases, fatal CVD events were not considered as an event of interest but were rather censored at the date of death. Third, alternative threshold was used to classify SB (<45 mg) and LIPA (45-99 mg) (308). Fourth, results were provided by using time spent in movement behaviours without normalizing to 16 hour waking day period and was adjusted additionally for total waking day duration.

Software

All analyses were conducted using STATA statistical software version (StataCorp, College Station, Texas), R version 3.6.3 (for CVD) with a two-sided $P < 0.05$ considered statistically significant.

3.2 Results: Cardiovascular Disease

Of the 6308 participants in the 2012-2013 data collection wave, 4880 were invited to participate in the accelerometer sub-study based on the location (4680 seen at the London clinic and 200 seen at their home), 4282 agreed to participate and had no contradictions such as allergies to plastic or metal or were travelling abroad during the study period, with ultimately 4006 successfully returning the accelerometer with valid data (**Figure 18**). Excluding participants with prevalent CVD ($n=674$: CHD (611, 90.6%), stroke (43, 6.4%) and heart failure (20, 3%)) or those with missing covariate data ($n = 13$), led to an analytical sample of 3319 participants. Compared with participants invited to participate in the accelerometer sub-study ($n=4880$) and eventually included in the analyses ($n = 3319$), participants not included ($n = 1561$) were on average older (included vs excluded participants: 68.9 vs 70.1 years, $P < 0.0001$), more likely to be non-white (6.2% vs 11.7%, $P < 0.001$) and from a lower occupational position (49.7% vs 52.9% , $P = 0.04$) (**Table 4**). Overall, 97.6%, 1.4%, 0.6%, and 0.5% of the analytic sample has valid data for 7, 6, 5 and 4 days, respectively.

Among the 3319 study participants, a total of 229 incident CVD cases were recorded over a mean follow-up 6.2 (standard deviation (SD) = 1.3) years. The mean (SD) age of the sample population was 68.9 (SD = 5.6) years (range, 59.7-82.2 years) at baseline in the accelerometer substudy. The average time spent in SB, LIPA and MVPA were 11hr 52min, 3h 33min, and 58min, respectively. Their corresponding geometric means were 11h 45min, 3h 21min, and 44min, respectively. Compared with participants who did not develop CVD over the follow-up period, those who did were more likely to be old, non-white men, less educated, obese, hypertensive and diabetic all $p < 0.05$) (**Table 5**). Participants with incident CVD were likely to spend more time in SB, LIPA and less in MVPA (**Table 5**).

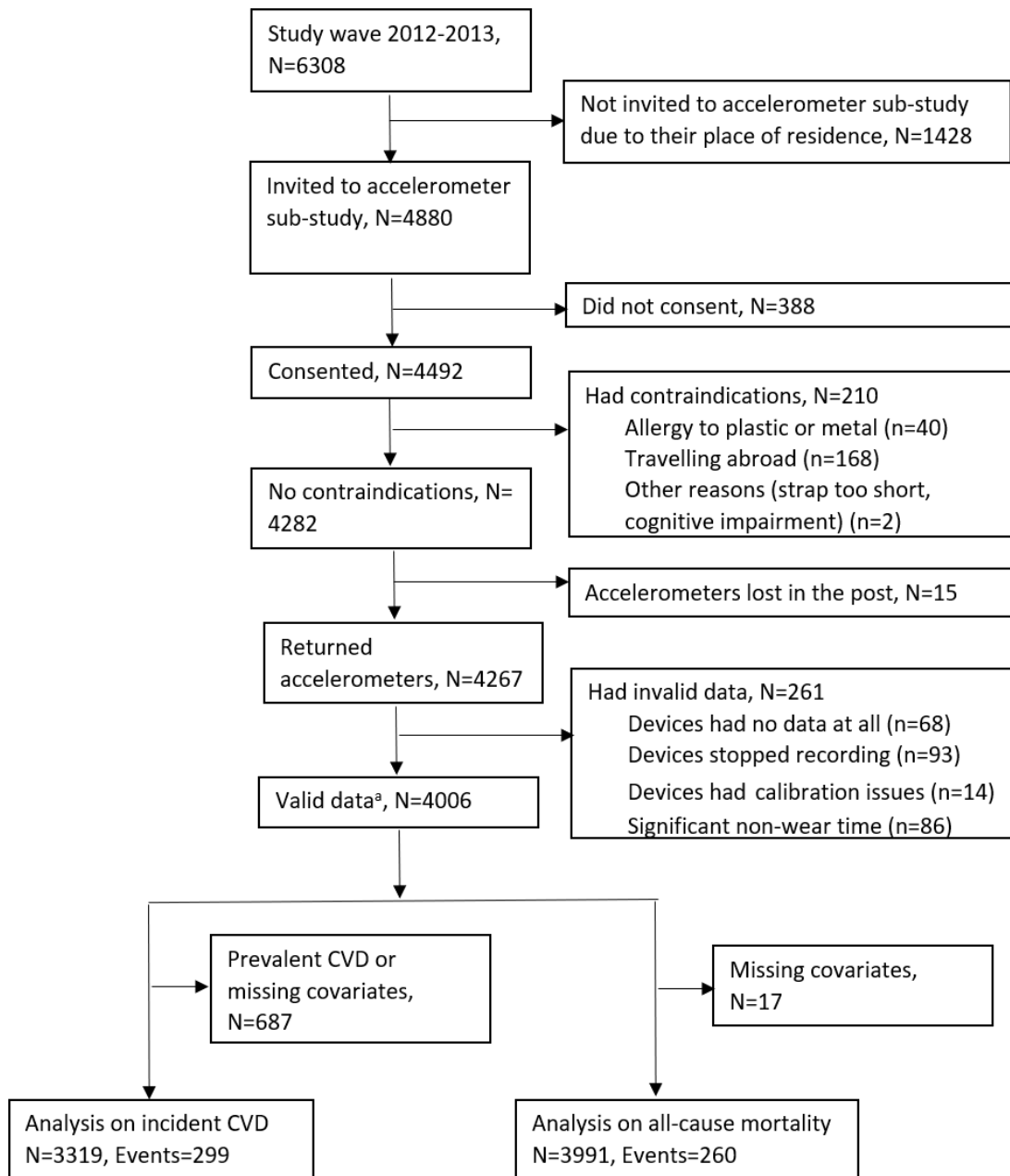


Figure 18 Participants flow chart

^aDefined as daily wear time $\geq 2/3$ of waking hours, for at least 2 weekdays and 2 weekend days.

Table 4 Characteristics of participants included in the study sample and those excluded for CVD outcome

Characteristics	Included in the study sample		P value
	No	Yes	
N (row %)	1561 (32.0)	3319 (68.0)	
Age (years), M (SD)	70.1 (5.9)	68.9 (5.6)	<0.0001
Women	443 (28.4)	885 (26.7)	0.21
Non-white	182 (11.7)	206 (6.2)	<0.001
Married/cohabitating	1147 (73.5)	2488 (75.0)	0.27
University or higher degree	492 (31.5)	1071 (32.3)	0.60
Low occupational position	825 (52.9)	1649 (49.7)	0.04

Increase of time in one daily movement behaviour relative to other behaviours

In the absence of any evidence of effect modification by age (P for interaction = 0.83), sex (P = 0.46), ethnicity (P = 0.40) and BMI (P = 0.14), the analyses were conducted in the full sample population.

Table 6 presents the CVD risk estimates associated with each movement behaviour relative to the remaining behaviours. There was no violation of the proportional hazards assumption according to Gramsch Therneau’s test using a scaling to time based on Kaplan-Meier curve. Increasing the time spent in SB while proportionally reducing time in physical activity of all intensities (LIPA and MVPA) was associated with a 34% (HR z_1^2 = 1.34; 95% CI: 1.01-1.79) higher CVD risk in model adjusted for sociodemographic and lifestyle variables. The association was no longer significant (HR z_1^1 = 1.24; 95% CI: 0.92-1.67) on further adjustment for health-related risk factors. More time in LIPA with proportional reductions in the other movement behaviours was not significantly associated with CVD risk (HR z_1^2 = 1.02; 95% CI: 0.68-1.54) in the fully adjusted model. Increasing MVPA with relative decrease in LIPA and SB was associated with 27% (HR z_1^3 = 0.73; 95% CI: 0.60-0.89) reduction in CVD risk when adjusted for sociodemographic and lifestyle factors, which slightly lowered to 21% on additional adjustment with health-related factors (HR z_1^3 = 0.79 ; 95% CI: 0.64-0.97).

Table 5 Participant characteristics at baseline (2012-2013) by incident CVD and all-cause mortality

Characteristics	Incident CVD (N=3319)			All-cause mortality (N=3898)		
	No	Yes	P value	No	Yes	P value
N (row %)	3020 (91.0)	299 (9.0)		3729 (93.5)	260 (6.5)	
Age (years), M (SD)	68.6 (5.5)	71.5 (5.9)	<0.001	69.1 (5.6)	73.7 (5.4)	<0.001
Women	830 (27.5)	55 (18.4)	0.001	967 (25.6)	63 (24.2)	0.55
Non-white	173 (5.7)	33 (11.0)	<0.001	272 (7.3)	23 (8.9)	0.36
Married/cohabitating	2262 (74.9)	226 (75.6)	0.79	2800 (75.1)	179 (68.9)	0.03
Higher education	995 (33.0)	76 (25.4)	0.01	1175 (31.5)	63 (24.2)	0.01
Low occupational position	1494 (49.5)	155 (51.8)	0.43	1884 (50.5)	146 (56.2)	0.08
Recent-ex/current smokers	151 (5.0)	23 (7.7)	0.05	204 (5.5)	16 (6.2)	0.64
1-14 units of alcohol per week	1712 (56.7)	166 (55.5)	0.92	2113 (56.7)	140 (53.9)	0.02
Daily intake of fruits & vegetable	2423 (80.2)	227 (75.9)	0.08	2971 (79.7)	193 (74.2)	0.04
BMI (kg/m ²), M (SD)	26.3 (4.2)	27.1 (4.4)	0.003	26.6 (4.3)	26.4 (4.3)	0.56
Hypertension ^a	1347 (44.6)	183 (61.2)	<0.001	1899 (50.9)	167 (64.2)	<0.01
Hyperlipidaemia ^b	1365 (45.2)	150 (50.2)	0.10	1885 (50.6)	136 (52.3)	0.58
Diabetes	311 (10.3)	58 (19.4)	<0.001	461 (12.4)	53 (20.4)	<0.01
Multimorbidity index (N chronic conditions) ^c			0.67			<0.001
0	2153 (71.3)	207 (69.3)		2248 (60.3)	112 (43.1)	
1	742 (24.6)	77 (25.8)		1103 (29.6)	87 (33.5)	
≥2	125 (4.1)	15 (5.0)		378 (10.1)	61 (23.5)	
Time in SB ^d (minutes/day), M (SD)	692.1 (88.4)	718.0 (96.8)	<0.001	697.4 (89.1)	741.5 (93.6)	<0.001
Time in LIPA ^d (minutes/day), M (SD)	209.5 (65.1)	195.2 (73.2)	<0.001	206.5 (65.3)	183.2 (75.1)	<0.001
Time in MVPA ^d (minutes/day), M (SD)	58.4 (37.6)	46.8 (36.4)	<0.001	56.0 (35.3)	37.5 (30.2)	<0.001

Values are N (col %) unless otherwise stated.

^aSystolic/diastolic blood pressure ≥140/90mmHg or use of antihypertensive drugs.

^bLow-density lipoprotein ≥4.1 mmol/l or use of lipid lowering drugs.

Ternary heatmap plots the predicted hazard ratios associated with CVD risk for different compositions of daily movement behaviours as compared to a reference composition (black dot; SB = 12hr 2min, LIPA = 3h 37min, MVPA = 21min per day) on a three-axis scatter plot (**Figure 19**). It visually illustrates that the same HR i.e., denoted by similar colouring within the plot, could be observed by adhering to a range of daily movement behaviours time-use compositions. In comparison to the other behaviours, MVPA appears to be dominant in influencing the HR for CVD.

Table 6 Relative importance of movement behaviours (SB, LIPA and MVPA) for incident CVD (N=3319)

Ilr-coordinate	Adjusted for sociodemographic and lifestyle factors ^a		Additionally adjusted for health-related factors ^b	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Rotation 1: relative importance of SB				
z_1^1 (SB increase relative to LIPA and MVPA)	1.34 (1.01-1.79)	0.04	1.24 (0.92-1.67)	0.16
z_2^1 (LIPA increase relative to MVPA)	1.21 (0.88-1.67)	0.25	1.16 (0.84-1.62)	0.36
Rotation 2: relative importance of LIPA				
z_1^2 (LIPA increase relative to SB and MVPA)	1.02 (0.68-1.51)	0.93	1.02 (0.68-1.54)	0.91
z_2^2 (SB increase relative to MVPA)	1.42 (1.20-1.68)	<0.0001	1.30 (1.09-1.56)	0.004
Rotation 3: relative importance of MVPA				
z_1^3 (MVPA increase relative to SB and LIPA)	0.73 (0.60-0.89)	0.002	0.79 (0.64-0.97)	0.02
z_2^3 (SB increase relative to LIPA)	1.17 (0.80-1.72)	0.41	1.12 (0.75-1.66)	0.58

^aAdjusted for age, sex, ethnicity, marital status, education, occupational position, alcohol consumption, smoking status, and diet.

^bAdditionally adjusted for body mass index, diabetes, hypertension, hyperlipidaemia, and multimorbidity index.

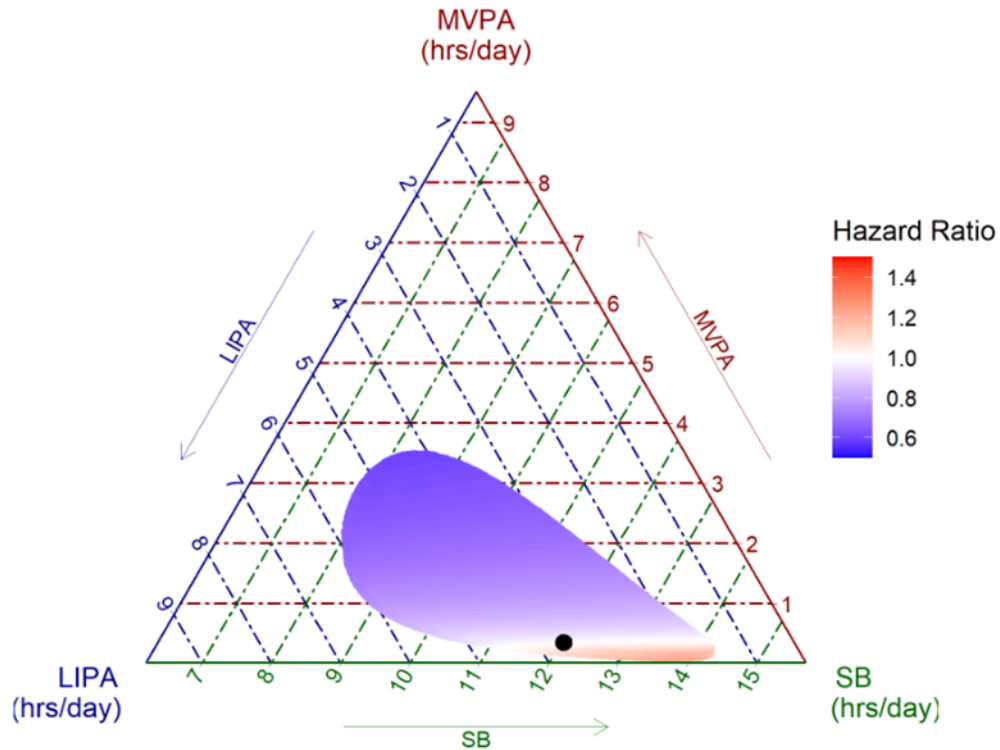


Figure 19 Heatmap ternary plot of the association of SB, LIPA and MVPA with CVD compared to reference movement behaviour composition indicated by black circle (SB= 12h 2min, LIPA=3h 37min, MVPA=21min per day)

Heatmap shows hazard ratio of CVD for different movement behaviour compositions compared to the reference composition (black circle). Analyses adjusted for age, sex, ethnicity, marital status, education, occupational position, alcohol consumption, smoking status, diet, body mass index, diabetes, hypertension, hyperlipidaemia, and multimorbidity index. Range of duration of SB, LIPA and MVPA in the plot reflects observed data in the study sample.

Pairwise reallocations of time between daily movement behaviours

Figure 20 shows the fully adjusted HRs for incident CVD associated with hypothetical pairwise reallocations of time (10-, 20-, 30-min) between two daily movement behaviours, while keeping the third movement behaviour fixed at the duration of the reference composition. These time reallocations were modelled around three reference compositions (**namely panels A, B, C in Figure 20**), each with a different MVPA duration. Given a reference composition of daily movement behaviours made of 10 minutes of MVPA (**Figure 20**, panel A; SB = 12hr 11min, LIPA = 3h 39min), reallocating 10 min per day from SB to MVPA (SB = 12h 1min, LIPA = 3h 39min, MVPA = 20min) was associated with 13% decrease in CVD risk (HR = 0.87, 95% CI: 0.78-0.98). Similar risk reduction was observed when reallocating time from LIPA to MVPA (**Table 7**). The magnitude of risk reductions was larger when displacing 20- and 30-min per day of SB or LIPA with MVPA (**Table 8**).

Smaller decreases in CVD risk were reported when displacing 10-, 20- or 30-min from SB to MVPA using referent compositions with MVPA duration set at the recommended values of 21- or 30-min per day (**Figure 20**; panel B and C). Given these two reference compositions, no evidence of association was found when time allocated to MVPA was taken from LIPA. Irrespective of the MVPA duration in the referent composition, displacing time from MVPA to either LIPA or SB was associated with greater risk in CVD (**Figure 20**), than the risk decrease associated with reallocating the same duration from either behaviour to MVPA. For instance (**Table 8**, reference composition B), reallocating 20 minutes of MVPA to SB was associated with 82% increase in risk (HR = 1.82, 95% CI: 1.10-3.03) than the 13% (HR = 0.87, 95% CI: 0.78-0.97) risk reduction in allocating time from SB to MVPA.

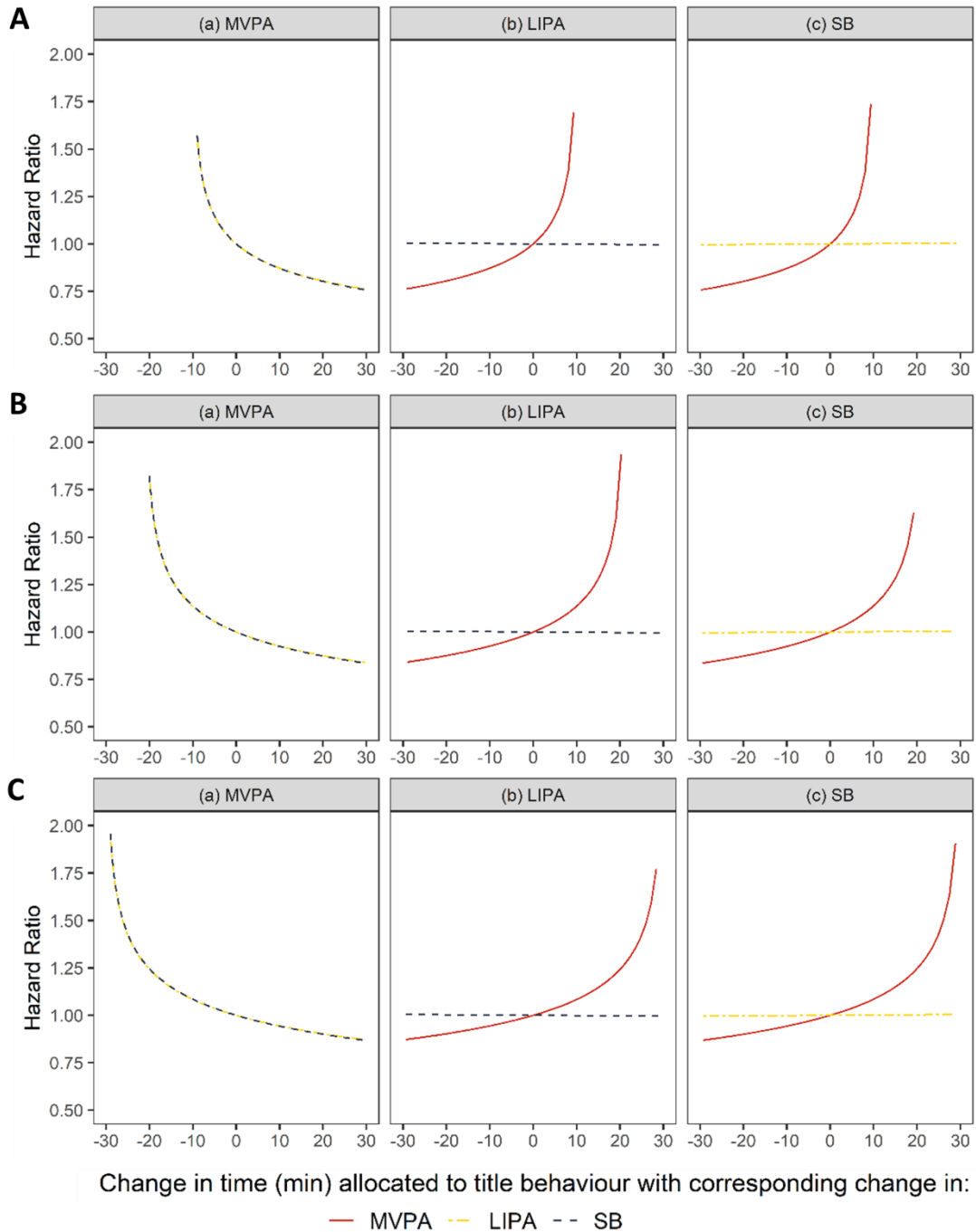


Figure 20 HRs for hypothetical time reallocation between movement behaviors. All analyses adjusted for sociodemographic, lifestyle, cardiometabolic risk factors and multimorbidity index. Time is displaced between title behavior (x-axis) and behavior indicated by the line, while holding the third behavior fixed with respect to reference composition. Time reallocation is modelled around reference composition values for MVPA, LIPA, SB set at **(A)** 10min, 3h39min, 12h11min; **(B)** 21min, 3h37min, 12h2min; **(C)** 30min, 3h34min, 11h56min. Time reallocation were not made beyond 10 minutes for reference composition where MVPA is set at 10 minutes **(A)**; and 30 minutes when the reference composition value is at either 21- **(B)** or 30- **(C)** minutes.

Table 7 HRs and 95% CI for incident CVD associated with hypothetical reallocation of 10 minutes in daily movement behaviours: impact of MVPA duration in the reference compositions (N=3319)

Reference A:^a less than recommended (MVPA = 10 min per day)			
Add 10 min per day to:			
Remove 10 min per day from:	SB	LIPA	MVPA
SB	-	1.00 (0.98-1.02)	0.87 (0.78-0.98)*
LIPA	1.00 (0.98-1.02)	-	0.87 (0.77-0.99)*
MVPA	--	--	-
Reference B:^a recommendation of 150 min per week (MVPA = 21 min per day)			
Add 10 min per day to:			
Remove 10 min per day from:	SB	LIPA	MVPA
SB	-	1.00 (0.98-1.02)	0.92 (0.87-0.99)*
LIPA	1.00 (0.98-1.02)	-	0.93 (0.86-1.00)*
MVPA	1.14 (1.02-1.27)*	1.14 (1.01-1.28)*	-
Reference C:^a recommendation of 30 min per day (MVPA = 30 min per day)			
Add 10 min per day to:			
Remove 10 min per day from:	SB	LIPA	MVPA
SB	-	1.00 (0.98-1.02)	0.94 (0.90-0.99)*
LIPA	1.00 (0.98-1.02)	-	0.94 (0.89-1.00)
MVPA	1.09 (1.01-1.16)*	1.08 (1.00-1.17)*	-

Data represents HR (95% CI). * indicates statistically significance at $p < 0.05$. All analyses adjusted for age, sex, ethnicity, marital status, education, occupational position, alcohol consumption, smoking, status, diet, body mass index, diabetes, hypertension, hyperlipidaemia, and multimorbidity index. ^a Reference composition represent individuals undertaking 10-, 21-, or 30- minutes in MVPA per day and time in SB and LIPA are set proportional to population mean at 77% and 23%, respectively, of the remaining waking time as observed in the data. This corresponds to SB set at 12h 11min, 12h 2min, and 11h 56min, and LIPA at 3h 39min, 3h 37min, and 3h 34min, respectively for references A, B, and C. -- Data not observed as MVPA cannot be decreased by 10 minutes when the reference composition value of MVPA is at 10 minutes.

Table 8 HRs and 95% CI for incident CVD associated with hypothetical reallocation of 20 and 30 minutes in daily movement behaviours: impact of MVPA duration in the reference compositions (N=3319)

Reference A:^a less than recommended (MVPA = 10 min per day)

Add 20 min per day to:				Add 30 min per day to:			
Remove 20 min per day from:	SB	LIPA	MVPA	Remove 30 min per day from:	SB	LIPA	MVPA
SB	-	1.00 (0.96-1.03)	0.80 (0.67-0.96)*	SB	-	1.00 (0.95-1.05)	0.76 (0.60-0.95)*
LIPA	1.00 (0.97-1.04)	-	0.81 (0.65-0.99)*	LIPA	1.00 (0.95-1.06)	-	0.76 (0.58-0.99)*
MVPA	--	--	-	MVPA	--	--	-

Reference B:^a recommendation of 150 min per week (MVPA = 21 min per day)

Add 20 min per day to:				Add 30 min per day to:			
Remove 20 min per day from:	SB	LIPA	MVPA	Remove 30 min per day from:	SB	LIPA	MVPA
SB	-	1.00 (0.96-1.03)	0.87 (0.78-0.97)*	SB	-	1.00 (0.94-1.05)	0.83 (0.72-0.97)*
LIPA	1.00 (0.97-1.04)	-	0.88 (0.76-1.00)	LIPA	1.00 (0.95-1.06)	-	0.84 (0.70-1.01)
MVPA	1.82 (1.10-3.03)*	1.82 (1.07-3.09)*	-	MVPA	--	--	-

Reference C:^a recommendation of 30 min per day (MVPA = 30 min per day)

Add 20 min per day to:				Add 30 min per day to:			
Remove 20 min per day from:	SB	LIPA	MVPA	Remove 30 min per day from:	SB	LIPA	MVPA
SB	-	1.00 (0.96-1.03)	0.90 (0.83-0.98)*	SB	-	1.00 (0.94-1.05)	0.87 (0.77-0.97)*
LIPA	1.00 (0.97-1.04)	-	0.90 (0.81-1.01)	LIPA	1.00 (0.95-1.07)	-	0.87 (0.75-1.02)
MVPA	1.25 (1.04-1.49)*	1.24 (1.01-1.53)*	-	MVPA	--	--	-

Data represents HR (95% CI). All analyses adjusted for age, sex, ethnicity, marital status, education, occupational position, alcohol consumption, smoking, status, diet, body mass index, diabetes, hypertension, hyperlipidaemia, and multimorbidity index.

^a Reference composition represent individuals undertaking 10-, 21-, or 30- minutes in MVPA per day and time in SB and LIPA are set proportional to population mean at 77% and 23%, respectively, of the remaining waking time as observed in the data. This corresponds to SB set at 12h 11min, 12h 2min, and 11h 56min, and LIPA at 3h 39min, 3h 37min, and 3h 34min, respectively for references A, B, and C. -- Data not observed as MVPA cannot be decreased by 30 minutes when the reference composition value of MVPA is at either 21- or 30- minutes. * indicates statistically significance at $p < 0.05$.

For a given 10 min of MVPA, **Table 9** and **Table 10** show the association of hypothetical reallocations of 10-, 20- and 30-min per day in daily movement behaviour compositions defined by two varied durations of SB and LIPA with incident CVD. Compared to reference composition 1 (SB = 9h, LIPA = 6h 50min, MVPA = 10min), increasing MVPA by 10-, 20- or 30-min per day was associated with lower risk of CVD if that time was taken from either LIPA or SB. In comparison, using reference composition 2 (SB = 14h, LIPA = 1h 50min, MVPA = 10min) yielded similar risk reductions with reallocating time from SB to MVPA, but no association was found with displacing LIPA with MVPA, although results were at the limit of significance (P=0.05). Findings remained the same with 21 min per day of MVPA duration in the referent composition (**Figure 21**).

Table 9 HRs and 95% CI for incident CVD associated with hypothetical reallocation of 10 minutes in daily movement behaviours: impact of SB and LIPA duration in the reference composition for a given MVPA duration of 10 minutes per day (N=3319)

Reference 1: ^a SB (9h per day) & LIPA (6 h 50 min per day)			
Add 10 min per day to:			
Remove 10 min per day from:	SB	LIPA	MVPA
SB	-	1.00 (0.99-1.01)	0.87 (0.78-0.98)*
LIPA	1.00 (0.99-1.02)	-	0.87 (0.77-0.99)*
MVPA	--	--	-
Reference 2: ^a SB (14h per day) & LIPA (1 h 50 min per day)			
Add 10 min per day to:			
Remove 10 min per day from:	SB	LIPA	MVPA
SB	-	1.00 (0.97-1.03)	0.87 (0.78-0.98)*
LIPA	1.00 (0.97-1.03)	-	0.87 (0.76-1.00)
MVPA	--	--	-

Data represents HR (95% CI). * indicates statistical significance at p <0.05.

All analyses adjusted for age, sex, ethnicity, marital status, education, occupational position, alcohol consumption, smoking, status, diet, body mass index, diabetes, hypertension, hyperlipidaemia, and multimorbidity index.

^a Reference composition represent individuals with SB set at 9h and 14h corresponding to the 5th and 95th percentile, respectively as observed in the data. Time in LIPA is set at the remaining waking time after considering time in SB and MVPA

-- Data not observed as MVPA cannot be decreased by 10 minutes when the reference composition value of MVPA is at 10 minutes.

Table 10 HRs and 95% CI for incident CVD associated with hypothetical reallocation of 20 and 30 minutes in daily movement behaviours: impact of SB and LIPA duration in the reference composition for a given MVPA duration of 10 minutes per day (N=3319)

Reference 1: ^a SB (9h per day) & LIPA (6 h 50 min per day)							
Add 20 min per day to:				Add 30 min per day to:			
Remove 20 min per day from:	SB	LIPA	MVPA	Remove 30 min per day from:	SB	LIPA	MVPA
SB	-	0.99 (0.97-1.02)	0.80 (0.67-0.96)*	SB	-	0.99 (0.96-1.03)	0.75 (0.60-0.95)*
LIPA	1.01 (0.98-1.03)	-	0.81 (0.66-0.98)*	LIPA	1.01 (0.97-1.05)	-	0.76 (0.59-0.98)*
MVPA	--	--	-	MVPA	--	--	-

Reference 2: ^a SB (14h per day) & LIPA (1 h 50 min per day)							
Add 20 min per day to:				Add 30 min per day to:			
Remove 20 min per day from:	SB	LIPA	MVPA	Remove 30 min per day from:	SB	LIPA	MVPA
SB	-	1.00 (0.94-1.06)	0.80 (0.67-0.96)*	SB	-	1.00 (0.91-1.09)	0.76 (0.60-0.95)*
LIPA	1.00 (0.93-1.07)	-	0.80 (0.63-1.02)	LIPA	1.00 (0.89-1.12)	-	0.76 (0.55-1.04)
MVPA	--	--	-	MVPA	--	--	-

Data represents HR (95% CI). * indicates statistically significance at p <0.05.

All analyses adjusted for age, sex, ethnicity, marital status, education, occupational position, alcohol consumption, smoking, status, diet, body mass index, diabetes, hypertension, hyperlipidaemia, and multimorbidity index

^a Reference composition represent individuals with SB set at 9h and 14h corresponding to the 5th and 95th percentile, respectively as observed in the data. Time in LIPA is set at the remaining waking time after considering time in SB and MVPA

-- Data not observed as MVPA cannot be decreased by 20- or 30- minutes when the reference composition value of MVPA is at 10 minutes.

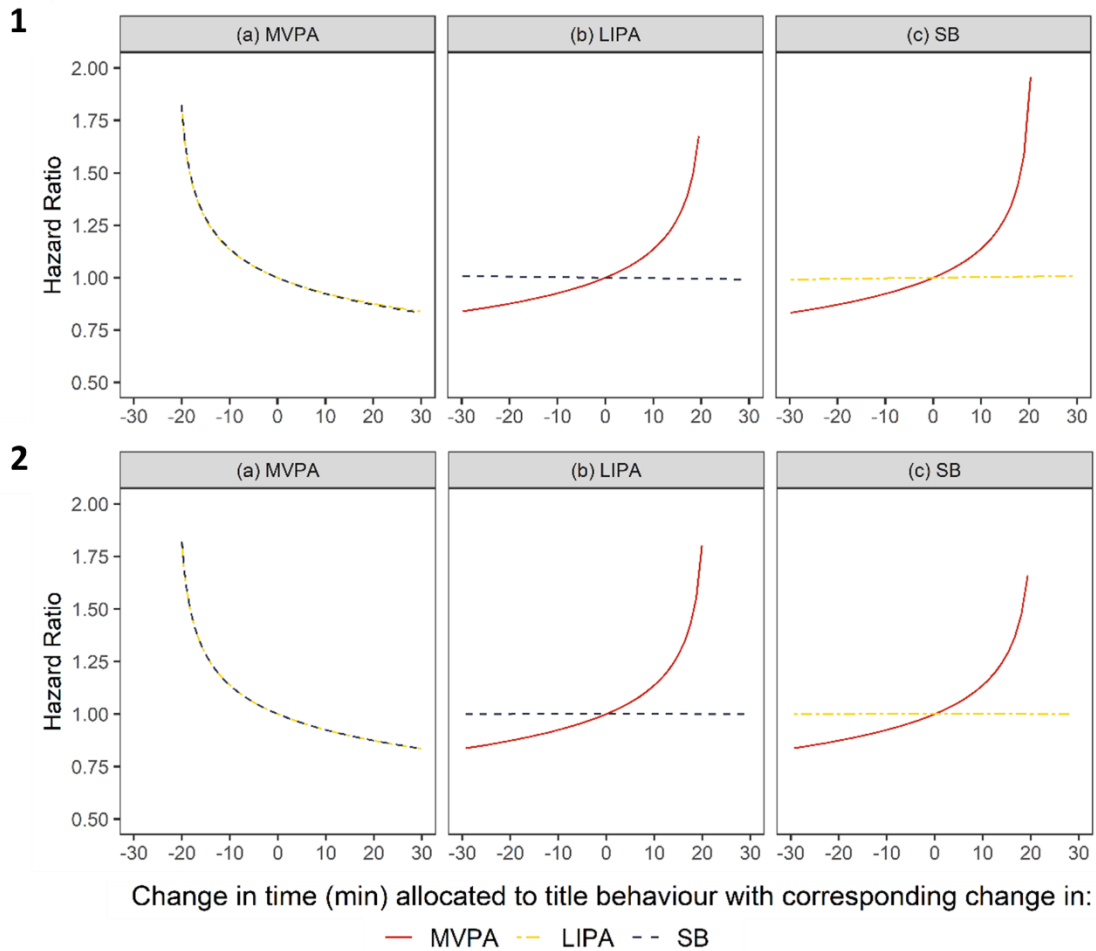


Figure 21 HRs for hypothetical time reallocation between movement behaviours with MVPA at 21 min per day in the reference composition.

All analyses adjusted for sociodemographic, lifestyle, cardiometabolic risk factors and multimorbidity index. Time is displaced between title behaviour (x-axis) and behaviour indicated by the line, while holding the third behaviour fixed with respect to reference composition. Time reallocation is modelled around reference composition values for MVPA, LIPA, SB set at **(1)** 21min, 6h39min, 9h; **(2)** 21min, 1h39min, 14h. Time reallocation by removing 30 minutes of MVPA was not done as the reference was set at 21 minutes.

Sensitivity analyses

Removing the CVD events occurring within the first two years of follow-up (n = 88) completely attenuated the association of MVPA relative to remaining movement behaviours in the fully adjusted model (P = 0.06), though the magnitude of risk reduction did not change (**Table 11**; HR $z_2^3 = 0.79$; 95% CI: 0.62-1.01). The relative proportion of SB to MVPA continued to remain significant, albeit borderline (HR $z_2^2 = 1.25$; 95% CI: 1.00-1.55, P = 0.05). The results were largely on the same line when the analysis restricted outcome to non-fatal CVD events (**Table 12**). Analyses using a different cut-off to distinguish SB from LIPA (**Table 13**), and utilizing non-normalized movement behaviours (**Table 14**), yielded findings that were comparable to that main results (**Table 6**).

Table 11 Relative importance of SB, LIPA, & MVPA for incident CVD excluding CVD events occurring within first 2 years of follow-up
(N cases/total N=211/3231)

IIR-coordinate ^a	Adjusted for sociodemographic and lifestyle factors ^a		Additionally adjusted for health-related factors ^b	
	HR (95% CI)	P value	HR (95% CI)	P value
Rotation 1: relative importance of SB				
z_1^1 (SB increase relative to LIPA and MVPA)	1.28 (0.90-1.81)	0.16	1.16 (0.81-1.67)	0.41
z_2^1 (LIPA increase relative to MVPA)	1.23 (0.83-1.80)	0.30	1.20 (0.81-1.78)	0.37
Rotation 2: relative importance of LIPA				
z_1^2 (LIPA increase relative to SB and MVPA)	1.05 (0.65-1.70)	0.83	1.09 (0.67-1.77)	0.74
z_2^2 (SB increase relative to MVPA)	1.37 (1.12-1.68)	<0.01	1.25 (1.00-1.55)	0.05
Rotation 3: relative importance of MVPA				
z_1^3 (MVPA increase relative to SB and LIPA)	0.74 (0.59-0.94)	0.01	0.79 (0.62-1.01)	0.06
z_2^3 (SB increase relative to LIPA)	1.12 (0.70-1.78)	0.64	1.04 (0.65-1.67)	0.87

^aAdjusted for age, sex, ethnicity, marital status, education, occupational position, alcohol consumption, smoking status, and diet.

^bAdditionally adjusted for body mass index, diabetes, hypertension, hyperlipidaemia, and multimorbidity index.

Table 12 Relative importance of SB, LIPA, & MVPA for incident non-fatal CVD events (N cases/total N=289/3319)

llr-coordinate ^a	Adjusted for sociodemographic and lifestyle factors ^a		Additionally adjusted for health-related factors ^b	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Rotation 1: relative importance of SB				
z_1^1 (SB increase relative to LIPA and MVPA)	1.31 (0.98-1.76)	0.07	1.20 (0.89-1.63)	0.24
z_2^1 (LIPA increase relative to MVPA)	1.19 (0.86-1.66)	0.29	1.14 (0.82-1.60)	0.44
Rotation 2: relative importance of LIPA				
z_1^2 (LIPA increase relative to SB and MVPA)	1.02 (0.68-1.53)	0.93	1.02 (0.68-1.55)	0.91
z_2^2 (SB increase relative to MVPA)	1.38 (1.16-1.64)	<0.001	1.25 (1.04-1.51)	0.02
Rotation 3: relative importance of MVPA				
z_1^3 (MVPA increase relative to SB and LIPA)	0.75 (0.61- 0.92)	0.01	0.81 (0.66-1.00)	0.05
z_2^3 (SB increase relative to LIPA)	1.16 (0.78-1.71)	0.47	1.10 (0.73-1.64)	0.65

^aAdjusted for age, sex, ethnicity, marital status, education, occupational position, alcohol consumption, smoking status, and diet.

^bAdditionally adjusted for body mass index, diabetes, hypertension, hyperlipidaemia, and multimorbidity index.

Table 13 Relative importance of SB, LIPA, & MVPA for incident CVD (N=3319) using cut-off <45 mg for SB, 45-99 mg for LIPA and \geq 100 mg for MVPA (N=3319)

IIr-coordinate ^a	Adjusted for sociodemographic and lifestyle factors ^a		Additionally adjusted for health-related factors ^b	
	HR (95% CI)	P value	HR (95% CI)	P value
Rotation 1: relative importance of SB				
z_1^1 (SB increase relative to LIPA and MVPA)	1.31 (1.00-1.72)	0.05	1.21 (0.91-1.61)	0.18
z_2^1 (LIPA increase relative to MVPA)	1.26 (0.91-1.74)	0.17	1.20 (0.86-1.68)	0.27
Rotation 2: relative importance of LIPA				
z_1^2 (LIPA increase relative to SB and MVPA)	1.06 (0.72-1.57)	0.76	1.07 (0.71-1.59)	0.75
z_2^2 (SB increase relative to MVPA)	1.42 (1.21-1.67)	<0.0001	1.30 (1.09-1.55)	0.004
Rotation 3: relative importance of MVPA				
z_1^3 (MVPA increase relative to SB and LIPA)	0.72 (0.58-0.88)	0.002	0.77 (0.62-0.96)	0.02
z_2^3 (SB increase relative to LIPA)	1.13 (0.78-1.64)	0.52	1.08 (0.74-1.58)	0.70

^aAdjusted for age, sex, ethnicity, marital status, education, occupational position, alcohol consumption, smoking status, and diet.

^bAdditionally adjusted for body mass index, diabetes, hypertension, hyperlipidaemia, and multimorbidity index.

Table 14 Relative importance of SB, LIPA, & MVPA for incident CVD without normalization to a 16-hour waking day

llr-coordinate ^a	Adjusted for sociodemographic and lifestyle factors ^a		Additionally adjusted for health-related factors ^b	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Rotation 1: relative importance of SB				
z_1^1 (SB increase relative to LIPA and MVPA)	1.36 (1.02-1.81)	0.04	1.25 (0.93-1.68)	0.14
z_2^1 (LIPA increase relative to MVPA)	1.19 (0.87-1.64)	0.27	1.15 (0.83-1.59)	0.40
Rotation 2: relative importance of LIPA				
z_1^2 (LIPA increase relative to SB and MVPA)	1.00 (0.68-1.49)	0.99	1.01 (0.67-1.51)	0.97
z_2^2 (SB increase relative to MVPA)	1.42 (1.20-1.68)	<0.0001	1.30 (1.09-1.56)	0.004
Rotation 3: relative importance of MVPA				
z_1^2 (LIPA increase relative to SB and MVPA)	0.74 (0.61-0.89)	0.002	0.79 (0.65-0.97)	0.03
z_2^2 (SB increase relative to LIPA)	1.19 (0.81-1.75)	0.37	1.13 (0.77-1.67)	0.53

^aAdjusted for age, sex, ethnicity, marital status, education, occupational position, alcohol consumption, smoking status, and diet.

^bAdditionally adjusted for body mass index, diabetes, hypertension, hyperlipidaemia, and multimorbidity index.

4 OBJECTIVE 2: METHODS AND RESULTS

The thesis' second objective was to assess the association of objectively measured total sedentary time and the pattern of its accumulation with incident CVD and all-cause mortality. We also examined whether the relationships were independent of moderate-to-vigorous physical activity. In the absence of a gold standard measure of sedentary accumulation pattern throughout the waking day, we examined the association using 8 different metrics, including those that characterise the distribution of sedentary bouts, as recommended by a recent review of sedentary accumulation metrics (280).

4.1 Statistical methods

Pearson correlation coefficients were calculated between each exposure. The shape of the associations of total sedentary time and sedentary accumulation pattern metrics (continuous variables) assessed in 2012-2013 wave of data collection with incident CVD and all-cause mortality was examined using the restricted cubic spline regressions with Harrell knots. The potential for non-linear association was tested by using the likelihood ratio test to compare the fully adjusted Cox regression models with only the linear term against the model with linear and cubic spline terms (309). As the relationships were determined to be linear, exposure variables were treated as continuous. Exposures were standardized (mean = 0, standard deviation = 1) using the mean and SD from the biggest analytical sample, one with death as the outcome, for simplicity of interpretation and comparability.

Cox proportional hazards regression was used to model all associations. The proportional hazards assumption was assessed using the Schoenfeld's test. Analyses were first adjusted for sociodemographic factors and total day duration (time between awakening and sleep onset), followed by lifestyle risk factors, then further for health-related factors, and finally for MVPA (<150 and \geq 150 minutes per week). Age was used as the timescale. Follow-up for incident CVD was from the date of clinical examination in 2012-2013 (baseline) until the date of CVD (fatal or nonfatal), non-CVD based death to consider competing risks, or end of follow-up (31st March 2019), whichever came first. For all-cause mortality, participants were censored at the date of date of death from any cause or end of follow-up (31st March 2019), whichever came first.

Table 15 presents the Pearson correlation coefficients between total sedentary time, sedentary accumulation metrics, and time in MVPA, in the maximum sample (for mortality outcome). The correlations of total sedentary time with the 8 metrics of sedentary accumulation ranged from 0.45 to 0.88 in absolute term. Total sedentary time was highly correlated with time in prolonged sedentary bout ($r = 0.88$), followed with breaks per sedentary hour ($r = 0.80$). Correlation of time in MVPA with other variable was mainly moderate (r ranges from 0.27 to 0.67 in absolute term).

Table 15 Correlation matrix between total sedentary time, sedentary accumulation patterns, and MVPA duration

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(9)	(10)	(11)
(1) Total sedentary time	1.00									
(2) Mean sedentary bout duration	0.62	1.00								
(3) Time in prolonged (≥ 30 min) sedentary bouts	0.88	0.78	1.00							
(4) Gini index	0.45	0.41	0.70	1.00						
(5) Number of sedentary breaks	0.51	0.76	0.78	0.52	1.00					
(6) Breaks per sedentary hour	0.80	0.74	0.91	0.58	0.90	1.00				
(7) Alpha	0.77	0.71	0.77	0.24	0.82	0.92	1.00			
(8) Transition probability from sedentary to LIPA state	0.77	0.73	0.88	0.56	0.90	0.99	0.92	1.00		
(9) Transition probability from sedentary to MVPA state	0.52	0.36	0.53	0.43	0.35	0.49	0.40	0.37	1.00	
(10) MVPA duration	0.65	0.39	0.58	0.37	0.27	0.49	0.43	0.42	0.67	1.00

Bold cells are negative values.

Because of moderate to strong correlations between total sedentary time and sedentary accumulation pattern metrics, they could not be included in the same model. Instead, interaction was tested with each sedentary accumulation pattern metric by defining total sedentary time dichotomously using median split (≤ 717.71 and > 717.71 minutes). Interactions were tested for all SB measures with age (≤ 68.43 and > 68.43 years (median split)), sex, obesity ($< 30 \text{ kg/m}^2$ (not obese) and $\geq 30 \text{ kg/m}^2$ (obese)) and morbidity (0 and ≥ 1 prevalent chronic ailment). If interaction was found, analyses were conducted separately for each group. For all-cause mortality outcome, significant interactions were detected between

sedentary accumulation metrics and age, so we stratified the age groups as <74 years and ≥74 years to ensure that each group has enough cases.

Sensitivity analysis

To explore the possibility of reverse causation, all cases of CVD and death occurring within the first two years of follow-up were removed. The main analyses were repeated with MVPA considered as a continuous variable rather than a dichotomous variable in the final adjustment model. For all-cause mortality, an alternative age cut-point based on median split was used to stratify analysis.

Software

All analyses were conducted using STATA statistical software version (StataCorp, College Station, Texas), and R version 3.6.3 with a two-sided $P < 0.05$ considered statistically significant.

4.2 Results: Cardiovascular Disease

Of the 4880 participants in the 2012-2013 wave of data collection invited to take part in the accelerometer substudy, 4492 agreed to participate and 4008 (82%) returned an accelerometer with valid data (**Figure 22**). 687 participants excluded had prevalent CVD ($n = 670$) or had missing information for covariates ($n = 13$) or both ($n = 4$), leading to a total of 3321 participants included in the full analyses for incident CVD. Over a mean follow-up of 6.2 (SD = 1.3) years, 299 CVD (CHD (62.9%), stroke (17.7%) and heart failure (19.4%)) events occurred among 3321 participants with complete case data. Compared to participants included in the analyses ($n = 3321$), those excluded ($n = 1559$) were more likely to be older (included vs excluded: 68.9 vs 70.1 years; $P < 0.0001$), have non-white ethnicity (6.2% vs 11.67%; $P < 0.0001$), and had a lower occupational position (49.7% vs 52.9%; $P = 0.04$) (**Table 16**).

Compared to participants who did not develop incident CVD over the follow-up period, those who did were older, men, likely to be non-white and less educated; to smoke and to be diabetic and hypertensive; and less likely to follow MVPA recommendation (**Table 17**). When compared to participants who had incident CVD, those without the event of interest spent more time in SB, accumulated sedentary time in longer bouts and with fewer breaks, and were less likely to shift from sedentary to LIPA and MVPA states (**Table 18**).

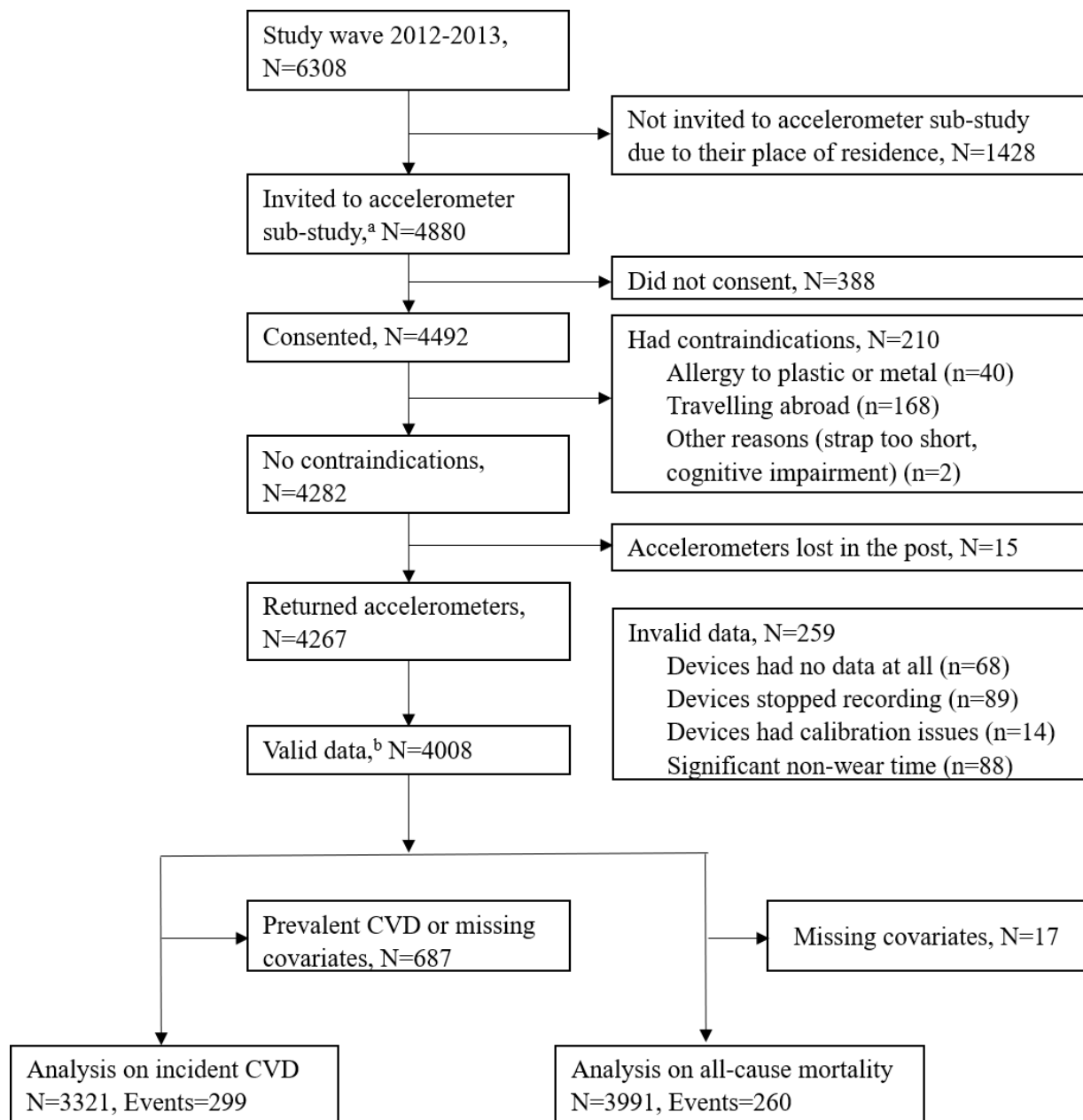


Figure 22 Flow chart of study participants

Table 16 Characteristics of participants included in the study sample and those excluded for CVD outcome

Characteristics	Included in the study sample		P value
	No	Yes	
N (row %)	1559 (32.0)	3321 (68.1)	
Age (years), M (SD)	70.1 (5.9)	68.9 (5.5)	<0.0001
Women	443 (28.4)	885 (26.7)	0.20
Non-white	182 (11.7)	206 (6.2)	<0.0001
Married/cohabitating	1145 (73.4)	2490 (75.0)	0.25
University or higher degree	492 (31.6)	1071 (32.6)	0.63
Low occupational position	824 (52.9)	1650 (50.0)	0.04

In the absence of evidence for a non-linear relationship between total sedentary time and sedentary accumulation metrics with incident CVD (P for nonlinearity ranged from 0.06 to 0.72), all exposures in the analysis models were treated as continuous variables. The SB measures were all standardized so that 1-SD equals 100.2 minutes for total sedentary time, 6.1 minutes for mean sedentary bout duration, 143.2 minutes for time in prolonged (≥ 30 min) sedentary bouts, 0.036 for Gini Index, 16.0 for number of sedentary breaks, 6.2 for breaks per sedentary hour, 0.127 for Alpha, and 3.1%, and 0.5% for transition probability from sedentary to LIPA and MVPA states, respectively.

Table 17 Baseline characteristics of study participants

Characteristics	Incident CVD (N=3321)			All-cause mortality (N=3991)		
	No	Yes	P value	No	Yes	P value
N (row %)	3022 (91.0)	299 (9.0)		3731 (93.5)	260 (6.5)	
Age (years), M (SD)	68.6 (5.5)	71.5 (5.9)	<0.001	69.1 (6.0)	73.7 (5.4)	<0.001
Women	830 (27.5)	55 (18.4)	0.001	967 (25.9)	63 (24.2)	0.55
Non-white	173 (5.7)	33 (11.0)	<0.001	272 (7.3)	23 (8.9)	0.35
Married/cohabitating	2264 (74.9)	226 (75.6)	0.80	2802 (75.1)	179 (68.9)	0.03
University or higher degree	995 (32.9)	76 (25.4)	0.01	1175 (31.5)	63 (24.2)	0.01
Low occupational position	1495 (49.5)	155 (51.8)	0.42	1885 (50.5)	146 (56.2)	0.08
Recent-ex/current smokers	152 (5.0)	23 (7.7)	0.05	205 (5.5)	16 (6.2)	0.65
>14 units of alcohol per week	716 (23.7)	72 (24.1)	0.88	875 (23.5)	50 (19.2)	0.12
Daily intake of fruits & vegetable	2424 (80.2)	227 (75.9)	0.08	2972 (79.7)	193 (74.2)	0.04
BMI ≥ 30 kg/m ²	496 (16.4)	62 (20.7)	0.06	678 (18.2)	45 (17.3)	0.73
Hypertension ^a	1347 (44.6)	183 (61.2)	<0.001	1899 (50.9)	167 (64.2)	<0.001
Hyperlipidaemia ^b	1365 (45.2)	150 (50.2)	0.10	1885 (50.5)	136 (52.3)	0.58
Diabetes	311 (10.3)	58 (19.4)	<0.001	461 (12.4)	53 (20.4)	<0.001
Multimorbidity index ^c M (SD)	0.33 (0.6)	0.36 (0.6)	0.36	0.52 (0.7)	0.89 (1.0)	<0.001
Following recommendations of 150 min/day of MVPA	2592 (85.8)	216 (72.2)	<0.001	3116 (83.5)	154 (59.2)	<0.001

Values are N (col %) unless otherwise stated.

^aSystolic/diastolic blood pressure $\geq 140/90$ mmHg or use of antihypertensive drugs.

^bLow-density lipoprotein ≥ 4.1 mmol/l or use of lipid lowering drugs.

^cNumber of chronic conditions among: cancer, arthritis, chronic obstructive pulmonary disease, depression, Parkinson disease, and dementia for incident CVD. Addition of coronary heart disease, stroke and heart failure for all-cause mortality.

Table 18 Description of total sedentary time and sedentary accumulation pattern metrics of study participants by outcomes

	Incident CVD (N=3321)			All-cause mortality (N=3991)		
	No	Yes	P value	No	Yes	P value
Daily sedentary time, min/d	709.5 (98.2)	741.3 (110.0)	<0.001	714.9 (99.1)	760.5 (105.6)	<0.001
Mean sedentary bout duration	11.0 (5.2)	12.9 (9.5)	<0.001	11.3 (5.8)	13.9 (8.8)	<0.001
Time in prolonged (\geq 30 min) sedentary bouts, min/d	372.5 (138.1)	417.5 (162.4)	<0.001	380.1 (140.5)	452.3 (164.0)	<0.001
Gini index	0.67 (0.04)	0.68 (0.03)	0.004	0.68 (0.04)	0.69 (0.04)	<0.001
Number of sedentary breaks	71.7 (15.4)	68.8 (18.1)	0.002	71.2 (15.7)	65.8 (18.4)	<0.001
Breaks per sedentary hour	6.4 (1.9)	5.9 (2.1)	<0.001	6.3 (1.9)	5.5 (2.0)	<0.001
Alpha	1.76 (0.13)	1.73 (0.14)	<0.001	1.76 (0.13)	1.71 (0.14)	<0.001
Transition probability (%) from						
sedentary to LIPA state	9.9 (3.0)	8.8 (3.3)	0.001	10.0 (3.0)	9.4 (3.3)	<0.001
sedentary to MVPA state	0.55 (0.48)	0.32 (0.36)	<0.001	0.57 (0.49)	0.43 (0.41)	<0.001

Values are Mean (SD) unless otherwise stated.

Associations of total sedentary time and sedentary accumulation pattern metrics with incident CVD are shown in **Table 19**. In a model adjusted for sociodemographic factors, all accumulation metrics except for the Gini index were significantly related to CVD risk. An increase of 1-SD (= 100.2 min) in total sedentary time was associated with a 20% higher risk of incident CVD (HR = 1.20, 95% CI: 1.06-1.37), which corresponds to the greatest gain in risk. While, a 1-SD increase in transition probability from sedentary to MVPA state had the largest reduction in CVD risk at 19% (HR = 0.81, 95% CI = 0.70-0.94). Adjustment for lifestyle-related risk factors did not meaningfully change the associations. Further adjustment for health-related risk factors completely attenuated all associations except for mean sedentary bout duration (HR = 1.14, 95% CI: 1.03-1.26), which also became non-significant once MVPA recommendation was taken into consideration (HR = 1.09, 95% CI: 0.98-1.23).

In models adjusted for MVPA but not for health-related factors, association remained significant only for mean sedentary bout duration, although the significance was borderline (**Table 20**; HR = 1.12, 1.00-1.24, $P = 0.045$). Comparatively, in a model controlling for sociodemographic, lifestyle and health-related factor, the HR for fulfilling the MVPA recommendation of 150 min per week was 0.69 (**Table 21**; 95% CI: 0.52-0.92, $P = 0.01$). No difference in the association of sedentary accumulation metrics with CVD risk based on total sedentary time was observed (P for interaction ranges from 0.07 to 0.57). There was no statistical evidence of effect modification by age, sex, obesity or morbidity status with either total sedentary time nor by sedentary accumulation metrics in relation to risk of CVD (P for interaction >0.07).

Table 19 Associations of total sedentary time and sedentary accumulation patterns with incident CVD (N total = 3321, N events = 299, mean follow-up (SD) = 6.2 (1.3) years)

	HR (95% CI)			
	Adjusted for sociodemographic factors ^a	Additionally adjusted for lifestyle factors ^b	Additionally adjusted for health-related factors ^c	Additionally adjusted for MVPA ^d
Total sedentary time	1.20 (1.06-1.37)	1.20 (1.05-1.37)	1.11 (0.97-1.27)	1.02 (0.88-1.19)
Sedentary accumulation pattern metrics^e				
(1) Mean sedentary bout duration	1.18 (1.08-1.30)	1.19 (1.08-1.30)	1.14 (1.03-1.26)	1.09 (0.98-1.23)
(2) Time in prolonged (≥30 min) sedentary bouts	1.18 (1.06-1.33)	1.19 (1.06-1.33)	1.11 (0.99-1.26)	1.05 (0.92-1.20)
(3) Gini index	1.06 (0.94-1.19)	1.07 (0.95-1.21)	1.03 (0.91-1.16)	0.99 (0.88-1.12)
(4) Number of sedentary breaks	0.87 (0.77-0.97)	0.86 (0.77-0.97)	0.91 (0.81-1.02)	0.94 (0.84-1.07)
(5) Breaks per sedentary hour	0.86 (0.76-0.97)	0.86 (0.76-0.97)	0.92 (0.81-1.04)	0.97 (0.85-1.10)
(6) Alpha	0.84 (0.75-0.95)	0.85 (0.75-0.95)	0.90 (0.79-1.01)	0.94 (0.82-1.07)
Transition probability from				
(7) sedentary to LIPA state	0.88 (0.78-0.99)	0.87 (0.78-0.99)	0.93 (0.82-1.05)	0.98 (0.86-1.11)
(8) sedentary to MVPA state	0.81 (0.70-0.94)	0.82 (0.70-0.95)	0.87 (0.75-1.01)	0.92 (0.79-1.08)

^aModels adjusted for age (time-scale), sex, ethnicity, education, occupation position, marital status and total waking day duration.

^bModels additionally adjusted for smoking status, alcohol consumption and fruits and vegetables consumption.

^cModels additionally adjusted for prevalent diabetes, BMI, hypertension, hyperlipidaemia and multimorbidity index.

^dModels additionally adjusted for MVPA recommendation.

^eMetrics are standardized based on sample mean & SD resulting in HRs corresponding to one SD higher value. For metrics 1-3, an increase of 1-SD corresponds to less favourable sedentary accumulation pattern. For metrics 4-8, an increase of 1-SD corresponds to more favourable sedentary accumulation pattern. 1 SD represents 100.2 minutes for total sedentary time, 6.1 minutes for mean sedentary bout duration, 143.2 minutes for time in prolonged (≥30 min) sedentary bouts, 0.036 for Gini Index, 16.0 for number of sedentary breaks, 6.2 for breaks per sedentary hour, 0.127 for Alpha, and 3.1%, and 0.5% for transition probability from sedentary to LIPA and MVPA states, respectively.

Table 20 Associations of total sedentary time and sedentary accumulation patterns with incident CVD adjusted for sociodemographic, lifestyle factors and MVPA

	HR (95% CI)	
	Adjusted for lifestyle and sociodemographic factors ^a	Additionally adjusted for MVPA ^b
Total sedentary time	1.20 (1.05-1.37)	1.08 (0.93-1.26)
Sedentary accumulation patterns^c		
(1) Mean sedentary bout duration	1.19 (1.08-1.30)	1.12 (1.00-1.24)
(2) Time in prolonged (≥30 min) sedentary bouts	1.19 (1.06-1.33)	1.10 (0.96-1.25)
(3) Gini index	1.07 (0.95-1.21)	1.02 (0.90-1.15)
(4) Number of sedentary breaks	0.86 (0.77-0.97)	0.92 (0.81-1.03)
(5) Breaks per sedentary hour	0.86 (0.76-0.97)	0.93 (0.81-1.05)
(6) Alpha	0.85 (0.75-0.95)	0.90 (0.80-1.03)
Transition probability from		
(7) sedentary to LIPA state	0.87 (0.78-0.99)	0.94 (0.83-1.06)
(8) sedentary to MVPA state	0.82 (0.70-0.95)	0.88 (0.76-1.03)

^aModels adjusted for age (time-scale), sex, ethnicity, education, occupation position, marital status, total waking day duration, smoking status, alcohol consumption and fruits and vegetables consumption.

^bModels additionally adjusted for MVPA recommendation.

^cMetrics are standardized based on sample mean & SD resulting in HRs corresponding to one SD higher value. For metrics 1-3, an increase of 1-SD corresponds to less favourable sedentary accumulation pattern. For metrics 4-8, an increase of 1-SD corresponds to more favourable sedentary accumulation pattern. 1 SD represents 100.2 minutes for total sedentary time, 6.1 minutes for mean sedentary bout duration, 143.2 minutes for time in prolonged (≥30 min) sedentary bouts, 0.036 for Gini Index, 16.0 for number of sedentary breaks, 6.2 for breaks per sedentary hour, 0.127 for Alpha, and 3.1%, and 0.5% for transition probability from sedentary to LIPA and MVPA states, respectively.

Table 21 Association of MVPA with incident CVD and all-cause mortality

	HR (95% CI)	
	Incident CVD	All-cause mortality
Following recommendation of 150 min per week of MVPA		
No	1.00	1.00
Yes	0.69 (0.52-0.92)	0.59 (0.44-0.78)
Daily time in MVPA, per 1 SD (38.6 min)	0.90 (0.78-1.04)	0.70 (0.59-0.85)

All models adjusted for age (time-scale), sex, ethnicity, education, occupation position, marital status, total waking day duration, smoking status, alcohol consumption, fruits and vegetables consumption, prevalent diabetes, BMI, hypertension, hyperlipidaemia, and multimorbidity index.

4.3 Results: All-cause mortality

Of the 4008 participants who returned an accelerometer with valid data, 17 participants with incomplete data on covariates were excluded, leading to an analytical sample of 3991 participants for all-cause mortality (**Figure 22, page 109**). Compared to participants included in the analyses (n = 3991), those excluded (n = 889) were more likely to be young (included vs excluded: 69.4 vs 68.9 years; P = 0.03), women (25.8% vs 33.5%; P<0.001), with non-white ethnicity (7.4% vs 10.5%; P<0.01), and had a higher level of education (31.0% vs 36.6%; P<0.01) (**Table 22**).

Table 22 Characteristics of participants included in the study and those excluded for all-cause mortality

Characteristics	Included in the study sample		P value
	No	Yes	
N (row %)	889 (18.2)	3991 (81.8)	
Age (years), M (SD)	68.9 (5.6)	69.4 (5.7)	0.03
Women	298 (33.5)	1030 (25.8)	<0.001
Non-white	93 (10.5)	395 (7.4)	<0.01
Married/cohabitating	654 (73.6)	2981 (74.7)	0.49
University or higher degree	325 (36.6)	1238 (31.0)	<0.01
Low occupational position	443 (49.8)	2031 (50.9)	0.57

During a mean follow-up of 6.4 (SD = 0.8) years, 260 deaths occurred. Participants who died during the follow-up were on average older, married/cohabitating, less educated, and they had a poorer diet, a worse cardiometabolic profile, and more morbidities than the survivors (**Table 17, page 111**). Those who died had higher total sedentary time, longer mean sedentary bout duration, accumulated sedentary duration in small bouts of lengthier duration, and transitioned less from sedentary to active states (**Table 18, page 112**). There was no evidence for a non-linear relationship between total sedentary time and sedentary accumulation metrics with all-cause mortality (P for non-linearity ranged from 0.14 to 0.94), which led to us treating all exposures as continuous variables in the analytical models.

Table 23 presents the association of total sedentary time and sedentary accumulation pattern metrics with all-cause mortality. Substantial increase in mortality risk was observed by a 1-SD increase in total sedentary time (HR = 1.35, 95% CI: 1.17-1.56), mean sedentary bout duration (HR = 1.10, 95% CI: 1.03-1.17) and prolonged sedentary bout duration (HR = 1.27, 95% CI: 1.13-1.43) in models adjusted for sociodemographic factors. A 1-SD increase in the number of sedentary breaks (HR = 0.83, 95% CI: 0.74-0.94), breaks per sedentary hour (HR = 0.80, 95% CI: 0.70-0.91), Alpha (HR = 0.81, 95% CI: 0.72-0.92), transition probability from sedentary to LIPA (HR = 0.82, 95% CI: 0.72-0.93) and MVPA (HR = 0.69, 95% CI: 0.57-0.84) states, were each associated with a lower mortality risk. Further adjustments for lifestyle and health-related risk factors minimally affected the risk estimates. None of the associations remained significant on additional adjustment for MVPA. In comparison, engaging in the recommended duration of 150 min per week of MVPA decreased the risk of mortality by 41% (**Table 21; page 116**; HR = 0.59, 95% CI: 0.44-0.78). The association of sedentary accumulation metrics with mortality did not vary by total sedentary time (P for interaction ranges from 0.42 to 0.75).

Table 23 Associations of total sedentary time and sedentary accumulation patterns with all-cause mortality (N total = 3991, N events = 260, mean follow-up (SD) = 6.4 (0.8) years)

	HR (95% CI)			
	Adjusted for sociodemographic factors ^a	Additionally adjusted for lifestyle factors ^b	Additionally adjusted for health-related factors ^c	Additionally adjusted for MVPA ^d
Total sedentary time	1.35 (1.17-1.56)	1.32 (1.15-1.53)	1.29 (1.11-1.49)	1.16 (0.98-1.38)
Sedentary accumulation pattern metrics^e				
(1) Mean sedentary bout duration	1.10 (1.03-1.17)	1.08 (1.01-1.15)	1.07 (1.00-1.15)	1.03 (0.95-1.11)
(2) Time in prolonged (≥30 min) sedentary bouts	1.27 (1.13-1.43)	1.25 (1.11-1.40)	1.22 (1.08-1.38)	1.12 (0.98-1.29)
(3) Gini index	1.13 (1.00-1.29)	1.13 (0.99-1.28)	1.11 (0.97-1.26)	1.06 (0.93-1.20)
(4) Number of sedentary breaks	0.83 (0.74-0.94)	0.85 (0.75-0.95)	0.86 (0.77-0.97)	0.92 (0.81-1.05)
(5) Breaks per sedentary hour	0.80 (0.70-0.91)	0.81 (0.72-0.93)	0.83 (0.73-0.95)	0.90 (0.78-1.04)
(6) Alpha	0.81 (0.72-0.92)	0.83 (0.73-0.94)	0.84 (0.75-0.96)	0.92 (0.80-1.05)
Transition probability from				
(7) sedentary to LIPA state	0.82 (0.72-0.93)	0.83 (0.73-0.95)	0.85 (0.75-0.97)	0.92 (0.80-1.06)
(8) sedentary to MVPA state	0.69 (0.57-0.84)	0.71 (0.58-0.86)	0.74 (0.61-0.90)	0.82 (0.67-1.01)

^aModels adjusted for age (time-scale), sex, ethnicity, education, occupation position, marital status and total waking day duration.

^bModels additionally adjusted for smoking status, alcohol consumption and fruits and vegetables consumption.

^cModels additionally adjusted for prevalent diabetes, BMI, hypertension, hyperlipidaemia and multimorbidity index.

^dModels additionally adjusted for MVPA recommendation.

^eMetrics are standardized based on sample mean & SD resulting in HRs corresponding to one SD higher value. For metrics 1-3, an increase of 1-SD corresponds to less favourable sedentary accumulation pattern. For metrics 4-8, an increase of 1-SD corresponds to more favourable sedentary accumulation pattern. 1 SD represents 100.2 minutes for total sedentary time, 6.1 minutes for mean sedentary bout duration, 143.2 minutes for time in prolonged (≥30 min) sedentary bouts, 0.036 for Gini Index, 16.0 for number of sedentary breaks, 6.2 for breaks per sedentary hour, 0.127 for Alpha, and 3.1%, and 0.5% for transition probability from sedentary to LIPA and MVPA states, respectively.

There was consistent interaction between age and sedentary measures for all-cause mortality (P for interaction ranges from 0.001 to 0.009), with the exception of transition probability from sedentary to MVPA state (P for interaction = 0.18). When analyses were stratified by age, all SB metrics were significantly associated with mortality among individuals aged <74 years in model adjusted for sociodemographic factors (**Table 24**; N = 3001, N death = 114). In fully adjusted models (**Figure 23**), associations were slightly attenuated but remained significant for most metrics except for mean sedentary bout duration and transition probability from sedentary to MVPA state. Among those aged ≥74 years, no association was observed with any of the metrics (**Table 25**; N = 990, N = 146). In post-hoc analyses we explored the underlying reasons for the differential association of sedentary time variables with mortality by age group, and found that there was no difference in the causes of death between the two age groups (**Table 26**), although the younger group's sedentary accumulation pattern metrics were on average on the better side (**Table 27**).

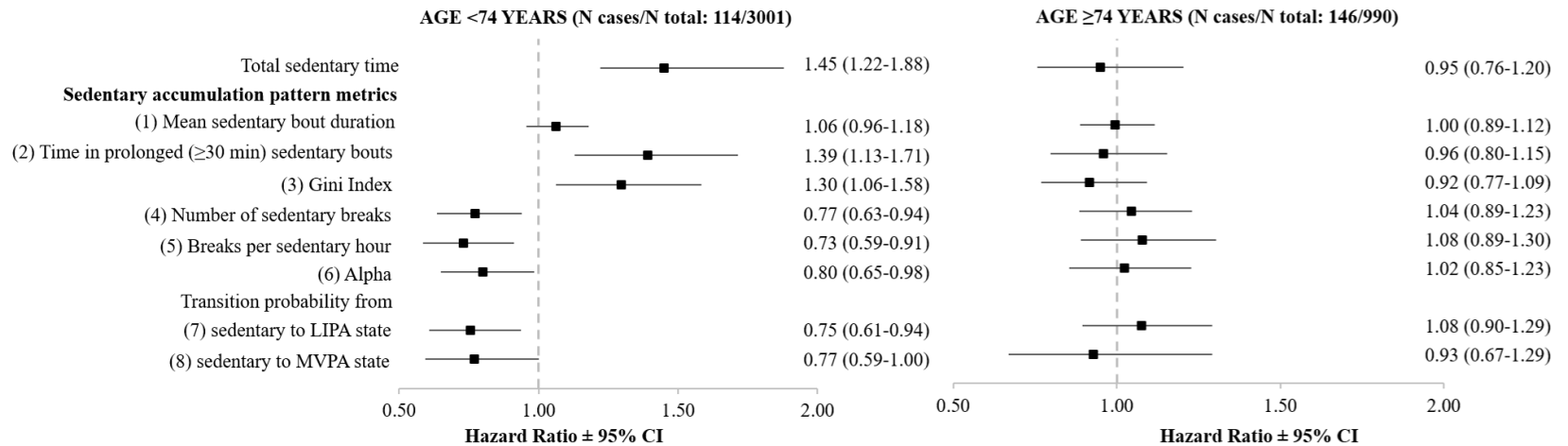


Figure 23 Association of total sedentary time and sedentary accumulation patterns with all-cause mortality stratified by age by a split of 74 years.

All models adjusted for age (as timescale), sociodemographic, lifestyle, health-related risk factors, and MVPA recommendation.

Table 24 Associations of total sedentary time and sedentary accumulation patterns with all-cause mortality among participants aged <74 years (N total = 3001, N events = 114, mean follow-up (SD) = 6.5 (0.7) years, mean age (SD) = 66.7 (3.6) years)

	HR (95% CI)			
	Adjusted for sociodemographic factors ^a	Additionally adjusted for lifestyle factors ^b	Additionally adjusted for health-related factors ^c	Additionally adjusted for MVPA ^d
Total sedentary time	1.56 (1.26-1.94)	1.55 (1.24-1.92)	1.56 (1.25-1.95)	1.45 (1.12-1.88)
Sedentary accumulation patterns^e				
(1) Mean sedentary bout duration	1.11 (1.02-1.20)	1.11 (1.01-1.21)	1.11 (1.02-1.22)	1.06 (0.96-1.18)
(2) Time in prolonged (≥30 min) sedentary bouts	1.49 (1.25-1.77)	1.47 (1.23-1.76)	1.48 (1.23-1.77)	1.39 (1.13-1.71)
(3) Gini index	1.38 (1.13-1.67)	1.37 (1.13-1.66)	1.36 (1.12-1.66)	1.30 (1.06-1.58)
(4) Number of sedentary breaks	0.71 (0.59-0.85)	0.71 (0.59-0.86)	0.72 (0.60-0.87)	0.77 (0.63-0.94)
(5) Breaks per sedentary hour	0.67 (0.55-0.82)	0.68 (0.55-0.83)	0.68 (0.55-0.83)	0.73 (0.59-0.91)
(6) Alpha	0.73 (0.60-0.88)	0.73 (0.60-0.89)	0.74 (0.61-0.90)	0.80 (0.65-0.98)
Transition probability from				
(7) sedentary to LIPA state	0.69 (0.56-0.85)	0.70 (0.57-0.86)	0.70 (0.57-0.86)	0.75 (0.61-0.94)
(8) sedentary to MVPA state	0.69 (0.53-0.89)	0.69 (0.54-0.89)	0.70 (0.54-0.90)	0.77 (0.59-1.00)

^aModels adjusted for age (time-scale), sex, ethnicity, education, occupation position, marital status and total waking day duration.

^bModels additionally adjusted for smoking status, alcohol consumption and fruits and vegetables consumption.

^cModels additionally adjusted for prevalent diabetes, BMI, hypertension, hyperlipidaemia and morbidity index.

^dModels additionally adjusted for MVPA recommendation.

^eMetrics are standardized based on sample mean & SD resulting in HRs corresponding to one SD higher value. For metrics 1-3, an increase of 1-SD corresponds to less favourable sedentary accumulation pattern. For metrics 4-8, an increase of 1-SD corresponds to more favourable sedentary accumulation pattern. 1 SD represents 100.2 minutes for total sedentary time, 6.1 minutes for mean sedentary bout duration, 143.2 minutes for time in prolonged (≥30 min) sedentary bouts, 0.036 for Gini Index, 16.0 for number of sedentary breaks, 6.2 for breaks per sedentary hour, 0.127 for Alpha, and 3.1%, and 0.5% for transition probability from sedentary to LIPA and MVPA states, respectively.

Table 25 Associations of total sedentary time and sedentary accumulation patterns with all-cause mortality among participants aged ≥ 74 years (N total = 990, N events = 146, mean follow-up (SD) = 6.2 (1.2) years, mean age (SD) = 77.5 (2.2) years)

	HR (95% CI)			
	Adjusted for sociodemographic factors ^a	Additionally adjusted for lifestyle factors ^b	Additionally adjusted for health-related factors ^c	Additionally adjusted for MVPA ^d
Total sedentary time	1.22 (1.01-1.47)	1.19 (0.98-1.43)	1.12 (0.92-1.36)	0.95 (0.76-1.20)
Sedentary accumulation patterns^e				
(1) Mean sedentary bout duration	1.08 (0.99-1.19)	1.06 (0.97-1.17)	1.04 (0.94-1.15)	1.00 (0.89-1.12)
(2) Time in prolonged (≥ 30 min) sedentary bouts	1.14 (0.98-1.33)	1.12 (0.96-1.31)	1.07 (0.91-1.26)	0.96 (0.80-1.15)
(3) Gini index	0.98 (0.83-1.17)	0.98 (0.83-1.17)	0.96 (0.80-1.14)	0.92 (0.77-1.09)
(4) Number of sedentary breaks	0.93 (0.80-1.08)	0.94 (0.81-1.10)	0.98 (0.83-1.15)	1.04 (0.89-1.23)
(5) Breaks per sedentary hour	0.90 (0.76-1.07)	0.92 (0.78-1.09)	0.97 (0.81-1.16)	1.08 (0.89-1.30)
(6) Alpha	0.88 (0.75-1.03)	0.89 (0.76-1.05)	0.93 (0.79-1.10)	1.02 (0.85-1.23)
Transition probability from				
(7) sedentary to LIPA state	0.92 (0.78-1.08)	0.94 (0.79-1.10)	0.98 (0.82-1.16)	1.08 (0.90-1.29)
(8) sedentary to MVPA state	0.69 (0.51-0.93)	0.71 (0.53-0.97)	0.79 (0.58-1.08)	0.93 (0.67-1.29)

^aModels adjusted for age (time-scale), sex, ethnicity, education, occupation position, marital status and total waking day duration.

^bModels additionally adjusted for smoking status, alcohol consumption and fruits and vegetables consumption.

^cModels additionally adjusted for prevalent diabetes, BMI, hypertension, hyperlipidaemia and multimorbidity index.

^dModels additionally adjusted for MVPA recommendation.

^eMetrics are standardized based on sample mean & SD resulting in HRs corresponding to one SD higher value. For metrics 1-3, an increase of 1-SD corresponds to less favourable sedentary accumulation pattern. For metrics 4-8, an increase of 1-SD corresponds to more favourable sedentary accumulation pattern. 1 SD represents 100.2 minutes for total sedentary time, 6.1 minutes for mean sedentary bout duration, 143.2 minutes for time in prolonged (≥ 30 min) sedentary bouts, 0.036 for Gini Index, 16.0 for number of sedentary breaks, 6.2 for breaks per sedentary hour, 0.127 for Alpha, and 3.1%, and 0.5% for transition probability from sedentary to LIPA and MVPA states, respectively.

Table 26 Cause of death for the stratified by age groups

Cause of death	Age<74 years	Age≥74 years	P value ^a
			0.076
Cardiovascular disease	18 (15.8)	35 (24.0)	
Cancer	62 (54.4)	60 (41.1)	
Respiratory	5 (4.4)	14 (9.6)	
Others	29 (25.4)	37 (25.3)	

Values are n (col%), unless otherwise stated.

The sum of all cells equals to 260, corresponding to the total number of deaths over the follow-up period of 6.4 (SD = 0.8) years.

^achi-square test to compare differences in cause of death by age.

Table 27 Differences in the means of total sedentary time and sedentary accumulation patterns by age group

	Age<74 years	Age≥74 years	P value ^a
N	3001	990	
Total sedentary time	707.0 (97.8)	750.7 (100.3)	<0.001
Sedentary accumulation patterns^b			
(1) Mean sedentary bout duration	10.9 (5.2)	13.1 (7.9)	<0.001
(2) Time in prolonged (≥30 min) sedentary bouts	366.8 (135.8)	439.2 (151.2)	<0.001
(3) Gini index	0.67 (0.04)	0.69 (0.04)	<0.001
(4) Number of sedentary breaks	73.0 (15.2)	68.4 (17.7)	<0.001
(5) Breaks per sedentary hour	6.4 (1.9)	5.7 (2.0)	<0.001
(6) Alpha	1.76 (0.17)	1.73 (0.10)	<0.001
Transition probability (%) from			
(7) sedentary to LIPA state	10.0 (3.0)	9.1 (3.1)	<0.001
(8) sedentary to MVPA state	0.61 (0.50)	0.32 (0.33)	<0.001

^aT-test to compare the differences in mean by age.

^bFor metrics 1-3, an increase of value corresponds to less favourable sedentary accumulation pattern. For metrics 4-8, an increase of value corresponds to more favourable sedentary accumulation pattern.

Sensitivity Analyses

Apart for mean sedentary bout duration, all associations were completely attenuated in model adjusted for sociodemographic factors alone when the 88 CVD events within the first two years of follow-up were removed (**Table 28**). For all-cause mortality, no evidence of reverse causality was found after excluding 45 events that occurred within the first 2 years of follow-up in either the full sample (**Table 29**) or by age group (**Table 30**) as the findings were not affected. Using a median age split for all-cause mortality yielded results comparable to the main analyses, with associations being evident only with the youngest old group (**Figure 24**; <68.4 years). In the final adjustment model, adjusting for MVPA as a continuous rather than a dichotomous variable had no effect on results (**Table 31** and **Table 32**).

Table 28 Associations of total sedentary time and sedentary accumulation patterns with incident CVD using a 2-year wash-out period (N total = 3233, N events = 211, mean follow-up (SD) = 6.3 (0.9) years)

	HR (95% CI)			
	Adjusted for sociodemographic factors ^a	Additionally adjusted for lifestyle factors ^b	Additionally adjusted for health-related factors ^c	Additionally adjusted for MVPA ^d
Total sedentary time	1.12 (0.96-1.30)	1.10 (0.95-1.28)	1.01 (0.86-1.18)	0.94 (0.79-1.13)
Sedentary accumulation patterns				
(1) Mean sedentary bout duration	1.13 (1.01-1.27)	1.14 (1.01-1.28)	1.08 (0.95-1.23)	1.05 (0.91-1.21)
(2) Time in prolonged (≥30 min) sedentary bouts	1.09 (0.95-1.25)	1.09 (0.95-1.25)	1.01 (0.87-1.17)	0.96 (0.81-1.13)
(3) Gini index	0.94 (0.82-1.07)	0.95 (0.83-1.10)	0.91 (0.79-1.05)	0.89 (0.77-1.02)
(4) Number of sedentary breaks	0.94 (0.82-1.08)	0.94 (0.82-1.08)	1.00 (0.86-1.15)	1.03 (0.89-1.19)
(5) Breaks per sedentary hour	0.94 (0.82-1.09)	0.95 (0.83-1.09)	1.02 (0.89-1.18)	1.07 (0.92-1.25)
(6) Alpha	0.89 (0.77-1.02)	0.90 (0.78-1.03)	0.96 (0.83-1.11)	0.99 (0.85-1.15)
Transition probability from				
(7) sedentary to LIPA state	0.95 (0.83-1.09)	0.96 (0.83-1.10)	1.03 (0.89-1.18)	1.07 (0.92-1.24)
(8) sedentary to MVPA state	0.93 (0.79-1.10)	0.94 (0.80-1.11)	1.00 (0.85-1.18)	1.05 (0.88-1.24)

^aModels adjusted for age (time-scale), sex, ethnicity, education, occupation position, marital status and total waking day duration.

^bModels additionally adjusted for smoking status, alcohol consumption and fruits and vegetables consumption.

^cModels additionally adjusted for prevalent diabetes, BMI, hypertension, hyperlipidaemia and multimorbidity index.

^dModels additionally adjusted for MVPA recommendation.

Table 29 Associations of total sedentary time and sedentary accumulation patterns with all-cause mortality using a 2-year wash-out period (N total = 3946, N events = 215, mean follow-up (SD) = 6.4 (0.6) years)

	HR (95% CI)			
	Adjusted for sociodemographic factors ^a	Additionally adjusted for lifestyle factors ^b	Additionally adjusted for health-related factors ^c	Additionally adjusted for MVPA ^d
Total sedentary time	1.39 (1.19-1.62)	1.37 (1.17-1.60)	1.33 (1.13-1.56)	1.21 (1.00-1.46)
Sedentary accumulation patterns				
(1) Mean sedentary bout duration	1.11 (1.04-1.18)	1.10 (1.02-1.17)	1.09 (1.01-1.17)	1.04 (0.96-1.13)
(2) Time in prolonged (≥30 min) sedentary bouts	1.28 (1.13-1.45)	1.27 (1.11-1.44)	1.23 (1.08-1.41)	1.13 (0.97-1.32)
(3) Gini index	1.12 (0.97-1.29)	1.11 (0.97-1.28)	1.08 (0.94-1.25)	1.03 (0.89-1.19)
(4) Number of sedentary breaks	0.83 (0.73-0.94)	0.84 (0.74-0.95)	0.86 (0.75-0.98)	0.92 (0.80-1.05)
(5) Breaks per sedentary hour	0.79 (0.69-0.91)	0.80 (0.69-0.92)	0.82 (0.71-0.95)	0.89 (0.76-1.05)
(6) Alpha	0.79 (0.69-0.90)	0.80 (0.70-0.91)	0.82 (0.71-0.94)	0.88 (0.76-1.03)
Transition probability from				
(7) sedentary to LIPA state	0.81 (0.70-0.93)	0.82 (0.71-0.94)	0.84 (0.73-0.97)	0.91 (0.78-1.06)
(8) sedentary to MVPA state	0.70 (0.57-0.87)	0.71 (0.58-0.88)	0.75 (0.61-0.93)	0.84 (0.67-1.05)

^aModels adjusted for age (time-scale), sex, ethnicity, education, occupation position, marital status and total waking day duration.

^bModels additionally adjusted for smoking status, alcohol consumption and fruits and vegetables consumption.

^cModels additionally adjusted for prevalent diabetes, BMI, hypertension, hyperlipidaemia and multimorbidity index.

^dModels additionally adjusted for MVPA recommendation.

Table 30 Associations of total sedentary time and sedentary accumulation patterns with all-cause mortality using a 2-year wash-out period stratified by age

	HR (95% CI)			
	Age<74 years ^a		Age≥74 years ^b	
	Adjusted for sociodemographic factors ^c	Fully adjusted ^d	Adjusted for sociodemographic factors ^c	Fully adjusted ^d
Total sedentary time	1.51 (1.19-1.91)	1.48 (1.11-1.98)	1.23 (1.01-1.51)	0.98 (0.76-1.26)
Sedentary accumulation patterns				
(1) Mean sedentary bout duration	1.09 (1.00-1.20)	1.07 (0.95-1.21)	1.10 (1.00-1.22)	1.02 (0.91-1.15)
(2) Time in prolonged (≥30 min) sedentary bouts	1.42 (1.17-1.72)	1.38 (1.09-1.75)	1.14 (0.97-1.35)	0.96 (0.79-1.18)
(3) Gini index	1.30 (1.05-1.62)	1.24 (1.00-1.55)	0.96 (0.79-1.16)	0.88 (0.73-1.07)
(4) Number of sedentary breaks	0.74 (0.61-0.91)	0.78 (0.63-0.97)	0.92 (0.77-1.08)	1.03 (0.86-1.23)
(5) Breaks per sedentary hour	0.68 (0.55-0.85)	0.72 (0.56-0.92)	0.87 (0.73-1.05)	1.06 (0.86-1.31)
(6) Alpha	0.74 (0.60-0.91)	0.78 (0.61-0.98)	0.85 (0.71-1.01)	0.98 (0.81-1.20)
Transition probability from				
(7) sedentary to LIPA state	0.72 (0.58-0.90)	0.76 (0.60-0.96)	0.90 (0.75-1.08)	1.05 (0.86-1.29)
(8) sedentary to MVPA state	0.73 (0.55-0.96)	0.79 (0.59-1.05)	0.77 (0.56-1.06)	1.07 (0.76-1.50)

^aN total = 2981, N events = 94, mean follow-up (SD) = 6.5 (0.5) years.

^bN total = 965, N events = 121, mean follow-up (SD) = 6.3 (0.9) years.

^cModels adjusted for age (time-scale), sex, ethnicity, education, occupation position, marital status and total waking day duration.

^dModels additionally adjusted for smoking status, alcohol consumption, fruits and vegetables consumption, prevalent diabetes, BMI, hypertension, hyperlipidaemia, multimorbidity index and MVPA recommendation.

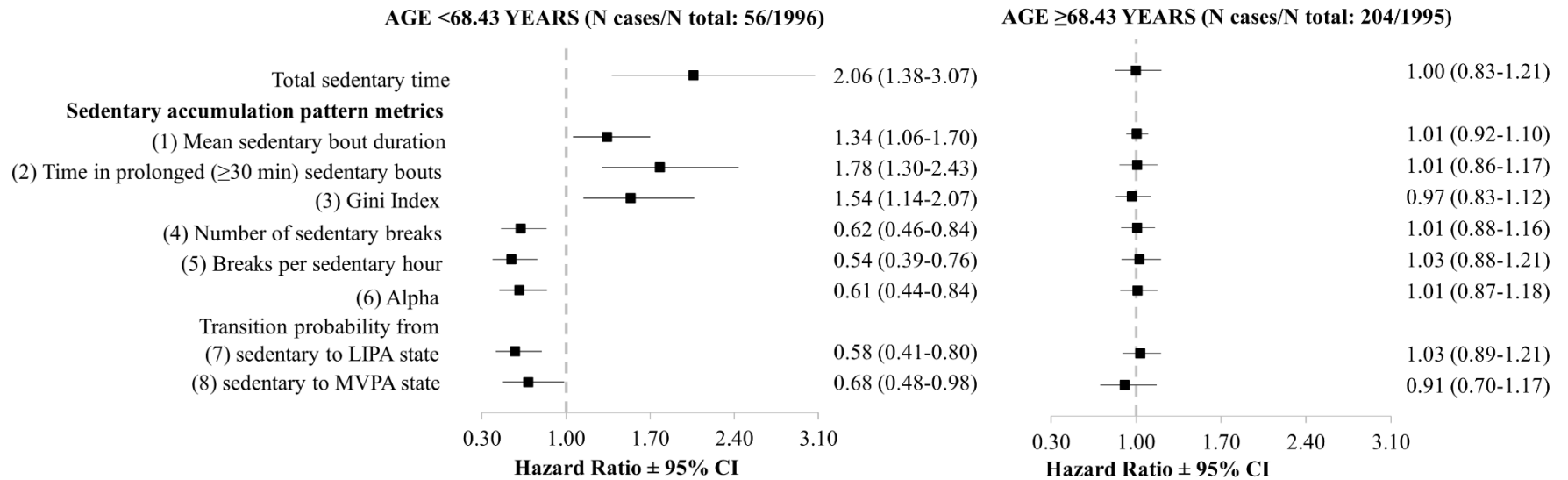


Figure 24 Association of total sedentary time and sedentary accumulation patterns with all-cause mortality stratified by age by a split at median age of 68.43 years.

Table 31 Associations of total sedentary time and sedentary accumulation patterns with incident CVD and all-cause mortality adjusting for MVPA as a continuous variable in the fully adjusted model

	HR (95% CI)			
	Incident CVD ^a		All-cause mortality ^b	
	Continuous MVPA ^c	Dichotomous MVPA ^d	Continuous MVPA ^c	Dichotomous MVPA ^d
Total sedentary time	1.06 (0.87-1.30)	1.02 (0.88-1.19)	1.09 (0.89-1.35)	1.16 (0.98-1.38)
Sedentary accumulation patterns				
(1) Mean sedentary bout duration	1.13 (1.01-1.26)	1.09 (0.98-1.23)	1.03 (0.95-1.11)	1.03 (0.95-1.11)
(2) Time in prolonged (≥30 min) sedentary bouts	1.09 (0.94-1.26)	1.05 (0.92-1.20)	1.09 (0.95-1.27)	1.12 (0.98-1.29)
(3) Gini index	1.00 (0.89-1.13)	0.99 (0.88-1.12)	1.03 (0.90-1.18)	1.06 (0.93-1.20)
(4) Number of sedentary breaks	0.92 (0.82-1.04)	0.94 (0.84-1.07)	0.92 (0.81-1.04)	0.92 (0.81-1.05)
(5) Breaks per sedentary hour	0.95 (0.82-1.09)	0.97 (0.85-1.10)	0.93 (0.80-1.08)	0.90 (0.78-1.04)
(6) Alpha	0.92 (0.80-1.05)	0.94 (0.82-1.07)	0.93 (0.81-1.07)	0.92 (0.80-1.05)
Transition probability from				
(7) sedentary to LIPA state	0.96 (0.84-1.10)	0.98 (0.86-1.11)	0.94 (0.81-1.08)	0.92 (0.80-1.06)
(8) sedentary to MVPA state	0.90 (0.74-1.08)	0.92 (0.79-1.08)	0.89 (0.70-1.13)	0.82 (0.67-1.01)

^aN total = 3321, N events = 299, mean follow-up (SD) = 6.2 (1.3) years.

^bN total = 3991, N events = 260, mean follow-up (SD) = 6.4 (0.8) years.

^cModels adjusted for sociodemographic, lifestyle, health-related factors and daily time in MVPA

^dModels adjusted for sociodemographic, lifestyle, health-related factors and MVPA recommendation.

Table 32 Associations of total sedentary time and sedentary accumulation patterns with all-cause mortality stratified by age adjusting for MVPA as a continuous variable in the fully adjusted model

	HR (95% CI)			
	Age<74 years ^a		Age≥74 years ^b	
	Continuous MVPA ^c	Dichotomous MVPA ^d	Continuous MVPA ^c	Dichotomous MVPA ^d
Total sedentary time	1.44 (1.03-2.01)	1.45 (1.12-1.88)	0.89 (0.67-1.17)	0.95 (0.76-1.20)
Sedentary accumulation patterns				
(1) Mean sedentary bout duration	1.06 (0.96-1.18)	1.06 (0.96-1.18)	1.00 (0.89-1.12)	1.00 (0.89-1.12)
(2) Time in prolonged (≥30 min) sedentary bouts	1.36 (1.08-1.70)	1.39 (1.13-1.71)	0.94 (0.77-1.14)	0.96 (0.80-1.15)
(3) Gini index	1.26 (1.02-1.54)	1.30 (1.06-1.58)	0.90 (0.75-1.08)	0.92 (0.77-1.09)
(4) Number of sedentary breaks	0.77 (0.64-0.93)	0.77 (0.63-0.94)	1.03 (0.88-1.22)	1.04 (0.89-1.23)
(5) Breaks per sedentary hour	0.75 (0.60-0.95)	0.73 (0.59-0.91)	1.09 (0.90-1.33)	1.08 (0.89-1.30)
(6) Alpha	0.82 (0.66-1.02)	0.80 (0.65-0.98)	1.03 (0.86-1.24)	1.02 (0.85-1.23)
Transition probability from				
(7) sedentary to LIPA state	0.78 (0.62-0.97)	0.75 (0.61-0.94)	1.09 (0.90-1.31)	1.08 (0.89-1.30)
(8) sedentary to MVPA state	0.85 (0.62-1.16)	0.77 (0.59-1.00)	0.99 (0.68-1.46)	1.08 (0.90-1.29)

^aN total = 3001, N events = 114.

^bN total = 990, N events = 146.

^cModels adjusted for sociodemographic, lifestyle, health-related factors and daily time in MVPA.

^dModels adjusted for sociodemographic, lifestyle, health-related factors and MVPA recommendation.

5 DISCUSSION, CONCLUSIONS & IMPLICATIONS

In this section, I will first discuss how the findings from the results on the daily composition of physical activity and sedentary behaviour are associated with incident cardiovascular disease, followed by the relation of sedentary accumulation pattern with incident cardiovascular disease and all-cause mortality in the context of previous research. Following that, a discussion of the strengths and weaknesses will take place. The final section will include closing remarks on the thesis's findings and contributions, as well as implications for public health practice.

5.1 Daily composition of wake-time movement behaviours in relation to incident CVD:

Interpretation of research findings

5.1.1 Summary of findings

The first objective of the thesis aimed to examine the combined association of objectively-assessed movement behaviours during waking period of day with incident CVD among older adults. Several findings emerged from this prospective study with a mean follow-up of approximately 6 years. Independent of sociodemographic, lifestyle and health-related risk factors, higher duration of MVPA was associated with a reduced risk of CVD, irrespective of the time spent in LIPA and SB. When LIPA was increased at the expense of SB, no evidence of a decreased CVD risk was found. Decreasing MVPA duration below the current level of PA recommendation, coupled with either an increase in LIPA or SB, had a detrimental impact on risk of CVD; this effect estimate was higher than the beneficial effect observed by increasing MVPA above the current recommendations.

5.1.2 Interpretation of CVD findings in the light of previous studies

Findings from our study were consistent with earlier longitudinal studies using self-reported (310) and objectively-assessed movement behaviours (220-222, 311), which also observed a curvilinear dose-response relationship between MVPA and CVD, wherein the greatest benefits were seen up to the recommended MVPA duration. In a meta-analysis of 33 prospective studies using self-reported data with an average follow-up of 12.8, the steepest risk reduction in CVD was found going from no physical activity to undertaking in levels of physical activity equivalent to the recommended 150 min/week of MVPA (≈ 11.25 MET-h/week), beyond which fewer

benefits were found (310). A study on middle-aged and older adults with a follow-up of 5.7 years also reported a non-linear association between objectively-assessed MVPA and CVD risk, with the greatest reduction observed among those engaging at least 10 to 20 min/day of MVPA as compared none, with associations flattening at higher MVPA durations (220).

The asymmetrical response to an increase or a decrease in MVPA duration is highlighted in our work, which advances the current understanding of the relationship of MVPA with CVD risk. Decrement in MVPA duration was found to have a larger harmful effect on risk of CVD than the gains obtained from increasing MVPA duration by reducing time in LIPA or SB. Such asymmetrical associations with mortality (306) and cardiometabolic health (238, 258, 312) have also been reported in other studies using similar compositional methodology. An explanation for this phenomenon could be attributed to the rapid weight gain or deconditioning with results in a decrease in MVPA against an equal amount of weight loss or conditioning which necessitates a considerably greater amount of exercise effort (238).

Although results based on objective measurements of SB (218, 220-222) were inconsistent, findings using self-reported data (209-211) consistently demonstrated that greater sedentariness was related with an increase in CVD risk. Findings from a study on older women found a detrimental association between objective measure of SB and incident CVD risk, even after adjusting for MVPA (218), while two other studies did not (220, 221). We found increase in CVD risk when an increment in the time spent in SB is accompanied with a decrease in MVPA. Unlike a study utilizing self-reported data (234) where substituting sitting with MVPA showed noticeable benefits for CVD mortality among individuals sitting for more than 6 h/day, in our study the magnitude of association was dependent on MVPA duration rather than SB. None of these studies took into consideration the compositional nature of movement behaviours, although studies did control for either total wear time (222) or MVPA (218). The nature of the measures (subjective and objective), the difference in target population, and adjustment for other movement behaviours are possible explanations for inconsistent results among the studies.

Results from studies examining the association of objectively-assessed LIPA with incident CVD were mixed (219-222, 252, 311, 313). In a study of 5750 older women with a mean follow-

up of 3.5 years, independent of MVPA duration, more LIPA was associated with reduced CVD risk, though the association was attenuated once cardiovascular risk factors were considered (311). Using the same dataset but different statistical approaches, one study found that an increase in LIPA coupled by an equal decrease in SB was associated with lower risk of CVD mortality (252), whereas in the other study no association between LIPA and CVD mortality was found when adjusted for SB and MVPA (313). In a another study with 5585 middle to older adults, the significant association observed between LIPA and incident CVD was attenuated after controlling for MVPA, with the exception of a higher risk of CVD when LIPA was less than 3 hours per day (220). Similar to our study, some prospective studies failed to find any evidence that LIPA reduces the risk of CVD (221, 222). Our findings indicate that when longer duration of LIPA is coupled with a short duration of SB, an increase in MVPA by reducing either LIPA or SB was beneficial. On the other hand, when LIPA duration is short and SB duration is high, an increase in MVPA at the expense of SB but not LIPA was protective against CVD risk.

5.2 Total sedentary time and its pattern of accumulation in relation to incident CVD and all-cause mortality: Interpretation of research findings

5.2.1 Summary of findings

The second objective of the thesis aimed to examine whether objectively-assessed total sedentary time and/or the pattern of sedentary accumulation are associated with incident CVD and all-cause mortality among older adults. Because there is no gold standard accumulation pattern measure, eight of them were evaluated, ranging from the most commonly used metric, breaks per sedentary hour, to a metric that examines the distribution of sedentary bouts, such as Alpha. Furthermore, the independence of associations from moderate-to-vigorous physical activity (MVPA) was also assessed.

This prospective study over a mean follow-up of 6 years yielded three main findings. First, total sedentary time and all SB pattern of accumulation metrics, except for the Gini index, were significantly associated with incident cardiovascular disease and all-cause mortality, after adjustment for sociodemographic and lifestyle risk factors. A higher sedentary time and a more prolonged sedentary bout accumulation pattern were related to an increased risk of CVD and death, whereas frequent interruptions to prolonged SB and transitions from sedentary to

physically active states were associated with a reduced risk of CVD and death. Second, the observed associations of total sedentary time and its pattern of accumulation with incident cardiovascular disease were explained by health-related risk factors (i.e., biological CVD risk factors and multimorbidity index) and MVPA. Third, in the younger older adults, even after , controlling for health-related risk factors and MVPA, total sedentary time and most sedentary accumulation pattern metrics were still significantly associated with all-cause mortality. However, regardless of the metrics utilized, no such associations were found among the oldest old.

5.2.2 Interpretation of CVD findings in the light of previous studies

According to findings based on self-reported data of SB in adults, higher sedentary time appears to be associated with a greater risk of incident CVD (209, 211). The conclusion from a small number of prospective studies on accelerometer-measured SB mainly in middle-aged and older adults was mixed, with some revealing a positive association between sedentary time and CVD risk (218, 219) and others not (220-222), when potential confounders were considered. Similar to our findings, others also found no statistical evidence of a nonlinear relationship between objectively-measured sedentary time and incident CVD (218, 220, 221). Contrastingly, a study of older men and women found a linear dose-response association, with every additional 1 hour of sedentary time per day being associated with a 38% greater risk of CVD when numerous risk factors were taken into consideration, but not high intensity physical activity (219), .

Only two prospective studies have previously examined the relation between sedentary accumulation pattern and CVD, with contrasting findings (218, 221). There was no association found between sedentary accumulation pattern, defined by breaks and bouts, and CVD among 1181 older men followed over a median 4.9 years (221). Whereas in a study focussed solely on older women (218), there was a significant increase in the risk of CVD related with longer mean sedentary duration, lower SB breaks, and accumulating sedentary time in long bouts. Despite accounting for biological CVD risk factors and MVPA, associations for mean sedentary bout duration and Alpha remained significant in the same study, even though they were not mutually adjusted but rather adjusted for in separate models. Unlike in the study among older women

(218), with the exception of mean sedentary bout duration, the associations in our analysis were fully explained after adjusting for health-related risk factors, which included biological risk factors for CVD. It implies that biological CVD risk markers play a key role in the relationship between sedentary accumulation pattern and CVD risk, which is in line with previous cross-sectional studies linking SB metrics to cardiometabolic risk factors in adults (269, 276, 314). However, following further adjustment for MVPA, either jointly or independently, this relationship of mean sedentary bout duration with CVD in our study was no longer significant.

Differences in the measures of accumulation pattern used, type and level of covariate adjustments made, and the usage of self-reported diagnosis data to assess morbidity prevalence (218), as opposed to our study's use of diagnostic data via record linkage, could be potential sources of inconsistencies in findings. Interestingly, sedentary accumulation pattern was previously found to be associated with incident CVD in women (218) but not in men (221); however, no indication of sex differences was detected in the current study as well as in another study among older adults (219).

5.2.3 Interpretation of all-cause mortality findings in the light of previous studies

A harmonised meta-analysis of eight prospective studies (mean age = 62.6 years), found a statistically greater risk of mortality after 9.5 hours or more of total sedentary time, even after adjustment for MVPA (225). Similarly, another study that focussed on middle aged and older adults (mean age = 68.9 years) showed that the relationship between sedentary time and death risk was non-linear, with significant risk observed beyond about 10.75 hours of sedentary time (220). In contrast, in our investigation, there was no evidence of non-linearity.

Two prospective studies have previously examined the association of sedentary accumulation pattern with all-cause mortality, however the findings are mixed (230, 277). In contrast to these previous studies, we found that the associations of total sedentary time and most of the sedentary accumulation pattern metrics with all-cause mortality varied according to age, with associations being seen only in the younger older adults after considering a wide range of covariates including health-related risk factors and MVPA. This may account for discrepancies between the results of earlier studies: one study on middle-to-older adults with a mean age of

63.5 years observed that having more breaks in sedentary time significantly reduced the risk of mortality (277), whereas a second study that focussed only on older adults with a mean age of 78.4 years found no such association using the same metric of sedentary accumulation pattern (230). A different study using the same population sample as the first one (mean age = 63.5 years) showed that replacing prolonged sedentary bouts with shorter sedentary bouts did not reduce the risk of mortality but that substituting with LIPA or MVPA did (251). This is consistent with our results that younger older adults who switch more frequently from a sedentary to either LIPA or MVPA states had lower mortality risks.

The overall levels of SB measures were better for younger older adults than in the oldest old, which may be a contributing factor for the differential associations observed by age group. Another explanation could be because of changes in functional capacity, cardiovascular performance, respiratory capacity, and muscular strength over the course of an individual's life, where the peak is seen in early adulthood and then linearly declines with advancing age, creating a gap in capacity across the population known as the "fitness gap" (315, 316). Therefore, we would not expect to see an association between SB measures with mortality if the oldest old are not functionally capable itself.

5.3 Strengths

There are several strengths to this thesis. We used objective-measures of movement behaviours, a prospective study design, included both men and women unlike previous well-known studies that are based only on one sex (218, 221, 230), and exclusively focussed on older adults. We used an innovative method, the compositional Cox regression, which considers the relative and co-dependent nature of the daily movement behaviours. In the absence of a gold standard metric, we utilized a wide range of metrics, including ones that characterize the distribution of different bout lengths of SB, to evaluate the pattern of sedentary accumulation. We also took into account a wide range of risk factors, such as CVD biomarkers, the prevalence of diabetes, and multimorbidity, which were ascertained through numerous objective sources, as opposed to self-reporting, such as clinical examination and record-linkage to hospital data.

5.4 Limitations

There are limitations which should be noted. Our sample population is drawn from the occupational cohort of the British Whitehall II study, which means by nature, the participants are healthier than the general population (“the healthy-worker effect”) (317). They are also on average more motivated and interested in their health, and hence less likely to have unfavourable health event, which may limit the generalizability of our findings (318). However, despite differences in disease incidence and risk factors, it has been previously shown that the associations of cardiovascular risk factors, including physical activity, from this occupational cohort (Whitehall II) were similar to that of a UK-wide general population based study (the British Regional Heart Study of men) and a community-based US study (the Framingham study of men and women) (319). We use a wrist-worn accelerometer that does not distinguish between different postures, such as sitting and standing (164). This might lead to misclassification between SB and lower levels of physical activity i.e., LIPA, with some discrepancies in sitting time reported by studies using thigh-worn accelerometer (164). Nevertheless, findings from wrist accelerometers can accurately classify movement behaviours based on metabolic intensity (308). Also, because there is no gold standard cut-off for identifying movement behaviours among the older adults, there may be variation of findings between studies. Although despite our study’s sensitivity analysis using a different cut-off, the results were unaffected (320).

We included participants in the analytical sample if they had accelerometer data for at least two weekdays and two weekend days (97.6% of the sample has at least seven days of recording), which may not be representative of the individual’s habitual physical activity over the course of the follow-up period. But according to earlier studies, 4 to 6 days, including the weekends, are ideal for accurately capturing weekly habitual physical activity (184, 185). Moreover, our sample had a good test-retest reliability for all measures of movement behaviours. Finally, even though we adjust for a wide range of confounders, there is always a chance that an additional, unmeasured factor could still be able to further explain the association.

5.5 Conclusion and implications for public health practice

In the last decade, sedentary behaviour, or “too much sitting” has emerged as a risk factor distinct from “too little exercise”, which may have important implications for cardiovascular health (134). The 2018 Physical Activity Guidelines Advisory Committee Scientific Report concluded that there was strong evidence that greater time spent in sedentary behaviour was significantly associated with higher risk of incident CVD and all-cause mortality (307). However, most of the evidence came from self-reported measures, including measures such as time spent in front the TV, which are subject to reporting bias, highlighting importance to use newly objective measures of sedentary time. In recent times, there has been considerable interest in the interplay between SB, LIPA, MVPA, and sleep as they together represent the 24 hours of the day (200). Given the behavioural approach of this thesis, our focus was on the wake-time movement behaviours wherein the time spent in different movement behaviours is an individual’s choice. Accounting for the inter-relation between behaviours is important as they share the total waking day duration, such that any change in time spent in one behaviour results in change in time spent in other behaviours, and the relation of a specific behaviour depends on the other behaviours (243).

A pertinent question for public health relevance that stems from this is that if individuals would like to replace their sedentary time with more of other behaviours, replacement with which behaviour would be more beneficial? Should they engage in higher intensive physical activity or simply undertaking light activities enough? To address this question by assessing the joint associations of wake-time movement behaviours with incident CVD, the first objective of the thesis utilised a novel approach, compositional Cox regression, which takes into consideration the constrain of the wake-time movement behaviours summing to a full waking day period, and its related collinearity. To the best of our knowledge, this was the first study to examine how different compositions of SB, LIPA, and MVPA in a waking day are associated with incident CVD using a compositional analysis approach (321). We used pre-defined time-use compositions based on the recommendations for PA which are more realistic to undertake.

Unlike some of the studies using self-reported data on movement behaviours, we found that the magnitude of association with CVD was dependent on the duration of MVPA rather than

on SB or LIPA. Using compositional approach highlighted the asymmetrical response to an increment or decrement of MVPA duration. We found that the reduction in time spent in MVPA was far more detrimental on CVD risk than the gains obtained from increase in MVPA, especially if it exceeds beyond the recommended duration per day of 21 minutes, which approximates 150 minutes per week of MVPA. This suggests that if individuals are unable to increase their level of MVPA, they should be recommended to at least maintain their current engagement levels of MVPA. The duration of MVPA even below the level of the recommended criteria was able to reduce the risk of CVD even among older adults. This could be aligned with the public health messaging that *“some exercise is better than none, but more is better”*.

Increasing MVPA by reducing SB and LIPA was important in reducing risk of CVD among older adults. However, among those highly sedentary with short duration of LIPA, it might be beneficial to increase MVPA by lowering SB alone. This suggests that some LIPA may be needed for better CVD health and highlights the importance of examining composition of movement behaviours. It was also not in line with the public health messaging promoted by World Health Organisation that *“every move counts”* (322), given that the replacement behaviour varies on how an individual’s waking day composition is constructed of different behaviours. In a recent individual level intervention study, the average daily sitting reduced which was achievable was approximately 0.5 hours or 30 minutes per day for adults and older adults (249). Given this, it might be possible to replace 30 minutes per day of SB with a mix of MVPA and LIPA to lower the risk of developing CVD.

Physical activity guidelines have previously stated that there was insufficient evidence to determine whether bouts or breaks in sedentary behaviour are important risk factors in the relationship between sedentary behaviour and health outcomes (307, 322). Therefore, in our second objective we examined whether, and how incident CVD and all-cause mortality were related to a behavioural pattern of accumulating SB for prolonged period using eight metrics. There was no suggestion of a threshold effect for sedentary accumulation pattern or total sedentary time for either of the outcomes. Associations of total sedentary time and pattern of sedentary accumulation with risk of CVD were no longer evident once MVPA was taken into consideration. In line with the findings of objective 1, our findings from objective 2 on CVD

confirm the importance of MVPA for CVD risk reduction among older adults. Since the publication of our paper on sedentary accumulation pattern (323), the findings for CVD have also been confirmed by another study (324). Both the total and pattern of sedentary behaviour were important risk factors for mortality in younger older adults, which lend support to the 2020 Canadian recommendation (200) suggesting to limit and frequently interrupt long periods of sedentary time. Although further investigations are required to replicate these findings and to why no associations were found in the oldest old age group. Several metrics were used including those assessing the distribution of sedentary bout length as recommended by previous literature (280), among which our findings suggest that Alpha was the most robustly associated. Additionally, breaks per sedentary hour, a simple metric frequently used was also consist.

Using objective measurements of movement behaviour allowed us to investigate all daily movement behaviours across the day and assess sedentary accumulation pattern. Compositional approach provided us with additional insights into the inter-relation of behaviours which were not seen using traditional regression techniques or by mutual adjustment of one behaviour with another without the inclusion of the third behaviour. Main conclusionary notes is that MVPA is cardioprotective against CVD risk among older adults and that a more fragmented pattern of sedentary time independent of MVPA prevents premature death in younger older adults. Future studies should take into consideration the interdependency of movement behaviours, as well as the sedentary accumulation pattern, rather than just the overall time in SB.

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PUBLICATIONS

RESEARCH

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Association of daily composition of physical activity and sedentary behaviour with incidence of cardiovascular disease in older adults

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Abstract

Background: Moderate-to-vigorous physical activity (MVPA) is proposed as key for cardiovascular diseases (CVD) prevention. At older ages, the role of sedentary behaviour (SB) and light intensity physical activity (LIPA) remains unclear. Evidence so far is based on studies examining movement behaviours as independent entities ignoring their co-dependency. This study examines the association between daily composition of objectively-assessed movement behaviours (MVPA, LIPA, SB) and incident CVD in older adults.

Methods: Whitehall II accelerometer sub-study participants free of CVD at baseline ($N = 3319$, 26.7% women, mean age = 68.9 years in 2012–2013) wore a wrist-accelerometer from which times in SB, LIPA, and MVPA during waking period were extracted over 7 days. Compositional Cox regression was used to estimate the hazard ratio (HR) for incident CVD for daily compositions of movement behaviours characterized by 10 (20 or 30) minutes greater duration in one movement behaviour accompanied by decrease in another behaviour, while keeping the third behaviour constant, compared to reference composition. Analyses were adjusted for sociodemographic, lifestyle, cardiometabolic risk factors and multimorbidity index.

Results: Of the 3319 participants, 299 had an incident CVD over a mean (SD) follow-up of 6.2 (1.3) years. Compared to daily movement behaviour composition with MVPA at recommended 21 min per day (150 min/week), composition with additional 10 min of MVPA and 10 min less SB was associated with smaller risk reduction – 8% (HR, 0.92; 95% CI, 0.87–0.99) – than the 14% increase in risk associated with a composition of similarly reduced time in MVPA and more time in SB (HR, 1.14; 95% CI, 1.02–1.27). For a given MVPA duration, the CVD risk did not differ as a function of LIPA and SB durations.

Conclusions: Among older adults, an increase in MVPA duration at the expense of time in either SB or LIPA was found associated with lower incidence of CVD. This study lends support to public health guidelines encouraging increase in MVPA or at least maintain MVPA at current duration.

Keywords: Cardiovascular disease, Compositional data analysis, Light intensity physical activity, Longitudinal cohort, Moderate-to-vigorous physical activity, Older adults, Sedentary behaviour

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Background

Physical activity is a modifiable risk factor for cardiovascular diseases (CVD) [1, 2], with 17 to 25% lower CVD risk among those following the current recommended 150 min per week of moderate-to-vigorous physical activity (MVPA) [3]. These recommendations are not met by the majority of the population, particularly older adults [4] in part due to declining physiological ability to perform higher intensity activity [5]. Older adults spend around two-thirds of the day in sedentary behaviour (SB) [6] which is increasingly thought to be an independent risk factor for CVD [7–9]. Light intensity physical activity (LIPA) such as strolling may be easier than MVPA [10] and could potentially confer some benefits in those not fit enough to engage in physical activity at higher intensity [11].

The evidence on the association between multiple movement behaviours during the day (i.e. SB, LIPA, MVPA) and CVD is primarily based on self-reported physical activity [12], which are subject to recall and response bias [13]. Further limitations of such data include their inability to capture incidental, short periods of movements and light intensity activities that are spread over the day and thus less easy to report with accuracy [12–14]. Such measurements are likely to affect precision of estimates of the associations between movement behaviours and health outcomes [15]. Prospective studies are beginning to use movement sensor devices such as accelerometers to objectively measure duration in movement behaviours and assess their associations with incident CVD [11, 16–20]. These studies have found higher duration of MVPA to be associated with reduced risk of CVD [16–18, 20], while results on the impact of LIPA [11, 16–18, 20] and SB [16–20] are inconsistent.

Each day is limited in time, with increase in time spent in one movement behaviour done at the expense of time in other movement behaviours [21]. Most prospective studies using objective measures have not accounted for this co-dependency and treated SB [19, 20], LIPA [11, 20, 22] and MVPA [3, 20] as independent behaviours. Recent epidemiological research calls to account for the relative nature of movement behaviours and to use appropriate statistical methods to deal with such data [23, 24]. We aim to use an innovative approach, the compositional Cox regression [25] to better examine how different compositions of SB, LIPA, and MVPA in a waking day are associated with incident CVD in older adults. This approach explicitly considers the compositional nature of movement data, that is the durations in SB, LIPA, and MVPA are part of a composite whole corresponding to the waking period of a day.

Methods

Study participants

The Whitehall II study is an ongoing prospective cohort established in 1985–1988 among 10,308 London-based

civil servants (67% males) aged 35–55 years [26]. Since the inception of the study, sociodemographic, lifestyle and health-related factors have been assessed using questionnaires and clinical examinations. Follow-up assessments have taken place approximately every 4–5 years, with the latest wave completed in 2015–2016. Participants provided written informed consent. Research ethics approval was obtained from the University College London ethics committee (reference number 85/0938), renewed at each contact. The accelerometer sub-study was undertaken during the 2012–2013 wave of data collection for participants seen at the London clinic and for those living in the South-Eastern regions of England who underwent clinical examination at home.

Measures

Movement behaviours

Participants without contraindications (i.e., allergies to plastic or metal, travelling abroad in the following week) were asked to wear a tri-axial accelerometer (GENEActiv Original; Activinsights Ltd., Kimbolton, UK) on their non-dominant wrist during 9 consecutive days over 24 h. Data was sampled at 85.7 Hz, with acceleration expressed relative to gravity ($1g = 9.81 \text{ m/second}^2$).

Accelerometer data was processed in R software by using GGIR package [27] version 2.0–1 (<https://github.com/wadpac/GGIR/releases/tag/v2.0-1>). Data were corrected for calibration error [28] and Euclidean Norm of raw accelerations Minus 1 (ENMO) with negative numbers rounded to zero were calculated [29]. This metric has been shown to be a valid measure of time spent in metabolic equivalent of task (MET) levels as measured by indirect calorimetry [30]. Sleep periods were then detected using a validated algorithm guided by sleep log [31]. Data from the first waking up (day 2) to waking up on the day before the last day (day 8) were used, corresponding to 7 full days. Waking period was defined as the period between waking and onset of sleep. Participants were included in the analysis if they had daily wear time $\geq 2/3$ of waking hours, for at least 2 weekdays and 2 weekend days [32]. Non-wear period among valid days was corrected based on a previously reported algorithm [29]. As there is no gold standard to classify movement behaviours in older adults, we referred to cut-points from a study where adult participants undertook series of activities in a laboratory and mimic free-living posture/behaviours eliciting average accelerations similar to that observed in free living situations [33]. These cut-points are in agreement with a more recent study among older adults that showed good classification accuracy based on oxygen consumption during nine laboratory-based activities of daily living [34]. Based on these studies, movement behaviour during waking period was classified as SB when average acceleration over a 60-s epoch

was < 40 milligravity (mg), 40–99 mg for LIPA and ≥ 100 mg for MVPA [33, 34]. The daily time in each movement behaviour was calculated as the mean of measures over 7 days. For those with < 7 valid days, a weighted average was computed using data on weekend and week days [32]. Reliability of acceleration measures was assessed among 66 participants using retest data assessed on average for 26.5 (SD = 4.6) days after the first measure. There was a good test-retest reliability for all movement behaviours with strong correlation between the two measures (Pearson's $r = 0.81$ for SB, 0.77 for LIPA and 0.75 for MVPA).

Incidence of CVD

Incident CVD was defined as the first occurrence of fatal or nonfatal coronary heart disease (CHD), stroke or heart failure. Nonfatal events were traced from the Hospital Episode Statistics (HES) database using each participant's unique National Health Services (NHS) identification number based on the International Classification of Diseases (ICD) codes for CHD (ICD-10 codes I20–I25), stroke (ICD-10 codes I60–I64) and heart failure (ICD-10 code I50). CHD and stroke cases were also determined using Whitehall II study-specific 12-lead resting electrocardiogram recording and MONICA-Augsburg stroke questionnaire, respectively [26]. Further details of validation of CVD cases are provided in a separate publication [35]. CVD-related deaths were drawn from the UK national mortality register (NHS Central Registry).

Covariates

Covariates were assessed by questionnaire or at clinical examination during the 2012–2013 wave. Sociodemographic variables included age, sex, ethnicity (white, non-white), marital status (married/cohabitating, divorced/widowed/single), education (\leq primary school, lower secondary school, higher secondary school, university, higher degree) and last occupational position (high, intermediate, low). Lifestyle factors included alcohol consumption (0, 1–14, > 14 units per week), smoking status (current and recent ex-(less than 5 years) smokers, long-term ex-smokers, never smokers), and fruits & vegetables intake (less than once daily, once daily, more than once daily). Cardiometabolic risk factors included body mass index (BMI; categorized as < 24.9, 25–29.9, and ≥ 30 kg/m²), hypertension (systolic/diastolic blood pressure $\geq 140/90$ mmHg or use of antihypertensive drugs), prevalent diabetes (fasting glucose ≥ 7.0 mmol/l or self-reported doctor diagnosed diabetes or use of diabetes medication or hospitalizations ascertained through record linkage to the HES (ICD-9 codes 250 or ICD-10 code E11)), hyperlipidaemia (low-density lipoproteins (LDL) > 4.1 mmol/l or use of lipid-lowering drugs)

assessed at the clinical examination, and multimorbidity index (calculated as the count of the following chronic conditions: cancer, arthritis, chronic obstructive pulmonary disease, depression, Parkinson disease, and dementia; assessed using HES records and Whitehall II questionnaires as well as mental health records for depression).

Statistical analysis

Compositional data analysis was used to account for the co-dependency of movement behaviours during waking period [21]. This method assumes relative distribution of the movement behaviours and reduces the three-parts composition (SB, LIPA, MVPA) noted as z , into two exposure variables by transforming them into two isometric log-ratio (ilr) coordinates, referred to as z_1 and z_2 . The following vector of ilr-coordinates was first constructed by sequential binary partition to examine the importance of SB [36]: (Eq. 1)

$$z^1 = \begin{pmatrix} z_1^1 = \sqrt{\frac{2}{3}} \ln \frac{SB}{(LIPA \cdot MVPA)^{1/2}}, \\ z_2^1 = \sqrt{\frac{1}{2}} \ln \frac{LIPA}{MVPA} \end{pmatrix} \quad (1)$$

The first coordinate, z_1^1 represents the ratio of time spent in SB relative to the geometric mean of physical activity (LIPA and MVPA). Second coordinate, z_2^1 represents time spent in LIPA with respect to MVPA. Rotations of these coordinates, z^2 and z^3 , were then used to examine the importance of LIPA relative to SB and MVPA, and the importance of MVPA relative to LIPA and SB (Supplemental Methods Section). In order to facilitate interpretation of the results, daily time spent in SB, LIPA and MVPA were normalized to a 16-h waking day corresponding to the mean duration of waking period in our study population. Zero duration in any of the movement behaviours were imputed using log ratio Expectation–Maximization algorithm implemented using `lrEM` function in R package `zCompositions` [37]. Analyses were conducted using compositional Cox regression with incident CVD as the outcome [25]. The proportional hazards assumption was checked using the Grambsch–Therneau test statistic [38]. Follow-up time for incident CVD event was from the date of clinical examination at the 2012–2013 wave until the date of CVD (fatal or non-fatal), non-CVD related death to account for competing risks or end of follow-up (31st March 2019), whichever came first. Model 1 included waking day composition of z (z_1 , z_2), sociodemographic and lifestyle variables. Model 2 was additionally adjusted for cardiometabolic risk factors and multimorbidity index. We examined whether age (< 67.8 versus ≥ 67.8

years (median split)), sex (men versus women), ethnicity (white versus non-white) and BMI (not obese versus obese) modified associations. Effect modification was investigated by adding the interaction terms "effect modifier^{*z}₁" and "effect modifier^{*z}₂" to the fully adjusted model.

Results from the Cox compositional model [25] were used to extract the hazard ratios (HR) for CVD incidence in relation to compositions of movement behaviours (MVPA, LIPA, SB) in a waking day period. To do so, we defined a set of reference movement behaviour compositions to which we compared compositions with 10 (20- and 30-) minutes more time spent in one movement behaviour at the expense of time spent in another movement behaviour, keeping time spent in the third behaviour fixed at the reference composition. This approach is also referred to as reallocation of time between different movement behaviours [25]. First to assess the impact of MVPA duration, we defined three separate reference movement behaviour compositions corresponding to individuals with daily MVPA duration set at 10 min, 21 min (corresponding to the MVPA recommendation of 150 min per week) [39], and the recommended 30 min per day [39]. Time in SB and LIPA for these reference compositions were set at 77 and 23%, respectively, of the remaining waking time, based on the mean proportion of these movement behaviours as observed in the study sample.

To examine whether risk of CVD varied by duration in SB or LIPA, reallocation analyses were conducted using two reference daily compositions of movement behaviours with SB set at 9 h and 14 h corresponding to the 5th and 95th percentile, respectively and MVPA duration set at 10 min. LIPA was set at the remaining waking day by subtracting time spent in SB and MVPA from 16 h. We then examined whether similar findings were found when repeating these analyses with 21 min instead of 10 min of MVPA in the reference composition. All analyses were undertaken using STATA statistical software version 15 (StataCorp, College Station, Texas) and R version 3.6.3 with a two-sided $P < 0.05$ considered statistically significant.

Sensitivity analyses

The robustness of results was tested in further analyses. One, to examine the potential risk of reverse causation we repeated the primary analysis by excluding incident CVD events occurring within the first 2 years of follow-up. Two, the outcome was defined as incident non-fatal CVD events, where fatal CVD events were censored at date of death but not considered as an event of interest. Three, we repeated analysis by using an alternative cut-off to differentiate SB (< 45 mg) from LIPA (45–99 mg) [40]. Four, we also provide results using time in SB,

LIPA and MVPA without normalizing to 16-h waking day period and additionally adjusting for total waking day duration.

Results

Of the 6308 participants in the 2012–2013 wave, 4880 (4680 seen at the London clinic and 200 at home) were invited to participate in the accelerometer sub-study, with 4492 agreeing and 4006 returning the device with valid data (Fig. 1). Excluding pre-existing CVD ($n = 674$; CHD (90.6%), stroke (6.4%) and heart failure (3%)) or those with missing data for covariates ($n = 13$) led to an analytical sample of 3319 study participants. Compared with participants not included ($n = 2989$) in the analyses, those included ($n = 3319$) were on average younger (included vs excluded participants: 68.9 vs 70.9 years, $p < 0.001$), more likely to be men (73.3% vs 67.7%, $p < 0.001$) and from higher occupational position (55.4 vs 49.7%, $p < 0.001$). In total, 97.6% of the analytic sample had valid data for 7 days, 1.4% for 6 days, 0.6% for 5 days, and 0.5% for 4 days. Among the 3319 study participants, 299 incident CVD cases (CHD (62.9%), stroke (17.7%) and heart failure (19.4%)) were recorded over a mean follow-up of 6.2 years (standard deviation (SD) = 1.3). Participants with incident CVD were more likely to be older, men, non-white, less educated, have a worse cardiometabolic profile, and spend more time in SB and less time in LIPA and MVPA compared with participants who did not develop CVD during follow-up (Table 1).

There was no evidence of effect modification by age (P for interaction = 0.83), sex ($P = 0.46$), ethnicity ($P = 0.40$), and BMI ($P = 0.14$), thus analyses were conducted in the full study sample. Table 2 presents the results from compositional Cox regression on the association between daily composition of movement behaviours (SB, LIPA, MVPA) and incident CVD. The proportional hazard assumption was met. More time spent in SB relative to time spent in physical activity (LIPA and MVPA) was associated with increased risk of incident CVD (HR $z_1^1 = 1.34$, 95% CI: 1.01–1.79) in a model adjusted for socio-demographic and lifestyle variables. After additional adjustment for cardiometabolic risk factors and multimorbidity index, the association was no longer significant (HR 1.24, 95% CI: 0.92–1.67). Increase in MVPA relative to time spent in SB and LIPA was associated with reduced CVD risk (HR $z_1^3 = 0.73$, 95% CI: 0.60–0.89) when adjusted for sociodemographic and lifestyle factors, with a slight attenuation after adjusting for all covariates (HR 0.79, 95% CI: 0.64–0.97). Time spent in LIPA relative to other movement behaviours (z_1^2) was not associated with CVD risk. The heatmap ternary plot (Fig. 2) illustrates the dominance of MVPA relative to other movement behaviours in reducing CVD risk.

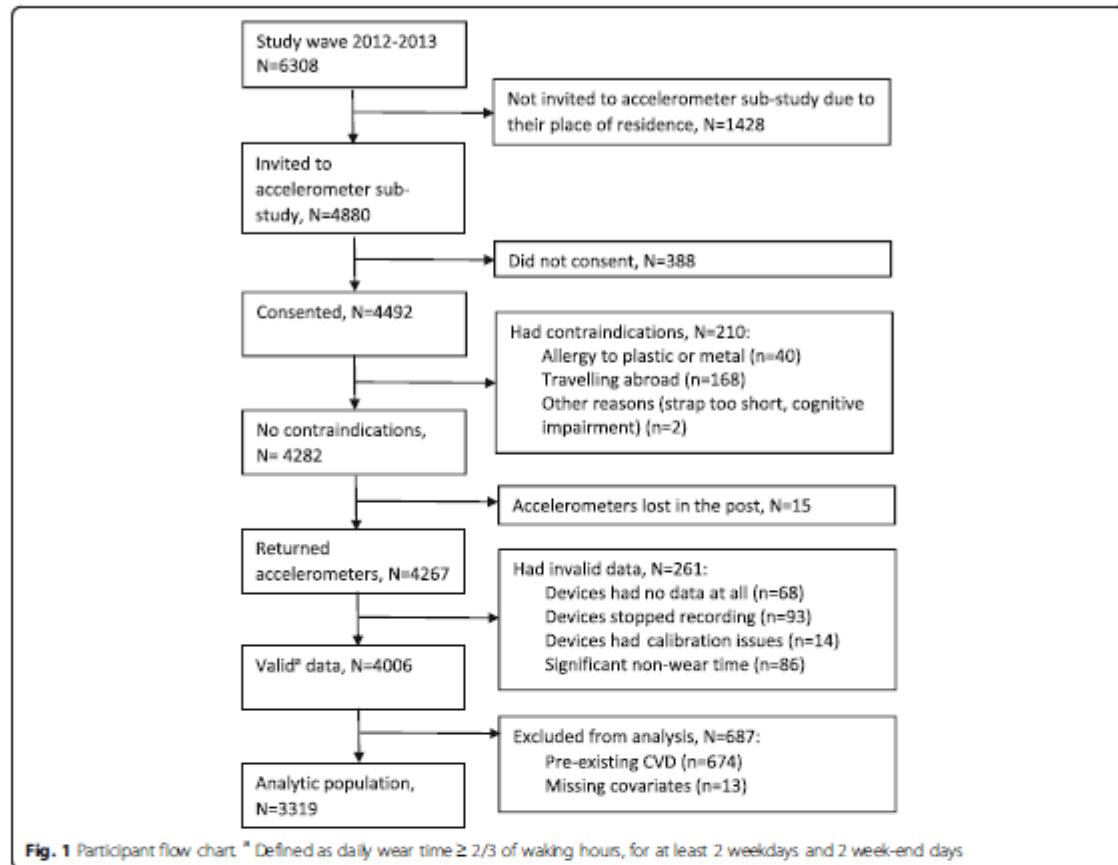


Figure 3 shows fully adjusted HRs for incident CVD associated with daily time reallocating from one movement behaviour to another, keeping the third fixed at the reference composition, using three reference compositions (panels A, B, C) characterised by varying MVPA duration. The estimates and their CI are detailed in Table 3 for 10-min reallocation and in Supplemental Table 1 (Additional file 2) for 20- and 30-min reallocation. Compared to a daily composition of movement behaviour made of 10 min of MVPA (reference A; SB = 12 h 11 min, LIPA = 3 h 39 min per day), a composition with 10 min less of SB and 10 min more of MVPA (SB = 12 h 1 min, LIPA = 3 h 39 min, MVPA = 20 min per day) was associated with 13% reduction in CVD risk (HR = 0.87, 95%CI: 0.78–0.98), see Table 3. Independently of time in MVPA in the reference compositions, reallocating time from MVPA to either SB or LIPA was associated with a larger risk of CVD (Fig. 3), than the reduction of risk associated with allocating the same time from either behaviour into MVPA. Compared to reference composition A, when using reference

composition B and C (made of 21 and 30 min of MVPA respectively) smaller reductions in CVD risk were observed for reallocation of 10-, 20- or 30- min of MVPA to SB (Fig. 3).

Table 4 and Supplemental Table 2 (Additional file 2) show the association of daily composition of movement behaviours with incident CVD compared to two reference compositions defined by varying SB and LIPA durations for a given 10 min of MVPA. Compared to a daily composition with 9 h of SB, 6 h 50 min of LIPA and 10 min of MVPA duration (reference 1), compositions with 10 (20- or 30-) minute decrease in either SB or LIPA and equal increase in MVPA were associated with lower risk of CVD. In comparison, when using reference 2 composed with 14h of SB, 1h 50 min of LIPA and 10 min of MVPA duration, same risk reductions were observed for movement behaviour compositions with greater MVPA coupled with equal less time in SB, but associations were not significant when coupled with less LIPA. Similar associations were found when the reference composition had 21 min instead of 10 min of MVPA duration (Supplemental Fig. 1 in Additional file 2).

Table 1 Characteristics of the study population at baseline (2012–2013) by incident CVD

Characteristics	Incident CVD (N = 3319)		P value
	No	Yes	
N (row %)	3020 (91.0)	299 (9.0)	
Age (years), M (SD)	68.6 (5.5)	71.5 (5.9)	< 0.001*
Women	830 (27.5)	55 (18.4)	0.001*
Non-white	173 (5.7)	33 (11.0)	< 0.001*
Married/cohabitating	2262 (74.9)	226 (75.6)	0.79
Higher education	995 (33.0)	76 (25.4)	0.01*
Low occupational position	1494 (49.5)	155 (51.8)	0.43
Recent-ex/current smokers	151 (5.0)	23 (7.7)	0.05
1–14 units of alcohol per week	1712 (56.7)	166 (55.5)	0.92
Daily intake of fruits & vegetable	2423 (80.2)	227 (75.9)	0.08
BMI (kg/m ²), M (SD)	26.3 (4.2)	27.1 (4.4)	0.003*
Hypertension ^a	1347 (44.6)	183 (61.2)	< 0.001*
Hyperlipidaemia ^b	1365 (45.2)	150 (50.2)	0.10
Diabetes	311 (10.3)	58 (19.4)	< 0.001*
Multimorbidity index (N chronic conditions) ^c			0.67
0	2153 (71.3)	207 (69.3)	
1	742 (24.6)	77 (25.8)	
≥ 2	125 (4.1)	15 (5.0)	
Time in SB ^d (minutes/day), M (SD)	692.1 (88.4)	718.0 (96.8)	< 0.001*
Time in LIPA ^d (minutes/day), M (SD)	209.5 (65.1)	195.2 (73.2)	< 0.001*
Time in MVPA ^d (minutes/day), M (SD)	58.4 (37.6)	46.8 (36.4)	< 0.001*

Notes: Values are N (column %) unless otherwise indicated

^aSystolic/diastolic blood pressure ≥ 140/90 mmHg or use of antihypertensive drugs

^bLow-density lipoprotein ≥ 4.1 mmol/l or use of lipid lowering drugs

^cCancer, arthritis, chronic obstructive pulmonary disease, depression, Parkinson disease, and dementia

^dNormalized to a 16-h (960 min) waking day

* indicates statistical significance at $p < 0.05$

Abbreviations: BMI body mass index; CVD cardiovascular disease; LIPA light intensity physical activity; M mean; MVPA moderate-to-vigorous physical activity; SD standard deviation; SB sedentary behaviour

Table 2 Relative importance of SB, LIPA & MVPA for incident CVD (N = 3319)

IIR-coordinate ^a	Model 1 ^b		Model 2 ^c	
	HR (95% CI)	P value	HR (95% CI)	P value
Rotation 1: relative importance of SB				
z_1^1 (SB increase relative to LIPA and MVPA)	1.34 (1.01–1.79)	0.04*	1.24 (0.92–1.67)	0.16
z_2^1 (LIPA increase relative to MVPA)	1.21 (0.88–1.67)	0.25	1.16 (0.84–1.62)	0.36
Rotation 2: relative importance of LIPA				
z_1^2 (LIPA increase relative to SB and MVPA)	1.02 (0.68–1.51)	0.93	1.02 (0.68–1.54)	0.91
z_2^2 (SB increase relative to MVPA)	1.42 (1.20–1.68)	< 0.0001*	1.30 (1.09–1.56)	0.004*
Rotation 3: relative importance of MVPA				
z_1^3 (MVPA increase relative to SB and LIPA)	0.73 (0.60–0.89)	0.002*	0.79 (0.64–0.97)	0.02*
z_2^3 (SB increase relative to LIPA)	1.17 (0.80–1.72)	0.41	1.12 (0.75–1.66)	0.58

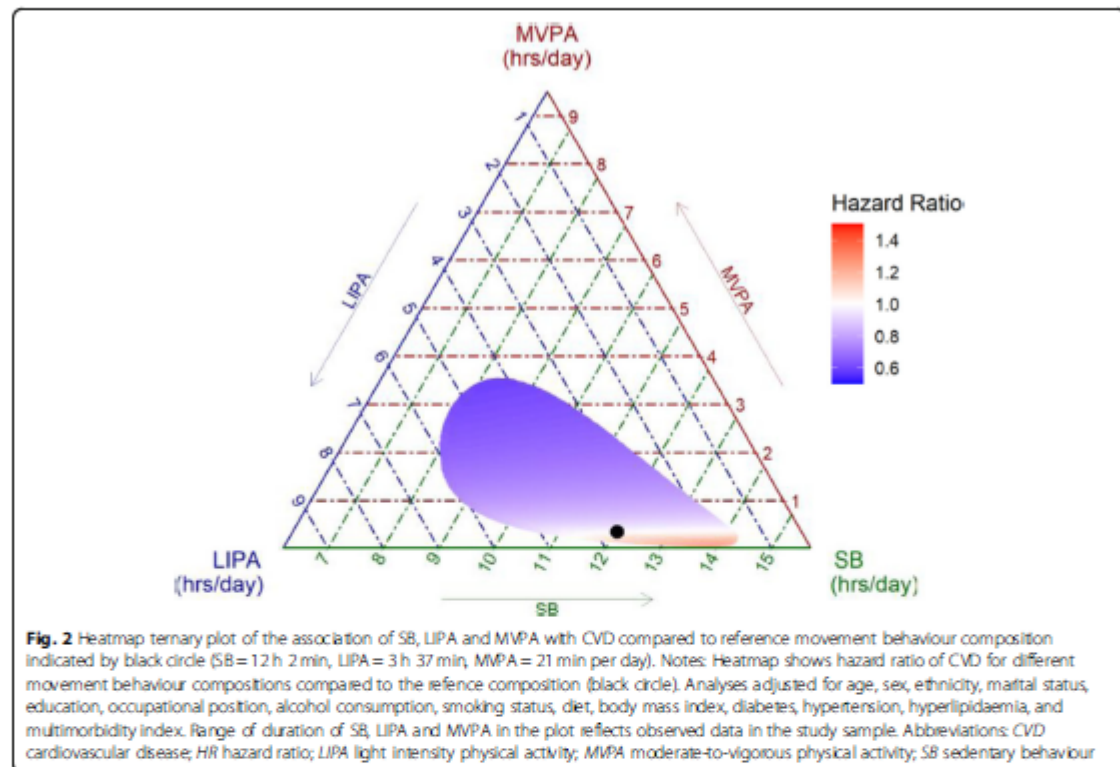
^aSee Methods in Additional file 1 for details of IIR coordinates z_1 and z_2 for all rotations

^bModel 1 is adjusted for age, sex, ethnicity, marital status, education, occupational position, alcohol consumption, smoking status, and diet

^cModel 2 is additionally adjusted for body mass index, diabetes, hypertension, hyperlipidaemia, and multimorbidity index

* indicates statistical significance at $p < 0.05$

Abbreviations: CI confidence interval; CVD cardiovascular disease; HR hazard ratio; IIR isometric log-ratio; LIPA light intensity physical activity; MVPA moderate-to-vigorous physical activity; SB sedentary behaviour



Sensitivity analyses

Excluding 88 CVD events within the first 2 years of follow-up (Supplemental Table 3 in Additional file 2) attenuated the association with MVPA relative to other movement behaviours ($P=0.06$), although the magnitude of risk reduction remains similar (HR $z_1^3 = 0.79$, 95% CI: 0.62–1.01). Analyses examining the association with non-fatal CVD events (Supplemental Table 4 in Additional file 2), those using an alternative cut-off to define movement behaviours (Supplemental Table 5 in Additional file 2) and those using non-normalized movement behaviours (Supplemental Table 6 in Additional file 2) yielded results similar to the main analysis (Table 2).

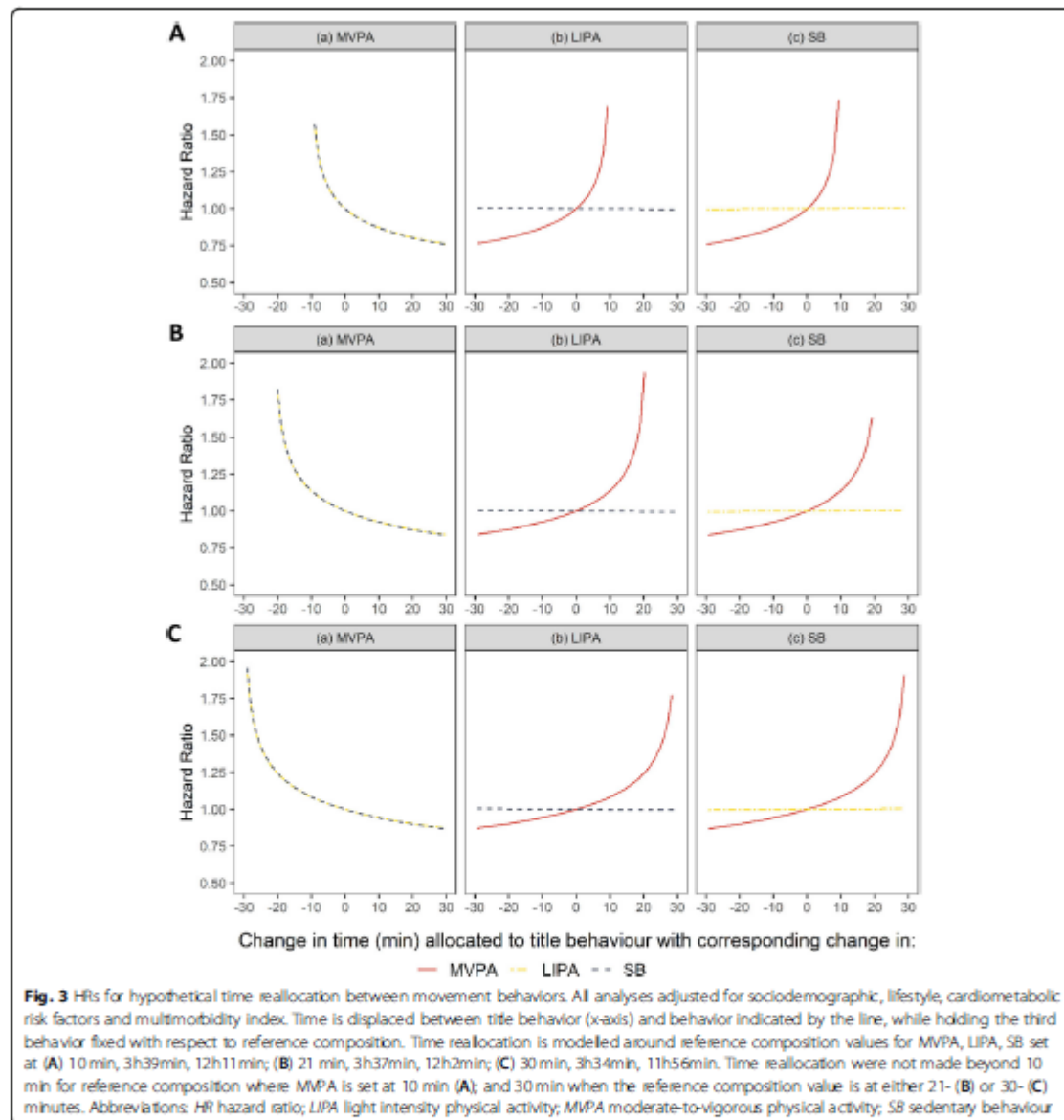
Discussion

In this longitudinal study of 3319 older adults, greater MVPA duration was associated with lower risk of CVD over a mean follow-up of 6 years irrespective of duration of SB and LIPA, independent of sociodemographic, lifestyle and cardiometabolic risk factors. There was no evidence of lower CVD risk when LIPA was increased at the expense of SB. We found that decrease in MVPA duration below the current recommendations accompanied by either an increase in SB or LIPA had an

adverse effect on CVD risk; the effect estimate was greater than the beneficial effect seen with increase in MVPA above current recommendations.

The present findings are consistent with previous prospective studies using self-reported [3] and objectively measured [11, 16–18] activity showing a curvilinear dose-response association between MVPA and CVD, with greatest benefit seen up to recommended MVPA duration. A meta-analysis of 33 prospective studies with mean follow-up of 12.8 years using self-reported physical activity found greatest CVD risk reduction moving from no physical activity to engaging in physical activity levels equivalent to the recommended 150 min of MVPA per week (11.25 metabolic equivalent of task (MET) h/week), with fewer benefits beyond this level [3]. One study based on 5585 middle to older aged participants followed for 5.7 years also reported a non-linear association between objectively-assessed MVPA and risk of incident CVD with the steepest decrease in risk observed among those undertaking 10 to 20 min/day of MVPA compared to none and a plateauing of the association at longer MVPA durations [16].

Our study adds to the current knowledge on the association between MVPA and CVD risk by highlighting the asymmetrical response to an increment or decrement in MVPA duration. Reduction in MVPA was



found to have larger detrimental effect on CVD risk than the gains obtained from an increase in MVPA duration by fall in SB or LIPA. Some studies using similar compositional approach have also reported asymmetric association in relation to mortality [41] and cardiometabolic biomarkers [21, 42–44]. This could be explained by the rapid pace of weight gain or deconditioning with reduction in MVPA against an equivalent amount of weight loss or conditioning which takes far greater exercise effort [21].

Findings on SB using self-reported data [7, 9, 45] show greater sedentariness to be associated with increase in CVD risk, although results using objective measurements are mixed [16–20]. A meta-analysis of 9 prospective cohort studies on 720,425 participants (mean age, 54.4 years) with median follow-up of 11 years found a nonlinear association between self-reported SB and CVD risk after adjustment for physical activity, with increased risk observed only at SB duration > 10 h/day [9]. Findings from the Objective Physical Activity and

Table 3 HRs and 95% CI for incident CVD associated with hypothetical reallocation of 10 min in daily movement behaviours impact of MVPA duration in the reference compositions (N = 3319)

Reference A: ^a less than recommended (MVPA = 10 min per day)			
	Add 10 min per day to:		
Remove 10 min per day from:	SB	LIPA	MVPA
SB	–	1.00 (0.98–1.02)	0.87 (0.78–0.98)*
LIPA	1.00 (0.98–1.02)	–	0.87 (0.77–0.99)*
MVPA	–	–	–
Reference B: ^a recommendation of 150 min per week (MVPA = 21 min per day)			
	Add 10 min per day to:		
Remove 10 min per day from:	SB	LIPA	MVPA
SB	–	1.00 (0.98–1.02)	0.92 (0.87–0.99)*
LIPA	1.00 (0.98–1.02)	–	0.93 (0.86–1.00)*
MVPA	1.14 (1.02–1.27)*	1.14 (1.01–1.28)*	–
Reference C: ^a recommendation of 30 min per day (MVPA = 30 min per day)			
	Add 10 min per day to:		
Remove 10 min per day from:	SB	LIPA	MVPA
SB	–	1.00 (0.98–1.02)	0.94 (0.90–0.99)*
LIPA	1.00 (0.98–1.02)	–	0.94 (0.89–1.00)
MVPA	1.09 (1.01–1.16)*	1.08 (1.00–1.17)*	–

Notes: Data represents HR (95% CI). * Indicates statistically significance at $p < 0.05$. All analyses adjusted for age, sex, ethnicity, marital status, education, occupational position, alcohol consumption, smoking, status, diet, body mass index, diabetes, hypertension, hyperlipidemia, and multimorbidity index
^a Reference compositions represent individuals undertaking 10-, 21-, or 30-min in MVPA per day and time in SB and LIPA are set proportional to population mean at 77 and 23%, respectively, of the remaining waking time as observed in the data. This corresponds to SB set at 12 h 11 min, 12 h 2 min, and 11 h 56 min, and LIPA at 3 h 39 min, 3 h 37 min, and 3 h 34 min, respectively for references A, B, and C
 - Data not observed as MVPA cannot be decreased by 10 min when the reference composition value of MVPA is at 10 min
 Abbreviations: CI confidence interval; CVD cardiovascular disease; HR hazard ratio; LIPA light intensity physical activity; MVPA moderate-to-vigorous physical activity; SB sedentary behaviour

Table 4 HRs and 95% CI for incident CVD associated with hypothetical reallocation of 10 min in daily movement behaviours: impact of SB and LIPA duration in the reference composition for a given MVPA duration of 10 min per day (N = 3319)

Reference 1: ^a SB (9 h per day) & LIPA (6 h 50 min per day)			
	Add 10 min per day to:		
Remove 10 min per day from:	SB	LIPA	MVPA
SB	–	1.00 (0.99–1.01)	0.87 (0.78–0.98)*
LIPA	1.00 (0.99–1.02)	–	0.87 (0.77–0.99)*
MVPA	–	–	–
Reference 2: ^a SB (14 h per day) & LIPA (1 h 50 min per day)			
	Add 10 min per day to:		
Remove 10 min per day from:	SB	LIPA	MVPA
SB	–	1.00 (0.97–1.03)	0.87 (0.78–0.98)*
LIPA	1.00 (0.97–1.03)	–	0.87 (0.76–1.00)
MVPA	–	–	–

Notes: Data represents HR (95% CI). * Indicates statistically significance at $p < 0.05$. All analyses adjusted for age, sex, ethnicity, marital status, education, occupational position, alcohol consumption, smoking, status, diet, body mass index, diabetes, hypertension, hyperlipidemia, and multimorbidity index
^a Reference compositions represent individuals with SB set at 9 h and 14 h corresponding to the 5th and 95th percentile, respectively as observed in the data. Time in LIPA is set at the remaining waking time after considering time in SB and MVPA
 - Data not observed as MVPA cannot be decreased by 10 min when the reference composition value of MVPA is at 10 min
 Abbreviations: CI confidence interval; CVD cardiovascular disease; HR hazard ratio; LIPA light intensity physical activity; MVPA moderate-to-vigorous physical activity; SB sedentary behaviour

Cardiovascular Health (OPACH) study on 5638 older women with mean follow-up of 4.9 years found a linear dose-response association between SB and CVD risk, after adjustment for MVPA [19]. However, three other studies did not find an association between objectively-assessed SB and incident CVD, two of these adjusted [16, 17] while another [18] did not for MVPA. Our results indicate that longer duration in SB increases risk of CVD when this is accompanied by reduction in MVPA. The magnitude of association was dependent on duration of MVPA rather than on SB unlike in a study using self-reported data [46] where replacing sitting with MVPA showed pronounced benefits for CVD mortality among those with > 6 h/day of sitting. Reasons for inconsistencies in findings across studies may relate to the nature of the measures (subjective and objective), difference in target population, and adjustment for other movement behaviours. Our study takes into account the relative co-dependency of movement behaviours within a day, unlike other studies where SB was controlled either for total wear time [18] or MVPA [19].

The association between objectively-assessed LIPA and incident CVD has been examined by a few studies but the results are inconsistent [11, 16–18, 20, 47–49]. In the OPACH study based on 5750 older women followed for 3.5 years, more LIPA was associated with decreased CVD risk independent of MVPA, although the association was attenuated upon adjustment for cardiovascular risk factors [11]. Two studies used data from the National Health and Nutrition Examination Survey (NHANES): one found increase in LIPA accompanied by an equivalent decrease in SB was associated with lower risk of CVD mortality [48], while the other did not find an association between LIPA and CVD mortality in analysis adjusted for SB and MVPA [49]. In another study on 5585 adults aged 40 to 79 years, the association between LIPA and incident CVD was attenuated after adjustment for MVPA, except higher risk of CVD when LIPA was < 3 h/day [16]. Some prospective studies found no evidence for LIPA lowering CVD risk [17, 18] as in our study. Our data show that when longer LIPA duration is coupled with shorter SB duration, increase in MVPA is beneficial either by reducing SB or LIPA. However, when LIPA duration is short and SB duration high, benefits for CVD risk are evident when MVPA is increased at the expense of SB rather than LIPA. This observation highlights the importance of considering the composition of movement behaviours rather than individual movement behaviours in isolation.

This paper adopts a behavioural approach wherein time in SB, LIPA and MVPA are at an individual's discretion leading us to conduct analyses based on waking period. Progression to older ages tends to be accompanied with increased sleep alteration, likely to be

influenced by underlying neurobiological processes [50] rather than individual choice. How circadian rhythm, a comprehensive marker of both sleep and physical activity features, is associated with risk of CVD requires further research.

The present study has several strengths including the use of objectively-assessed movement behaviours, a longitudinal design, the inclusion of men and women compared with previous prominent studies based only on one sex [17, 19], and the focus on older adults where the risk of CVD is high [51]. The innovation lies in use of methods that consider the finite time constraint and the daily composition of movement behaviours, an approach not used in previous studies on CVD risk. Our analyses were adjusted for a wide range of lifestyle and cardiovascular risk factors. A further advantage is ascertainment of cardiovascular risk factors and CVD events undertaken using multiple objective sources, including clinical examinations.

Our study has some limitations. A wrist accelerometer does not provide information on posture, not allowing differentiation between standing and sitting positions [52]. This could lead to some misclassification between SB and less intense LIPA, and discrepancies with estimates of sitting time reported by studies using thigh-worn accelerometers [52] but findings from wrist accelerometers are able to classify movement behaviours based on metabolic intensity with accuracy [40]. The Whitehall II study is an occupational cohort where study participants are healthier than the general population, although the association between cardiovascular risk factors and CVD risk has been shown to be similar to that in the general population [53]. The limited number of fatal CVD events ($n=10$) did not allow us to analyse those cases separately. Participants were included in the analysis if they had at least 2 weekdays and 2 weekend days of accelerometer recording (97.6% of the sample has 7 days of data), which might not be reflective of the long-term physical activity pattern over the follow-up period. Although, studies suggest 4 to 6 days of recording inclusive of weekend days as optimal to reliably capture weekly habitual physical activity [54, 55]. Furthermore, good test-retest reliability was for all movement behaviours. Finally, a gold standard cut-off to identify movement behaviours in older adults does not yet exist, this may lead to variability between studies. Sensitivity analysis in our study using a different cut-off did not affect findings.

This study highlights the importance of MVPA for CVD prevention among older adults, independent of duration of SB and LIPA. Among individuals who are highly sedentary, it might be better that increase in MVPA come with reduction in SB rather than LIPA. It is also important to identify those who reduce their

MVPA and encourage them to at least continue MVPA at their current durations. Overall our findings lend support to the current public health guidelines of 150min per week of MVPA [23].

Abbreviations

BMI: Body mass index; CHD: Coronary heart disease; CVD: Cardiovascular disease; HR: Hazard ratio; HES: Hospital episode statistics; IIR: Isometric log ratio; LDL: Low-density lipoproteins; LPA: Light intensity physical activity; MVPA: Moderate-to-vigorous physical activity; SB: Sedentary behaviour

Supplementary Information

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Additional file 1.

Additional file 2.

Additional file 3.

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Authors' contributions

SS and MSY conceived the objectives of the paper. MSY and DEM performed the statistical analyses. MSY and SS interpreted the data and wrote the paper. All authors commented on previous versions of the manuscript. SS designed the original study and obtained the funding. All authors read and approved the final manuscript.

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Availability of data and materials

Whitehall II data cannot be shared publicly because of constraints dictated by the study's ethics approval and IRB restrictions. The Whitehall II data are available for sharing within the scientific community. Researchers can apply for data access at <https://www.ucl.ac.uk/epidemiology-health-care/research/epidemiology-and-public-health/research/whitehall-ii/data-sharing>.

Declarations

Ethics approval and consent to participate

Ethics approval was obtained from the University College London ethics committee (reference number 85/0938), which was renewed for each contact. Each participant provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare they have no competing interests.

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Research Article

Objectively Measured Total Sedentary Time and Pattern of Sedentary Accumulation in Older Adults: Associations With Incident Cardiovascular Disease and All-Cause Mortality

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Abstract

Background: We examined associations of total duration and pattern of accumulation of objectively measured sedentary behavior (SB) with incident cardiovascular disease (CVD) and all-cause mortality among older adults.

Methods: Total sedentary time and 8 sedentary accumulation pattern metrics were extracted from accelerometer data of 3 991 Whitehall II study participants aged 60–83 years in 2012–2013. Incident CVD and all-cause mortality were ascertained up to March 2019.

Results: Two hundred and ninety-nine CVD cases and 260 deaths were recorded over a mean (standard deviation [SD]) follow-up of 6.2 (1.3) and 6.4 (0.8) years, respectively. Adjusting for sociodemographic and behavioral factors, 1-SD (100.2 minutes) increase in total sedentary time was associated with 20% higher CVD risk (hazard ratio [95% confidence interval]: 1.20 [1.05–1.37]). More fragmented SB was associated with reduced CVD risk (eg, 0.86 [0.76–0.97] for 1-SD [6.2] increase in breaks per sedentary hour). Associations were not evident once health-related factors and moderate-to-vigorous physical activity (MVPA) were considered. For all-cause mortality, associations with more fragmented SB (eg, 0.73 [0.59–0.91] for breaks per sedentary hour) were found only among the youngest older group (<74 years; *p* for interaction with age < .01) independently from all covariates.

Conclusions: In this study, no associations of total sedentary time and sedentary accumulation patterns with incident CVD and all-cause mortality were found in the total sample once MVPA was considered. Our findings of reduced mortality risk with less total and more fragmented SB independent from MVPA among individuals <74 years need to be replicated to support the recent recommendations to reduce and fragment SB.

Keywords: Accelerometer, Breaks in sedentary behavior, Moderate-to-vigorous physical activity, Prospective

Sedentary behavior (SB) such as sitting is increasingly recognized as a risk factor for all-cause mortality (1) and cardiovascular disease (CVD) (2,3), and the extent to which its impact depends on the level of moderate-to-vigorous physical activity (MVPA) is raising research interest (4). It is suggested that not just the total duration being sedentary but also the manner in which it accumulates throughout the day (eg, in few long bouts

or in several shorter bouts) might be important for health outcomes (5,6).

Experimental studies have reported that interrupting sedentary time with physical activity (PA) has acute benefits on controlling postprandial glucose and insulin levels (7,8). Such studies have shown that short PA breaks were slightly more effective for glycemic control than a continuous PA bout of a similar level of energy

expenditure (8). Breaks in prolonged sitting have been shown to improve a wide range of cardiovascular parameters, especially blood pressure and vascular function (9). Taken together, this has led to recent PA guideline to incorporate specific recommendation of limiting and frequently interrupting time in SB (10,11), although evidence for these recommendations remains limited (11,12). However, over the last century technological advances have been accompanied with a large increase in the prevalence of SB (13,14). Identifying specific SB features, such as total duration or bout length (5,15), detrimental for health is thus necessary to inform future tailored interventions to tackle the impact of SB on health. This is particularly important for older adults who spend almost 80% of their time being sedentary (16).

To date few prospective studies have investigated the pattern of sedentary accumulation, with inconsistent findings for both incident CVD (17,18) and all-cause mortality (19,20). Only 2 studies on CVD risk that were sex-specific focused exclusively on older adults (17,18). Additionally, barring a single study among older women (18), the rest emphasized on either sedentary breaks or length of sedentary bouts as accumulation pattern measures. However, concept such as breaks has been described as crude measure to quantify accrual patterns, limited by its dependence on accelerometer wear time and inability to provide precise information on nature of breaks in terms of length or intensity (7,15). Use of measures that capture distribution of sedentary bout length and are sensitive to changes in SB has recently been recommended (21,22).

This study aimed to assess the association of objectively measured total sedentary time and the pattern of its accumulation with incident CVD and all-cause mortality among older adults. We also examined whether or not the associations were independent of MVPA. In the absence of a gold standard measure of sedentary accumulation patterns throughout the day, we used a comprehensive approach by investigating the association using 8 measures of SB accumulation patterns.

Method

Study Population

The Whitehall II study is a prospective cohort established in 1985–1988 among 10 308 London-based civil servants (67% males) aged 35–55 years (23). Since the inception of the study, sociodemographic, behavioral, and health-related factors have been assessed using questionnaires and clinical examinations. Follow-up assessments have taken place approximately every 4–5 years, with the latest wave completed in 2015–2016. Participants provided written informed consent. Research ethics approval was obtained from the University College London ethics committee (reference number 85/0938), renewed at each contact.

Total Sedentary Time and Sedentary Accumulation Pattern

The accelerometer substudy was undertaken during the 2012–2013 wave of data collection for participants seen at the London clinic and for those living in the South-Eastern regions of England who underwent clinical examination at home. Participants were asked to wear a triaxial accelerometer (GENEActiv Original; Activinsights Ltd, Kimbolton, United Kingdom) on their nondominant wrist during 9 consecutive days over 24 hours. Data sampled at 85.7 Hz, with acceleration expressed relative to gravity ($1g = 9.81 \text{ m/s}^2$), were processed in R software using GGIR package (24) version 2.3-3

(<https://rdrr.io/cran/GGIR/>). Euclidean Norm of raw accelerations Minus One with negative numbers rounded to zero was calculated (25). Sleep periods were then detected using a validated algorithm guided by sleep log (26). Data from the first waking up (Day 2) to waking up on the day before the last day (Day 8) were used, corresponding to 7 full days. Waking period was defined as the period between waking and onset of sleep. Participants were included for analysis if they had daily wear time $\geq 2/3$ of waking hours, for at least 2 weekdays and 2 weekend days (27). Nonwear period among valid days was corrected based on a previously reported algorithm (25).

Wrist-worn accelerometers have been reported to accurately classify movement behaviors based on metabolic intensity (28). In absence of gold standard cut points to classify movement behaviors in older adults, we used cut points based on a study wherein adult participants undertook 10 activities in laboratory in order to mimic free-living posture/behaviors with the aim to elicit average accelerations that were similar to those observed in a free-living situation (29). These cut points were in agreement with a recent study among older adults which derived cut points using oxygen consumption when performing 9 laboratory-based activities of daily living and showed good classification accuracy (30). Based on these studies, movement behavior during waking period was classified as SB when average acceleration over a 60-second epoch was <40 milligravity (mg), 40–99 mg for light intensity physical activity (LIPA), and ≥ 100 mg for MVPA (29,31). Sedentary accumulation pattern was measured using 8 metrics: mean sedentary bout duration (5), time in prolonged sedentary bouts, Gini index (32,33), number of sedentary breaks (32,33), breaks per sedentary hour (34,35), Alpha (32), and transition probability from sedentary to LIPA or MVPA states (Figure 1; see Supplementary Methods for description) (33).

Metrics (total time and accumulation pattern) were calculated for each day and averaged over 7 days. For those with <7 valid days ($N = 95$ [2.4%] participants), a weighted average was computed using data on weekend and weekdays (27). Test–retest analysis conducted among 79 participants who wore the accelerometer for 7 days on average 26.5 (standard deviation [SD] = 4.6) days after the first measure suggests a good reliability of all the measures (correlations range: 0.62–0.82).

Ascertainment of CVD and All-Cause Mortality

CVD and mortality cases were ascertained by linkage to national registers up to the March 31, 2019 using the unique National Health Service identification number. CVD event was defined as occurrence of first fatal or nonfatal coronary heart disease (CHD), stroke, or heart failure. Nonfatal events were traced from the Hospital Episode Statistics (HES) database based on the International Classification of Diseases (ICD) codes for CHD (ICD-10 codes I20–25), stroke (ICD-10 codes I60–I64), and heart failure (ICD-10 code I50). CHD and stroke cases were also determined using Whitehall II study-specific 12-lead resting electrocardiogram recording and MONICA-Augsburg stroke questionnaire, respectively. Further details of validation of CVD cases are provided in a separate publication (36). CVD fatal events were drawn from the Office for National Statistics Mortality Register. *Death* from any cause was available from the UK Office for National Statistics Mortality Register.

Ascertainment of Covariates

Covariates were assessed using questionnaire or during the clinical examination at 2012–2013 wave, as well as data from electronic health records including HES and the Mental Health Services Data

Metric	Description	Interpretation of higher values
(1) Mean sedentary bout duration	Average length of a sedentary bout	Less fragmentation of sedentary time → <i>unfavorable</i>
(2) Time in prolonged sedentary bouts	Total duration of sedentary bouts lasting ≥30 minutes	Greater number and/or lengthier long sedentary bouts → <i>unfavorable</i>
(3) Gini index	Nonparametric summary of variability in length of sedentary bouts normalized by average duration	Range from 0 to 1; value towards 1 indicative that small proportion of longer sedentary bouts compose total sedentary time → <i>unfavorable</i>
(4) Number of sedentary breaks	Number of interruptions of sedentary bouts	More fragmented SB → <i>favorable</i>
(5) Breaks per sedentary hour	Number of sedentary breaks per hour of SB	Greater number of interruptions per hour of SB → <i>favorable</i>
(6) Alpha	Parametric summary of the distribution of length of sedentary bouts	Sedentary time composed of larger proportion of short length sedentary bouts → <i>favorable</i>
Transition probability from		
(7) sedentary to LIPA state	Probability of transitioning from sedentary to a physically active (either LIPA or	Range from 0 to 1; value towards 1 indicate frequent switching from sedentary to LIPA or
(8) sedentary to MVPA state	MVPA) state	MVPA state → <i>favorable</i>

Figure 1. Description of metrics of sedentary accumulation pattern. Notes: LIPA = light intensity physical activity; MVPA = moderate-to-vigorous physical activity; SB = sedentary behavior.

Set. Sociodemographic variables consisted of sex, ethnicity (White, non-White), marital status (married/cohabitating, divorced/widowed/single), education (<primary school, lower secondary, higher secondary school, university, higher degree; treated as continuous variable), last known occupational position (administrative, professional/executive, clerical/support). Behavioral factors included alcohol consumption (0, 1–14, >14 units per week), smoking status (current and recent ex-[less than 5 years] smokers, long-term ex-smokers, never smokers), fruits and vegetables consumption (<once daily, once daily, >once daily). Health-related factors consisted of prevalent diabetes (fasting glucose ≥ 7.0 mmol/L or self-reported doctor-diagnosed diabetes or use of diabetes medication or hospitalizations ascertained through record linkage to the HES [ICD-9 codes 250 or ICD-10 code E11]), body mass index (categorized as <24.9, 25–29.9, and ≥30 kg/m²), hypertension (systolic/diastolic blood pressure ≥ 140/90 mmHg or use of antihypertensive drugs), hyperlipidemia (low-density lipoproteins > 4.1 mmol/L or use of lipid-lowering drugs) assessed at the clinical examination, and morbidity index. For analysis on incident CVD, the morbidity index was calculated as the count of the following chronic conditions: cancer, arthritis, chronic obstructive pulmonary disease, depression, Parkinson disease, and dementia. For all-cause mortality the index additionally included CHD, stroke, and heart failure as chronic ailments.

Statistical Analysis

For analysis on incident CVD, participants were censored at date of CVD, non-CVD related death to account for competing risks, or March 31, 2019 (end of follow-up), whichever came first. For all-cause mortality, censoring date was either date of death or end of follow-up (March 31, 2019), whichever came first. Four models were constructed. First model was adjusted for sociodemographic variables and total day duration (between awaking and sleep onset). Then, additionally adjusted for behavioral factors, followed by further adjustment for health-related factors. The final model included MVPA recommendation (<150 vs ≥150 minutes per week).

Potential nonlinear associations of total sedentary time and sedentary accumulation pattern metrics at 2012–2013 wave with incident CVD and all-cause mortality risk were tested using likelihood ratio test comparing fully adjusted Cox regression models with only linear term against models with cubic spline terms (37). When associations were deemed linear, exposures were treated as continuous variables in analyses. For ease of interpretability and comparability, exposures were standardized (mean = 0, SD = 1) using mean and SD from the largest analytical sample, one with mortality as outcome. All analyses were conducted using Cox regression with age as timescale. Proportionality assumption was verified using Schoenfeld's test.

Owing to substantial correlations between total sedentary time and sedentary accumulation pattern metrics, they could not be mutually adjusted. Alternatively, we tested the interaction between total sedentary time (categorized using median split) and each sedentary accumulation pattern metric. We also tested interactions with age (continuous), sex, obesity (<30 and ≥30 kg/m²), and morbidity (0 and ≥1 prevalent chronic ailment). When interactions were found, analyses were repeated separately in each group (for age, groups were split as <74 and ≥74 years to allow enough cases in each group). All analyses were undertaken using Stata statistical software version 15 (StataCorp, College Station, TX) and R version 3.6.3 (<http://www.r-project.org>) with a 2-sided $p < .05$ considered statistically significant.

Sensitivity Analysis

Three sets of sensitivity analyses were conducted. First, to examine potential for reverse causation, main analysis was repeated by excluding CVD events and death occurring within first 2 years of follow-up for incident CVD and all-cause mortality outcomes, respectively. Second, the stratified analysis on age for all-cause mortality was repeated using an alternative age cut point based on median age split. Third, the main analyses were repeated by adjusting for MVPA as a continuous instead of as a dichotomous variable.

Table 1. Baseline Characteristics of Study Participants

Characteristics	Incident CVD (N = 3 321)			All-Cause Mortality (N = 3 991)		
	No	Yes	p Value	No	Yes	p Value
N (row %)	3 022 (91.0)	299 (9.0)		3 731 (93.5)	260 (6.5)	
Age (years), M (SD)	68.6 (5.5)	71.5 (5.9)	<.001	69.1 (6.0)	73.7 (5.4)	<.001
Women	830 (27.5)	55 (18.4)	.001	967 (25.9)	63 (24.2)	.55
Non-White	173 (5.7)	33 (11.0)	<.001	272 (7.3)	23 (8.9)	.35
Married/cohabitating	2 264 (74.9)	226 (75.6)	.80	2 802 (75.1)	179 (68.9)	.03
University or higher degree	995 (32.9)	76 (25.4)	.01	1 175 (31.5)	63 (24.2)	.01
Low occupational position	1 495 (49.5)	155 (51.8)	.42	1 885 (50.5)	146 (56.2)	.08
Recent-ex/current smokers	152 (5.0)	23 (7.7)	.05	205 (5.5)	16 (6.2)	.65
>14 units of alcohol per week	716 (23.7)	72 (24.1)	.88	875 (23.5)	50 (19.2)	.12
Daily intake of fruits and vegetable	2 424 (80.2)	227 (75.9)	.08	2 972 (79.7)	193 (74.2)	.04
BMI ≥ 30 kg/m ²	496 (16.4)	62 (20.7)	.06	678 (18.2)	45 (17.3)	.73
Hypertension [*]	1 347 (44.6)	183 (61.2)	<.001	1 899 (50.9)	167 (64.2)	<.001
Hyperlipidemia [†]	1 365 (45.2)	150 (50.2)	.10	1 885 (50.5)	136 (52.3)	.58
Diabetes	311 (10.3)	58 (19.4)	<.001	461 (12.4)	53 (20.4)	<.001
Morbidity index, [‡] M (SD)	0.33 (0.6)	0.36 (0.6)	.36	0.52 (0.7)	0.89 (1.0)	<.001
Following recommendations of 150 min/day of MVPA	2 592 (85.8)	216 (72.2)	<.001	3 116 (83.5)	154 (59.2)	<.001
Sedentary time variables, M (SD)						
Daily sedentary time, min/day	709.5 (98.2)	741.3 (110.0)	<.001	714.9 (99.1)	760.5 (105.6)	<.001
Mean sedentary bout duration	11.0 (5.2)	12.9 (9.5)	<.001	11.3 (5.8)	13.9 (8.8)	<.001
Time in prolonged (≥30 min) sedentary bouts, min/day	372.5 (138.1)	417.5 (162.4)	<.001	380.1 (140.5)	452.3 (164.0)	<.001
Gini index	0.67 (0.04)	0.68 (0.03)	.004	0.68 (0.04)	0.69 (0.04)	<.001
Number of sedentary breaks	71.7 (15.4)	68.8 (18.1)	.002	71.2 (15.7)	65.8 (18.4)	<.001
Breaks per sedentary hour	6.4 (1.9)	5.9 (2.1)	<.001	6.3 (1.9)	5.5 (2.0)	<.001
Alpha	1.76 (0.13)	1.73 (0.14)	<.001	1.76 (0.13)	1.71 (0.14)	<.001
Transition probability (%) from						
sedentary to LIPA state	9.9 (3.0)	8.8 (3.3)	.001	10.0 (3.0)	9.4 (3.3)	<.001
sedentary to MVPA state	0.55 (0.48)	0.32 (0.36)	<.001	0.57 (0.49)	0.43 (0.41)	<.001

Notes: BMI = body mass index; CVD = cardiovascular disease; LIPA = light intensity physical activity; M = mean; MVPA = moderate-to-vigorous physical activity; SD = standard deviation. Values are N (col %) unless otherwise stated.

^{*}Systolic/diastolic blood pressure ≥ 140/90 mmHg or use of antihypertensive drugs.

[†]Low-density lipoprotein ≥ 4.1 mmol/L or use of lipid-lowering drugs.

[‡]Number of chronic conditions among: cancer, arthritis, chronic obstructive pulmonary disease, depression, Parkinson disease, and dementia for incident CVD. Addition of coronary heart disease, stroke, and heart failure for all-cause mortality.

Results

Participant Characteristics

Among the 6 308 participants in the 2012–2013 wave, 4 880 were invited to participate in the accelerometer substudy, with 4 492 agreeing and 4 008 returning the devices successfully with valid data (Supplementary Figure 1). Excluding those with preexisting CVD (for incident CVD outcome) or missing covariates led to an analytical sample of 3 321 participants for analysis on incident CVD and 3 991 for all-cause mortality. Compared with participants invited to the accelerometer substudy ($n = 4 880$) and subsequently included ($n = 3 991$) in the analyses, participants not included ($n = 889$) were on average younger (excluded vs included participants: 68.9 vs 69.4 years, $p = .03$), more likely to be women (33.5% vs 25.8%, $p < .001$), non-White (10.5% vs 7.4%, $p < .01$), and had higher education level (36.6% vs 31.0%, $p < .01$) (Supplementary Table 1). During a mean follow-up of 6.2 ($SD = 1.3$) years, there were a total of 299 incident CVD events (CHD [62.9%], stroke [17.7%], and heart failure [19.4%]). A total of 260 all-cause deaths were recorded over a mean follow-up of 6.4 ($SD = 0.8$) years.

Participants with incident CVD events were more likely to be older, men, non-White, less educated, smokers, and have worse cardiometabolic profile compared to those who did not develop CVD over the follow-up (Table 1). Those who died were more likely to be

older, married/cohabitating, less educated, have poorer diet, worse cardiometabolic profile, and more comorbidities than surviving participants (Table 1). Participants with incident CVD or all-cause death were likely to spend more time in SB, accumulate sedentary time in longer bouts and with fewer interruptions, and were less likely to switch from sedentary to LIPA and MVPA states compared to those without the event of interest (Table 1). The correlations of total sedentary time with the 8 sedentary accumulation metrics ranged from 0.45 (Gini index) to 0.88 (time in prolonged [≥30 minutes] sedentary bouts) in absolute term (Supplementary Table 2). Time in MVPA was moderately correlated with most variables ($r = 0.27$ – 0.67 in absolute term).

There was no evidence of a nonlinear relationship of total sedentary time and sedentary accumulation metrics with incident CVD (p nonlinearity range: 0.06–0.72) and all-cause mortality (p nonlinearity range: 0.14–0.94), so all variables were examined as continuous variables in the models. All SB measures were standardized so that 1 SD represents 100.2 minutes for total sedentary time, 6.1 minutes for mean sedentary bout duration, 143.2 minutes for time in prolonged (≥30 minutes) sedentary bouts, 0.036 for Gini index, 16.0 for number of sedentary breaks, 6.2 for breaks per sedentary hour, 0.127 for Alpha, and 3.1% and 0.5% for transition probability from sedentary to LIPA and MVPA states, respectively.

Table 2. Associations of Total Sedentary Time and Sedentary Accumulation Patterns With Incident CVD (*N* total = 3 321, *N* events = 299, mean follow-up [*SD*] = 6.2 [1.3] years)

	HR (95% CI)			
	Adjusted for Sociodemographic Factors ^a	Additionally Adjusted for Behavioral Factors ^b	Additionally Adjusted for Health-Related Factors ^c	Additionally Adjusted for MVPA ^d
Total sedentary time	1.20 (1.06–1.37)	1.20 (1.05–1.37)	1.11 (0.97–1.27)	1.02 (0.88–1.19)
Sedentary accumulation pattern metrics^e				
(1) Mean sedentary bout duration	1.18 (1.08–1.30)	1.19 (1.08–1.30)	1.14 (1.03–1.26)	1.09 (0.98–1.23)
(2) Time in prolonged (≥30 min) sedentary bouts	1.18 (1.06–1.33)	1.19 (1.06–1.33)	1.11 (0.99–1.26)	1.05 (0.92–1.20)
(3) Gini index	1.06 (0.94–1.19)	1.07 (0.95–1.21)	1.03 (0.91–1.16)	0.99 (0.88–1.12)
(4) Number of sedentary breaks	0.87 (0.77–0.97)	0.86 (0.77–0.97)	0.91 (0.81–1.02)	0.94 (0.84–1.07)
(5) Breaks per sedentary hour	0.86 (0.76–0.97)	0.86 (0.76–0.97)	0.92 (0.81–1.04)	0.97 (0.85–1.10)
(6) Alpha	0.84 (0.75–0.95)	0.85 (0.75–0.95)	0.90 (0.79–1.01)	0.94 (0.82–1.07)
Transition probability from				
(7) sedentary to LIPA state	0.88 (0.78–0.99)	0.87 (0.78–0.99)	0.93 (0.82–1.05)	0.98 (0.86–1.11)
(8) sedentary to MVPA state	0.81 (0.70–0.94)	0.82 (0.70–0.95)	0.87 (0.75–1.01)	0.92 (0.79–1.08)

Notes: BMI = body mass index; CI = confidence interval; CVD = cardiovascular disease; HR = hazard ratio; LIPA = light intensity physical activity; MVPA = moderate-to-vigorous physical activity; *SD* = standard deviation.

^aModels adjusted for age (timescale), sex, ethnicity, education, occupation position, marital status, and total waking day duration.

^bModels additionally adjusted for smoking status, alcohol consumption, and fruits and vegetables consumption.

^cModels additionally adjusted for prevalent diabetes, BMI, hypertension, hyperlipidemia, and morbidity index.

^dModels additionally adjusted for MVPA recommendation.

^eMetrics are standardized based on sample mean and *SD* resulting in HRs corresponding to 1-*SD* higher value. For metrics 1–3, an increase of 1 *SD* corresponds to less favorable sedentary accumulation pattern. For metrics 4–8, an increase of 1 *SD* corresponds to more favorable sedentary accumulation pattern. 1 *SD* represents 100.2 minutes for total sedentary time, 6.1 minutes for mean sedentary bout duration, 143.2 minutes for time in prolonged (≥30 minutes) sedentary bouts, 0.036 for Gini index, 16.0 for number of sedentary breaks, 6.2 for breaks per sedentary hour, 0.127 for Alpha, and 3.1% and 0.5% for transition probability from sedentary to LIPA and MVPA states, respectively.

Association of Sedentary Time and Its Accumulation Pattern With Incident CVD

Table 2 shows the associations of total sedentary time and sedentary accumulation pattern metrics with incident CVD. In analysis adjusted for sociodemographic factors, 1-*SD* higher total sedentary time was associated with higher risk of incident CVD (hazard ratio [HR] 1.20, 95% confidence interval 1.06–1.37). All accumulation measures, except Gini index were significantly associated with CVD risk. A 1-*SD* increase in mean sedentary bout duration (HR 1.18, 1.08–1.30) and in prolonged sedentary bout duration (HR 1.18, 1.06–1.33) was associated with 18% increase in CVD risk while 1-*SD* increase in transition probability from sedentary to MVPA state (HR 0.81, 0.70–0.94) was associated with the largest decrease in CVD risk. No changes were observed in risk estimates when adjusting for behavioral factors. After additional adjustment for health-related factors, the association remained only for mean sedentary bout duration (HR 1.14, 1.03–1.26) and was no longer significant on further adjustment for MVPA (HR 1.09, 0.98–1.23). In models adjusted for MVPA but not health-related factors, associations were no more evident either, except for mean sedentary bout duration which had borderline significance (HR 1.12, 1.00–1.24, *p* = .045; Supplementary Table 3). As a comparison, the HR for meeting the MVPA recommendation of 150 minutes per week was 0.69 (0.52–0.92, *p* = .01) in a model adjusted for sociodemographic, behavioral, and health-related factors (Supplementary Table 4). Associations of sedentary accumulation metrics with CVD risk did not vary by total sedentary time (*p* interaction: .07–.57). There was no evidence that age, sex, obesity, or morbidity status modified the association of total sedentary time and metrics of sedentary accumulation pattern with incident CVD (all *p* interaction > .07).

Association of Sedentary Time and Its Accumulation Pattern With Mortality

The association of sedentary time and its accumulation pattern with all-cause mortality is shown in Table 3. In analysis adjusted for sociodemographic factors, a 1-*SD* increase in total sedentary time (HR 1.35, 1.17–1.56), mean sedentary bout duration (HR 1.10, 1.03–1.17), and prolonged sedentary bout duration (HR 1.27, 1.13–1.43) were associated with higher mortality risk. More fragmented SB pattern as shown by 1-*SD* increase in number of sedentary breaks (HR 0.83, 0.74–0.94), breaks per sedentary hour (HR 0.80, 0.70–0.91), Alpha (HR 0.81, 0.72–0.92), transition probability from sedentary to LIPA (HR 0.82, 0.72–0.93) and MVPA (HR 0.69, 0.57–0.84) states were associated with lower mortality risk. Additional adjustment for behavioral and health-related factors slightly attenuated the associations. On further adjustment for MVPA, none of the associations remained significant. Meeting the recommended MVPA duration was associated with a 41% reduction in mortality risk in the fully adjusted model (HR 0.59, 0.44–0.78; Supplementary Table 4). There was no evidence that the associations between sedentary accumulation metrics and mortality vary by sedentary time (*p* interaction: .42–.75).

For all-cause mortality, a consistent interaction was observed between age and SB measures (*p* interaction: .001–.009, except for transition probability from sedentary to MVPA state where *p* = .18). In fully adjusted analyses stratified by age (Figure 2), total sedentary time and most SB accumulation metrics were significantly associated with all-cause mortality among those aged <74 years (*N* = 3 001, *N* death = 114; Supplementary Table 5), whereas there was no association among the oldest group (age ≥ 74 years, *N* = 990, *N* death = 146; Supplementary Table 6). While causes of death did not differ in both age groups, SB measures were on average better among younger group (Supplementary Table 7).

Table 3. Associations of Total Sedentary Time and Sedentary Accumulation Patterns With All-Cause Mortality ($N_{\text{total}} = 3991$, $N_{\text{events}} = 260$, mean follow-up [SD] = 6.4 [0.8] years)

	HR (95% CI)			
	Adjusted for Sociodemographic Factors ^a	Additionally Adjusted for Behavioral Factors ^b	Additionally Adjusted for Health-Related Factors ^c	Additionally Adjusted for MVPA ^d
Total sedentary time	1.35 (1.17–1.56)	1.32 (1.15–1.53)	1.29 (1.11–1.49)	1.16 (0.98–1.38)
Sedentary accumulation pattern metrics^e				
(1) Mean sedentary bout duration	1.10 (1.03–1.17)	1.08 (1.01–1.15)	1.07 (1.00–1.15)	1.03 (0.95–1.11)
(2) Time in prolonged (≥ 30 min) sedentary bouts	1.27 (1.13–1.43)	1.25 (1.11–1.40)	1.22 (1.08–1.38)	1.12 (0.98–1.29)
(3) Gini index	1.13 (1.00–1.29)	1.13 (0.99–1.28)	1.11 (0.97–1.26)	1.06 (0.93–1.20)
(4) Number of sedentary breaks	0.83 (0.74–0.94)	0.85 (0.75–0.95)	0.86 (0.77–0.97)	0.92 (0.81–1.05)
(5) Breaks per sedentary hour	0.80 (0.70–0.91)	0.81 (0.72–0.93)	0.83 (0.73–0.95)	0.90 (0.78–1.04)
(6) Alpha	0.81 (0.72–0.92)	0.83 (0.73–0.94)	0.84 (0.75–0.96)	0.92 (0.80–1.05)
Transition probability from				
(7) sedentary to LIPA state	0.82 (0.72–0.93)	0.83 (0.73–0.95)	0.85 (0.75–0.97)	0.92 (0.80–1.06)
(8) sedentary to MVPA state	0.69 (0.57–0.84)	0.71 (0.58–0.86)	0.74 (0.61–0.90)	0.82 (0.67–1.01)

Notes: BMI = body mass index; CI = confidence interval; CVD = cardiovascular disease; HR = hazard ratio; LIPA = light intensity physical activity; MVPA = moderate-to-vigorous physical activity; SD = standard deviation.

^aModels adjusted for age (timescale), sex, ethnicity, education, occupation position, marital status, and total waking day duration.

^bModels additionally adjusted for smoking status, alcohol consumption, and fruits and vegetables consumption.

^cModels additionally adjusted for prevalent diabetes, BMI, hypertension, hyperlipidemia, and morbidity index.

^dModels additionally adjusted for MVPA recommendation.

^eMetrics are standardized based on sample mean and SD resulting in HRs corresponding to 1-SD higher value. For metrics 1–3, an increase of 1 SD corresponds to less favorable sedentary accumulation pattern. For metrics 4–8, an increase of 1 SD corresponds to more favorable sedentary accumulation pattern. 1 SD represents 100.2 minutes for total sedentary time, 6.1 minutes for mean sedentary bout duration, 143.2 minutes for time in prolonged (≥ 30 minutes) sedentary bouts, 0.036 for Gini index, 16.0 for number of sedentary breaks, 6.2 for breaks per sedentary hour, 0.127 for Alpha, and 3.1% and 0.5% for transition probability from sedentary to LIPA and MVPA states, respectively.

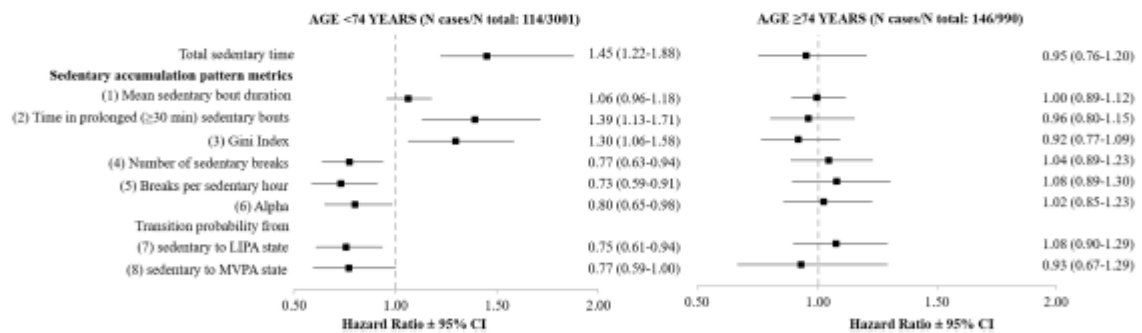


Figure 2. Associations of total sedentary time and sedentary accumulation patterns with all-cause mortality stratified by age. Notes: CI = confidence interval; LIPA = light intensity physical activity; MVPA = moderate-to-vigorous physical activity. Models adjusted for age (as timescale), sociodemographic, behavioral, health-related risk factors, and MVPA recommendation. Metrics are standardized based on sample mean and SD resulting in HRs corresponding to 1-SD higher value. For metrics 1–3, an increase of 1 SD corresponds to less favorable sedentary accumulation pattern. For metrics 4–8, an increase of 1 SD corresponds to more favorable sedentary accumulation pattern. 1 SD represents 100.2 minutes for total sedentary time, 6.1 minutes for mean sedentary bout duration, 143.2 minutes for time in prolonged (≥ 30 minutes) sedentary bouts, 0.036 for Gini index, 16.0 for number of sedentary breaks, 6.2 for breaks per sedentary hour, 0.127 for Alpha, and 3.1% and 0.5% for transition probability from sedentary to LIPA and MVPA states, respectively.

Sensitivity Analysis

Excluding 88 CVD events within the first 2 years of follow-up (Supplementary Table 8) completely attenuated associations, including in model adjusted only for sociodemographic factors except for mean sedentary bout duration. Removing 45 all-cause

mortality events within the first 2 years of follow-up either in the full population (Supplementary Table 9) or by age group (Supplementary Table 10) did not affect the findings. Using a median age split in analysis for all-cause mortality showed similar findings as in the main analyses with associations evident only in the youngest age group

(<68.4 years) (Supplementary Figure 2). Adjusting for MVPA as a continuous instead of dichotomous variable in the final adjustment model did not change the findings (Supplementary Tables 11 and 12).

Discussion

This prospective study based on objective measures of SB and PA in older adults with a mean follow-up of over 6 years presents 3 key findings. First, total sedentary time and all SB accumulation metrics, apart from the Gini index, were associated with incident CVD and death independently from sociodemographic and behavioral factors. Secondly, the observed association of total sedentary time and pattern of sedentary accumulation with incident CVD was explained by health-related factors and MVPA duration. Thirdly, among the youngest older adults, total sedentary time and most sedentary accumulation pattern measures remained associated with all-cause mortality even after accounting for health-related factors and MVPA, while no association was found irrespective of the metrics in the oldest old.

Studies based on self-reported measures (38,39) have found higher sedentary time to be associated with increased risk of CVD incidence, while conclusions are mixed for the limited number of studies using objective measures (17,18,40–42). A pooled analysis of 9 prospective studies, mean age of 54.4 years and median follow-up of 11 years, reported a nonlinear association of questionnaire assessed sedentary time with CVD incidence, with the increase in risk observed only at a duration greater than 10 hours/day, when adjusted for PA (38). In contrast using objectively assessed SB, the Objective Physical Activity and Cardiovascular Health (OPACH) study of older women found a linear dose–response relationship where each 1 additional hour of sedentary time was associated with 12% higher CVD risk (18) in model accounting for multiple risk factors and MVPA. In other studies the associations were attenuated on adjustment with higher intensity PA (17), health-related factors (41,42), or both (40), as also found in our study.

Till date 2 prospective studies have examined the association of sedentary accumulation pattern with incident CVD (17,18). A study based on older men did not find any association between sedentary breaks or bouts and CVD risk (17). In the OPACH study, longer mean sedentary bout duration, less breaks in sedentary time, and accumulating sedentary time in a prolonged manner were associated with higher CVD risk among older women (18). These associations persisted for mean sedentary bout duration and Alpha, on further adjustment for CVD risk factors and MVPA, albeit not mutually adjusted. In our study, adjustment for wide range of health-related factors including CVD risk markers attenuated the association apart for mean sedentary bout duration. This suggests a potential role of CVD risk markers in the association between SB metrics and CVD risk, which is in accordance with previous findings showing SB metrics associated with cardiometabolic risk factors in adults (43,44). In our case, this association was no more significant on either mutual or separate adjustment for MVPA. Findings might differ owing to metric utilized, adjustment level, and use of self-reported data for morbidity prevalence (18) unlike in our study which uses health-records linkage data.

A meta-analysis of 8 prospective studies found that longer accelerometer-assessed sedentary time was associated with increased all-cause mortality risk even after adjustment for MVPA (1). Only few observational studies have examined the associations between patterns of sedentary accumulation and all-cause mortality (19,20),

but findings reported were inconsistent. In the present study, associations of total sedentary time and most SB accumulation pattern metrics with all-cause mortality differed as a function of age and were evident only among the youngest older adults even when accounting for a large set of confounders including MVPA. This could explain differences in findings between previous studies where a study based on adults with mean age of 63.5 years found higher number of breaks to be associated with lower mortality risk (19), while another study among older men with mean age of 78.4 years did not report any association using same measure (20). Another study based on the sample used in the former study (mean age = 63.5) found replacing prolonged sedentary bouts with shorter sedentary bouts not to be associated with reduced mortality risk, although it was the case for replacement with LIPA or MVPA (45). This is in line with our finding that increase in switching from sedentary to either LIPA or MVPA states is associated with reducing mortality risk in youngest older adults.

A potential explanation of the differential associations observed by age group is the better overall level of SB measures seen in the younger compared to the oldest group. Another possible reason could be due to the change in functional capacity over the life course, also termed as “fitness gap” (46). Among the oldest old population, as the capacity itself is lacking we would not expect to see association of SB with all-cause mortality.

Our study has several strengths. It is longitudinal, based on both men and women as compared to the earlier notable studies based only on men (20) or women (18), with exclusive focus on older adults. We controlled analyses for a wide range of factors such as CVD biological risk factors and diabetes prevalence which were ascertained using multiple objective sources including clinical examinations rather than being self-reported. Additionally, in the absence of a gold standard measure of accumulation of sedentary time, we used a large and comprehensive range of metrics as exposures on the same outcomes.

The limitations should also be noted. First, the Whitehall II study is an occupational cohort wherein participants are healthier than the general population, but it has been shown previously that the associations between cardiovascular risk factors, including PA, and CVD risk are similar to that in the general population (47). Second, we adjusted for a broad range of confounders, but a possibility of an unmeasured factor to further explain the association still exists.

Conclusion

The 2018 United States of America Physical Activity guidelines and the 2020 World Health Organization guidelines on PA and SB concluded that there is insufficient evidence to indicate that sedentary breaks are important factors for incident CVD and all-cause mortality (11,12). In this study we examined associations of multiple sedentary accumulation pattern measures with both outcomes, given that different metrics might be indicative of distinct features of SB. Based on our findings, we reiterate the importance of MVPA for CVD prevention (42), as associations of total sedentary time and accumulation patterns with CVD risk were no more evident once MVPA was considered. In addition, there was evidence of higher all-cause mortality risk with increased total and less fragmented sedentary time independently from MVPA in the younger older adults. If these later findings are replicated in future studies, this would support the current Canadian recommendations (10) on limiting and interrupting long periods of sedentary time. Why such associations are not seen in the oldest group requires further investigation.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

None declared.

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Author Contributions

M.S.Y. and S.S. developed the research question and study design. M.S.Y. and V.T.v.H. performed the statistical analysis. M.S.Y. wrote the first and successive drafts of the manuscript. All authors conceived and designed the study, analyzed and interpreted the data, and drafted or critically revised the manuscript for important intellectual content, or, in addition, acquired data. M.S.Y. had full access to the data and took responsibility for the integrity of the data and the accuracy of the data analysis. M.S.Y. is the guarantor. The corresponding author attests that all listed authors meet authorship criteria.

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