Médecine d'urgence, nutrition et biomarqueurs du stress

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UFR DE MÉDECINE
ET DES PROFESSIONS PARAMÉDICALES
Université Clermont Auvergne

CLERMONT-FERRAND
CENTRE HOSPITALIER UNIVERSITAIRE

UNIVERSITÉ CLERMONT AUVERGNE

ÉCOLE DOCTORALE DES SCIENCES DE LA VIE, SANTÉ, AGRONOMIE, ENVIRONNEMENT

THÈSE D'UNIVERSITÉ

pour l'obtention du grade de DOCTEUR D'UNIVERSITÉ

par

Jean-Baptiste BOUILLON-MINOIS

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A mon jury, merci d'avoir fait le déplacement, certains de très loin, pour m'écouter ce jour. Je vous en suis éternellement reconnaissant.

A l'ensemble des soignants de l'urgence qui ont participé à ce protocole de recherche mais également à l'ensemble des soignants de l'urgence qui travaillent au quotidien pour le plus beau métier du monde.

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A ma famille et belle-famille pour m'avoir soutenu depuis tout ce temps

A mes amis, qu'ils soient Tuches, Colloc cantaloux ou gramégazé, merci point.

Et enfin à ma femme, Dr Globulologue professionnelle, sans qui je ne serai rien.

INTRODUCTION

« On ne peut pas être urgentiste toute sa vie. » Cette phrase, quiconque a un jour travaillé en service d'urgence ou s'est intéressé au métier d'urgentiste l'a entendue. L'a entendue de la part d'anciens urgentistes, d'urgentistes d'âge intermédiaire voire même de jeunes urgentistes, parfois encore internes. C'est d'ailleurs cette phrase dans un contexte particulier qui m'a fait douter pendant un certain temps de mon avenir hospitalo-universitaire. En effet, lors de mon stage en médecine d'urgence durant mon internat, j'étais un des seuls internes à participer activement au recrutement de participants pour un protocole de recherche sur le stress des soignants de l'urgence. Vous lirez toutes les facettes de ce protocole nommé SEEK, lors des 100 prochaines pages. Je ne m'étendrai donc pas ici dessus. Il me correspondait parfaitement puisque l'objectif principal était l'amélioration de la qualité de vie au travail des soignants de l'urgence. La partie qui me correspondait le plus était celle sur la nutrition. Je ne supporte pas de ne rien avoir à manger lorsque je suis fatigué. Or, c'est un des problèmes récurrents dans les hôpitaux. Cependant, le service était alors en plein doute entre des départs multiples annoncés de jeunes mais aussi et surtout d'anciens, de piliers du service. Je sortais au contraire de l'hôpital d'Aurillac où les praticiens étaient heureux de travailler, dans l'ensemble des spécialités. Le pôle Urgences y était plein. L'activité clinique de CH non universitaire correspondait totalement à mes attentes futures et je m'y voyais bien travailler. Oui mais « fuyez le naturel, il revient au galop ». A l'issue de mon internat, et après un an d'assistanat partagé entre Vichy et Clermont, j'ai décidé de me lancer dans l'aventure « HU ». J'avais derrière moi un mentor qui a révolutionné la médecine d'urgence auvergnate sur les 20 dernières années, le Professeur Jeannot Schmidt. Tout au long de mon cursus, depuis mes

premières années étudiantes où je suis venu le voir pour mettre en place l'AFGSU obligatoire pour tous les étudiants en médecine, jusqu'à ce jour, il a toujours su m'apporter son soutien et m'encourager à aller plus loin. Me voilà donc lancé à fond dans la carrière HU. J'ai donc logiquement recontacté l'investigateur principal du projet SEEK, devenu entre-temps Professeur en Santé au Travail, le Pr Frédéric Dutheil.

Le diagnostic et la prise en charge du stress au travail est une thématique clermontoise depuis de nombreuses années initiées par le Pr Alain Chamoux, membre actuel de l'académie de Médecine. Il a notamment œuvré pour la reconnaissance du burn-out comme maladie professionnelle. Le Pr Frédéric Dutheil, successeur du Pr Chamoux, a permis un essor de la recherche sur le stress, et en particulier le stress des soignants de l'urgence. En effet, son parcours personnel l'a amené à longtemps continuer les gardes aux urgences. Il a de plus réalisé la première étude JOBSTRESS évaluant l'impact du rythme de 24h de garde sur des biomarqueurs comme l'interleukine-8, les catécholamines ou encore la variabilité sinusale de la fréquence cardiaque. Il aime d'ailleurs dire que la médecine d'urgence représente le parfait laboratoire pour étudier les effets du stress et qu'aucun comité éthique n'accepterait jamais de reproduire en laboratoire ce que les soignants y subissent. Sa passion pour la recherche ainsi que sa capacité de travail en font de lui un des plus importants chercheurs de Clermont-Ferrand. C'est une chance inouïe que j'ai eue lorsqu'il a accepté de m'encadrer pour mon projet universitaire. Dès le début de mon clinicat, il a eu une vision plus large que le simple sujet de master 2 que je lui ai demandé. Plus large même que la vision que j'avais de valider mon master. Nous avons réouvert les archives de SEEK, un protocole auquel j'avais activement participé en tant qu'interne mais dont les données n'avaient jamais été analysées, mises au format adéquates pour réaliser des statistiques ou

encore être publiées. Le temps passé afin de monter directement une histoire pour déboucher sur un doctorat d'université me parut long mais a posteriori nécessaire et indispensable. Le plan de la thèse fut alors décidé. Nous avons également eu la chance de pouvoir compter sur le soutien du Laboratoire de Psychologie Sociale et Cognitive (LAPSCO) où le Pr Dutheil dirige une équipe de recherche intitulée « Stress Physiologique et Psychosocial, Bien-être ». Au sein du laboratoire et de l'équipe, nous avons pu compter sur l'expertise de plusieurs membres à la moindre occasion. De plus, nous avons également bénéficier du soutien préférentiel du département de biostatistique de la Direction de la Recherche Clinique et de l'Innovation (DRCI) du CHU de Clermont-Ferrand et notamment du Dr Bruno Pereira avec des rendez-vous quasi hebdomadaires et des réponses toujours pertinentes et aussi rapides que possible. Madame Sarah De Saint Vincent a su nous apporter une aide toujours précieuse et juste dans l'analyse et le dosage des biomarqueurs salivaires. Enfin, il apparaissait également essentiel d'avoir un regard extérieur sur le sujet. C'est pourquoi nous avons demandé au Professeure Marion Trousselard, experte de la prise en charge du stress au sein du service de santé des armées, de co-diriger cette thèse. Elle accepta rapidement, ce qui fut une joie et un honneur pour moi. Tous, nous partageons l'avis que la science, la recherche peut et doit prouver les difficultés avant de trouver et de prouver le bénéfice d'éventuelles solutions. Cela nous permettra d'être une base sur laquelle nous appuyer. Nous avons donc décidé de nous orienter sur l'impact des gardes de nuit et du stress sur la nutrition et les biomarqueurs des soignants de l'urgence. En effet, les services d'urgence sont ouverts 7 jours sur 7 et 24h sur 24. Le travail de nuit a de nombreuses conséquences sur la nutrition. De manière intéressante, ce sont quasiment les mêmes conséquences que le stress. Les

soignants de l'urgence devant travailler la nuit en milieu stressant, il apparaît intéressant et logique de l'étudier.

Ce travail de thèse rapporte le parcours du projet et est basé en cinq parties.

Premièrement le protocole SEEK mis au format publication

Deuxièmement l'évaluation du stress des participants en utilisant l'un des modèles les plus reconnus d'évaluation du stress, le modèle demande-contrôle-soutien de Karasek.

Troisièmement l'impact des gardes de nuit sur la nutrition des soignants de l'urgence.

Quatrièmement la réalisation de deux revues systématiques de la littérature et méta-analyses visant à démontrer que la ghréline et la leptine sont des biomarqueurs du stress.

Et enfin une étude holistique tenant compte de tous les facteurs confondants, sur l'impact des gardes de nuit, de la nutrition et du stress sur le taux de ghréline et de leptine.

REVUE DE LA LITTERATURE

1. La médecine d'urgence, une spécialité stressante avec des gardes de nuit

1.1. Historique

La médecine d'urgence française est une spécialité considérée comme « jeune » ayant évoluée rapidement, qui entre maintenant dans une phase de maturation avec la création en 2017 de la section du Conseil National des Universités et du Diplôme d'Études Spécialisées (1–3). L'accueil des patients dans les services d'urgence débute dans les années 40 où les hôpitaux doivent disposer d'un « poste de secours comportant un poste de pansements, un matériel pour soins urgents (réanimation, oxygène, réserve de sang), et quelques chambres individuelles » (4). En 1949, les services d'urgence deviennent indépendants avec un « fonctionnement rationnel conditionné par son autonomie vis-à-vis des autres services existants ». Les internes doivent y assurer une permanence médicale jour et nuit. Une période de transition s'installe alors où les médecins spécialistes d'organes se déplacent aux urgences au chevet du patient. Dans les années 70, le concept d'un service autonome s'impose, dirigé 24 h sur 24 par un chef de service unique, assisté d'une équipe médicale spécifique, affectée aux tâches d'accueil, d'examen, de diagnostic, de soins et du suivi des premières 24 heures des malades accueillis (5). Dans les années 90, la place des services d'urgences sera confortée en instaurant une présence médicale effective par des praticiens seniors (création massive de postes de praticiens hospitaliers urgentistes, et recrutement de personnels paramédicaux dédiés) et un transfert de tâches anciennement réservées aux chirurgiens vers les médecins urgentistes, notamment pour l'accueil initial de la traumatologie d'urgence (6). Dès lors, l'activité

des services d'urgence ne cessera de croître. Au début du 21e siècle, la filiarisation des urgences apparaît (7). Si les services d'urgence de proximité sont maintenus pour garantir une prise en charge homogène sur le territoire, des filières de soins (cardiologique, neurovasculaire, traumatisé sévère) s'organisent avec des équipes formées (8).

1.2 Panorama des services d'urgence

D'après la Fédération des observatoires régionaux des urgences (FEDORU), en 2019, 629 établissements de santé avaient une autorisation d'accueil des urgences pour un total de 697 structures d'urgences, dont 77% dans des structures publiques. Cette différence s'explique notamment lorsqu'un établissement possède une structure pédiatrique et une structure adulte. En 1996, l'ensemble des structures d'urgence a accueilli 10.1 millions de passages. Cette activité a augmenté régulièrement de 3.3% par an pour atteindre 21.2 millions en 2019 (Figure 1). Cependant, la répartition n'est pas homogène sur le territoire (Figure 2). En effet, 26% des structures accueillent plus de 40 000 passages par an (110 par jour) et prennent en charge 48% des passages. En 2020, à cause ou grâce au COVID-19, les entrées aux urgences ont diminué de 21.6% pour revenir quasiment au niveau d'avant COVID en 2021. Cette diminution a également été constatée au sein du service d'urgence adulte du Centre Hospitalier Universitaire de Clermont-Ferrand (9,10). Le rapport de la FEDORU, en partenariat avec la Société Française de Médecine d'Urgence (SFMU) et SAMU-Urgences de France (SUDF) dénombre 19 175 089 résumés de passage aux urgences en 2021. Ces derniers sont recueillis via les concentrateurs régionaux et analysés par les observatoires régionaux des urgences (ORU). Bien que les chiffres définitifs de 2021 ne soient pas encore disponibles, un rapport préliminaire confirme que la baisse de

5.7% par rapport à 2019 n'est due qu'au premier semestre (et donc aux conséquences du COVID). En effet, le second semestre s'oriente à la hausse en comparaison à l'année 2019. De manière très intéressante, et bien que ce ne soit pas son rôle, ce pré-rapport met en garde sur l'effet de l'épuisement des soignants de l'urgence – et plus généralement de l'ensemble des soignants – à cause de la pénibilité croissante et visible lors de la pandémie. Cet épuisement professionnel a de nombreuses conséquences organisationnelles évoquées dans ce rapport comme la fuite des professionnels vers d'autres activités (pas forcément en rapport avec le soin), ou vers une diminution du temps de travail. La médiatisation de l'épuisement professionnel entraine également un déficit de vocations. L'ensemble conduisant à des fermetures de lits d'aval, entravant encore plus le fonctionnement des urgences (11).

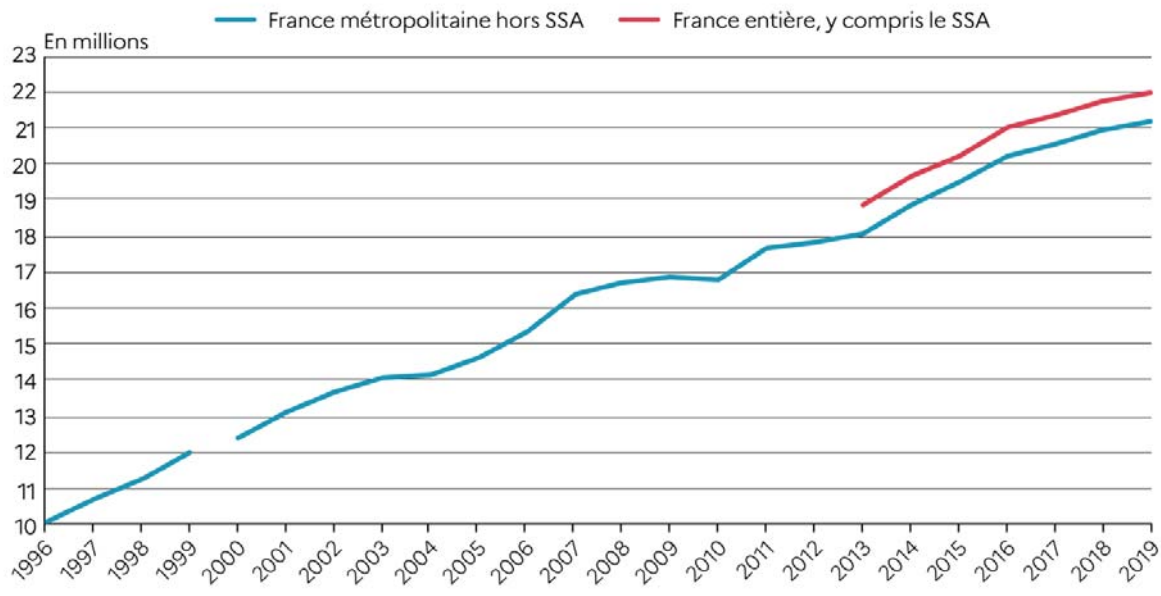

Figure 1. *Évolution du nombre de passages aux urgences en France entre 1996 et 2019. Source FEDORU. SSA=service de santé des armées*

Figure 2. *Carte de répartition des services d'accueil des urgences en France Métropolitaine en 2020 d'après la FEDORU*.

1.3. Une population à risque de stress

Les soignants sont une population particulièrement à risque en termes de risques psycho-sociaux. En effet, une revue systématique publiée dans le JAMA décrit une prévalence du burn-out de 44% chez les soignants, toutes spécialités confondues (12). Ces derniers sont également plus résilients (13). Parmi l'ensemble des spécialités, la

médecine d'urgence représente la spécialité avec la plus grande prévalence de burnout mais aussi le score de résilience le plus élevé en lien avec la prévalence du burn-out (12,13). Cela est assez compréhensible. En effet, leur travail est une interaction complexe entre le stress dû aux urgences vitales ; les plannings de travail complexes et inconstants ; l'enchaînement de travail de jour, de nuit et d'horaires décalés ; le surpeuplement du service des urgences ; le manque de sommeil ; la mauvaise alimentation ; et la fatigue accumulée (14,15). Pour aller au bout de la réflexion, les soignants sont considérés comme un groupe à haut risque de décès par suicide (16).

1.4. Travail posté, nutrition, et métabolisme

Les soignants de l'urgence sont des travailleurs postés avec un temps de travail défini à l'avance et des irrégularités de planning de travail. Ils travaillent le jour, la nuit, les jours fériés, les week-ends et avec des horaires changeant et décalés. Or, le travail posté est pourvoyeur d'une diminution de la qualité de vie (17) et un facteur de risque de dépression, d'anxiété, de troubles du sommeil et de maladies cardio-métaboliques (hypertension artérielle, dyslipidémie, obésité, coronaropathie, fibrillation auriculaire, et diabète notamment) (18–23). De plus ces travailleurs ont plus fréquemment une mauvaise hygiène de vie, accentuant encore plus les répercussions sur la santé (20). Les habitudes d'alimentation sont également différentes chez les travailleurs postés et en garde de nuit. Ils consomment plus de collations, de café, de confiseries et mangent plus fréquemment pendant la nuit, avec des conséquences sur la régulation circadienne. Cette dérégulation est principalement impactée par la sécrétion inappropriée d'insuline, de ghréline et de leptine, conduisant au diabète et au surpoids (24). Pour autant, il n'existe aucune étude sur les conséquences en termes d'apport

alimentaires du travail posté pour les soignants de l'urgence, d'autant plus intéressant compte tenu des spécificités majeures du métier.

1.5 Les principaux facteurs de risque psychosociaux des soignants de l'urgence

Parmi les soignants de l'urgence, on peut distinguer le corps médical du corps paramédical. En effet, les infirmières ont des exigences cognitives et sensorielles élevées, mais également un grand nombre de tâches sans grande signification, un faible degré de liberté au travail, un manque d'autonomie, moins de soutien social et un manque de rétroaction au travail (25,26). Bien que le concept de décision médicale partagée existe depuis des décennies, il est peu utilisé dans la pratique quotidienne entre infirmières et médecins, et surtout en médecine d'urgence (27). En effet, la prise en charge des patients aux urgences nécessite une prise de décision rapide et pluriquotidienne, avec un enjeu vital pour les patients ; et ce, dans un contexte de stress renforcé par le recours de plus en plus fréquent à la justice dans les cas d'erreur médicale (28). Le médecin, par rapport aux autres soignants, conserve le rôle central de décideur, ce qui pourrait expliquer en partie un sentiment de latitude décisionnelle par rapport aux autres soignants de l'urgence. Il a d'ailleurs été montré que les médecins ont une meilleure qualité de vie et une diminution du burn-out lorsqu'ils sont impliqués dans les décisions de service, de management et d'organisation (29). De plus, les infirmières partagent la conviction que le médecin doit décider et que le patient doit se fier à ses connaissances plutôt qu'aux siennes (30). Ceci sera surement – il faut en tout cas l'espérer – remis en question avec le développement des professions intermédiaires tel que les infirmiers de pratique avancées mention urgences dont les premières promotions arrivent en 2022 (31). Enfin, certaines études ont trouvé un lien

direct entre l'épuisement professionnel des médecins (dont la fatigue professionnelle est l'un des principaux facteurs de risque) et les évènements indésirables pour les patients (32). En revanche, les soignants de l'urgence pourraient bénéficier d'un niveau de soutien social plus élevé que les autres soignants. En effet, les travailleurs en santé et en particulier les médecins ont une longue histoire de soutien entre eux, parfois considérée comme une confrérie ou une fraternité (33,34). Le soutien social peut avoir un impact important sur les soins, car il lie en partie la relation entre l'épuisement professionnel des médecins et le professionnalisme basé sur le comportement (35). De plus, il agit comme facteur d'amélioration de la qualité de vie et de diminution de l'épuisement professionnel (36,37).

2. L'évaluation du stress

2.1 Le Questionnaire de Karasek

L'évaluation du stress de manière fiable et reproductible reste un challenge important. Dans le cadre du stress au travail, le gold-standard est l'utilisation d'un questionnaire autodéclaré. Parmi eux, le modèle job-demand, job-control, social support (JDCS) de Karasek est largement utilisé pour évaluer les facteurs psychosociaux au travail (38,39). Ce modèle a été créé dans les années 70 et publié en 1979 par Robert Karasek, Professeur de psychosociologie au département Travail et Environnement, Université Lowell, Boston, MS. Le corolaire initial de son travail est l'impact du stress sur la mortalité cardiovasculaire (39). Pour réaliser son travail, il a combiné deux bases de données – une Américaine et une Suédoise. Si la base de données Américaine contenait plus de données sur la précision du travail des répondants, la base de

données Suédoise a permis un suivi longitudinal puisque sur les 1915 répondants en 1968, 1635 ont accepté de participer au suivi longitudinal en 1974 (38).

2.2 La demande psychologique

Deux dimensions sont alors définies. Premièrement, la demande psychologique, job-demand dans l'article original. Karasek justifie la construction de l'échelle de demande psychologique comme la nécessité de mesurer les facteurs de stress psychologiques impliqués dans l'accomplissement de la charge de travail, les facteurs de stress liés à des tâches imprévues, et les facteurs de stress liés aux conflits personnels liés au travail – sans tentative de mesurer l'impact du travail physique. De manière très intéressante, il décrit les exigences liées à l'accomplissement de la tâche comme les principales sources de stress au travail. A l'issue de ses recherches, il conclue à sept items formant une échelle acceptable avec un Cronbach $\alpha = 0,64$ (40), pour construire un indice final d'exigences psychologiques du travail. Ces items permettent de discriminer les professions que l'on considérerait normalement comme psychologiquement exigeantes en utilisant la base de données Américaine. Il a, par la suite, validé ses questions sur la base de données Suédoise, à l'aide d'une Échelle de Guttman (41) – coefficient de reproductibilité 0,94 et coefficient d'évolutivité 0,78. Bien que les pressions liées aux tâches soient probablement les principales sources des exigences professionnelles mesurées ici, l'indicateur ne permet pas de détailler les causes des demandes psychologiques. Karasek confirme la validité de contenu de son indicateur par sa corrélation avec des facteurs de stress professionnels connus (travail à la chaine, absence de de pauses et anticipation de perte d'emploi). La demande psychologique n'est pas corrélée aux facteurs de stress d'autres sphères de la vie privée, comme les problèmes familiaux ou de garde d'enfants en bas âge.

2.3 La latitude décisionnelle

La deuxième dimension définie par Karasek est la latitude décisionnelle, job-control dans la publication initiale, définie comme le contrôle du travailleur sur ses tâches et son organisation au cours de la journée de travail. Afin de sélectionner les meilleurs items, Karasek a réuni deux mesures, présente dans les deux bases de données, « autorité décisionnelle » et « discrétion intellectuelle », en raison de leur similitude avec d'autres mesures de la littérature (42,43) et leur importance dans les stratégies de conception des emplois et des organisations. Elles semblent corrélées aux deux composantes du score de potentiel de motivation de Hackman et Oldham (44) et de Turner et Lawrence (45). De plus, un travail hautement qualifié avec peu de pouvoir décisionnel est une combinaison rare dans la pratique. Par conséquent, lors de l'analyse des données américaines, Karasek a additionné quatre mesures de l'autorité décisionnelle (base Américaine) et quatre mesures de la discrétion intellectuelle (base Suédoise) dans une échelle agrégée pour obtenir un Cronbach α de 0,82. L'indicateur suédois de discrétion intellectuelle a été construit à partir d'une mesure du niveau de compétence requis pour le travail et l'évaluation du travail comme répétitif. Un travail répétitif perd sa capacité de défi intellectuel après une répétition constante (43,46). Un travail répétitif et peu qualifié est l'échelon le plus bas de la mesure de la discrétion intellectuelle. Enfin, Karasek insiste sur la possibilité que la personnalité d'un travailleur affecte sa perception de la latitude décisionnelle (47). Grace à la base de données suédoise, qui fournit à la fois des auto-évaluations et des évaluations d'experts de la "discrétion intellectuelle", il conclue que ces deux mesures sont fortement corrélées en accord avec la littérature (44,46) et suggère que les auto-évaluations sont une mesure raisonnablement précise de la latitude de décision professionnelle (39).

2.4 Job-strain

Les deux dimensions initialement définies par Karasek forme son premier modèle job-demand-control (JDC), qu'il décompose en quatre quadrants (Figure 3). La combinaison d'une faible latitude décisionnelle et d'une faible demande psychologique défini un travail passif, une forte latitude décisionnelle et une faible demande psychologique un travail détendu, une forte latitude décisionnelle et une forte demande psychologique un travail actif et enfin, une faible latitude décisionnelle et une forte demande psychologique un travail tendu (« jobstrain ») (38). Si chaque situation a ses inconvénients et ses conséquences potentielles, c'est la dernière qui est le plus à risque dans le cadre des risques psychosociaux liés au travail. Les travailleurs dans la configuration appelée « jobstrain » sont particulièrement à risque de faible bien-être (48), d'épuisement professionnel et burnout (49) et de mauvaise santé (50). On observe également une augmentation des maladies cardiovasculaires (51,52). De plus, le modèle de stress au travail de Karasek est un facteur prédictif indépendant des événements coronariens aigus (53).

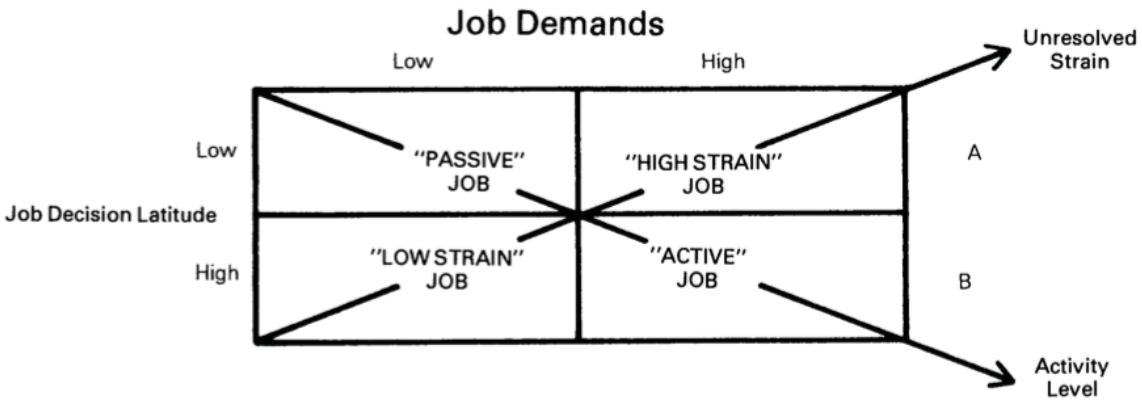

Figure 3. *Caractérisation du jobstrain à l'aide du modèle de demande psychologie et de latitude décisionnelle de Karasek.*

2.5 Le support social

En 1994, Karasek s'associe à Töres Theorell pour compléter son modèle et son questionnaire en ajoutant la dimension du soutien social (54). Il crée alors le modèle job-demand-control-support (JDCS). En effet, le soutien des collègues et/ou de la hiérarchie agit comme un tampon dans les situations de « jobstrain ». A contrario, en cas d'association de « jobstrain » avec un faible soutien social, on obtient une situation d' « isostrain » – donc association d'une forte demande psychologique, d'une faible latitude décisionnelle et d'un faible soutien social (55). L'« isostrain » est associé à de multiples pathologies, y compris une plus grande mortalité (56,57).

2.6 Les différents questionnaires de Karasek

De nombreuses versions du questionnaire existent depuis sa création. Initialement rédigée en anglais, il est aujourd'hui disponible et validé dans plus de 20 langues (58–69). De plus, si la version complète contient 112 items (questions), la version de référence, qui est maintenant la plus utilisée, est composée de 26 items, évaluant les trois dimensions du modèle de Karasek : la demande psychologique (Q10 + Q11 + Q12 + (5-Q13) + Q14 + Q15 + Q16 + Q17 + Q18), la latitude décisionnelle (4*Q4 + 4*(5-Q6) + 4* Q8 + 2*(5-Q2) + 2*Q5 + 2*Q7 +2*Q1 + 2*Q3 + 2*Q9), et le soutien social (Q19 + Q20 + Q21 + Q22 + Q23 + Q24 + Q25 + Q26). Chaque item est évalué sur une échelle de Likert avec 4 possibilités en fonction de la fréquence des situations vécues : de 1 (fortement en désaccord) à 4 (tout à fait d'accord). Une forte demande psychologique se définit par une demande psychologique supérieure à 21, une faible latitude décisionnelle est définie comme un score inférieur à 70, et une faible soutien social par un score inférieur à 24 (38). En France, l'étude SUMER a permis la passation du modèle de stress au travail de Karasek version 26 items chez 25 000 travailleurs.

Les niveaux de charge de travailleur et d'autonomie des principales professions ont pu être représentés (70,71). Il semble qu'aucun facteur sociodémographique (sexe, âge, indice de masse corporelle, état matrimonial, activité physique) ne soit un facteur de protection contre la fatigue professionnelle (71). Cependant, en cas d'association avec la "souche familiale" - stress lié à la famille et conflit familial - les femmes ont plus de dépression que les hommes (72). Cependant, aucune donnée concernant les scores des travailleurs de la santé d'urgence au questionnaire de Karasek n'était disponible, même si l'exposition à l'épuisement professionnel est un problème bien connu chez les travailleurs de la santé (73,74). Le questionnaire de Karasek est censé évaluer une perception stable à long terme du travail, malgré l'absence d'étude comparant les scores de Karasek dans différentes conditions chez le même participant. Il est également essentiel d'explorer les facteurs de protection qui pourraient aider à atténuer le stress perçu et qui sont relativement faciles à intégrer dans les organisations médicales ou le mode de vie quotidien (75).

2.7 Les limites du questionnaire de Karasek

Néanmoins, le questionnaire de Karasek n'est pas parfait. Premièrement, sa durée de rédaction est d'environ 15 minutes, ce qui l'empêche d'être réalisé en pratique courante (76). Une des pistes pourrait être la réalisation d'échelles visuelles analogiques. Notre équipe a validé des échelles visuelles analogiques (EVA) de demande psychologique (charge de travail) et de latitude décisionnelle (autonomie dans le travail) en comparaison au questionnaire de Karasek (76). Les résultats montrent une absence de différence entre les groupes (Tableau 1). Les coefficients de corrélation sont fiables avec 0.59 entre l'EVA demande psychologique (0 à 100) et la demande psychologique selon Karasek et 0.57 entre l'EVA latitude décisionnelle (0 à

100) et la latitude décisionnelle. Le coefficient de Cronbach α est à 0.68. Enfin le coefficient de concordance de Lin (77) dans le cadre d'un test re-test est de 0.73 (95CI 0.64 à 0.81) pour la demande psychologique mesurée en EVA vs le questionnaire de Karasek, et 0.71 (95CI 0.63 à 0.80) pour la latitude décisionnelle en EVA vs Karasek (Figure 4).

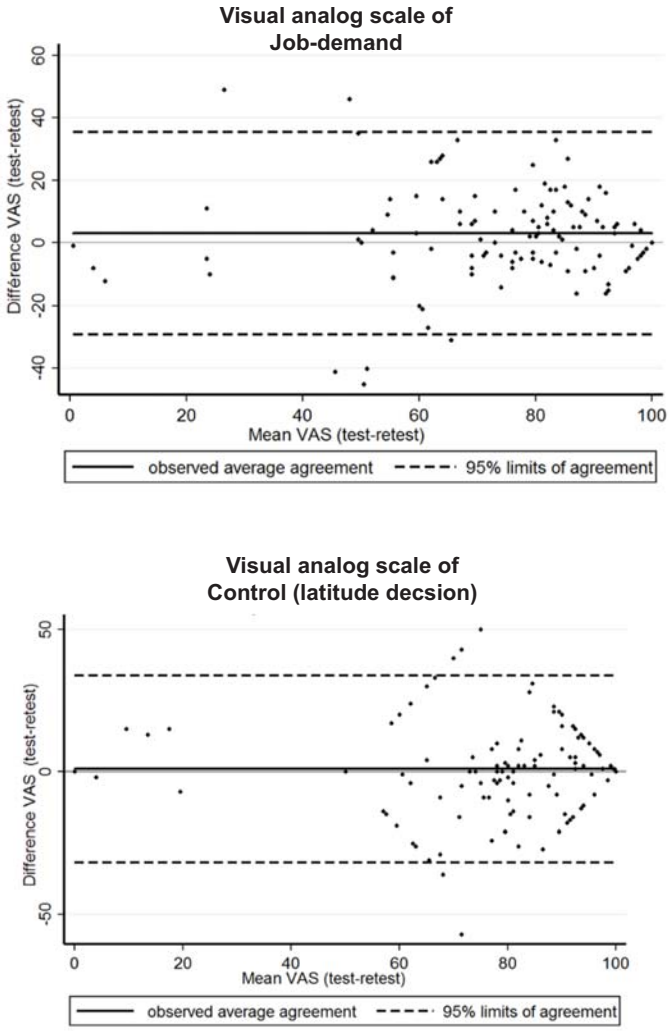

Figure 4. *Représentation visuelle de Bland et Altman sur la corrélation entre le score de Karasek évalué avec le questionnaire à 26 items et avec des échelles visuelles analogiques.*

Variables	Sample size n=190 (%)	Mean±SD
VAS		
VAS job-demand		**75.2±20.6**
VAS job-demand <75	83 (43.7)	53.8±19.2
VAS job-demand ≥75	107 (56.3)	88.3±8.3
VAS latitude decision		**81.9±21.9**
VAS latitude decision <75	52 (2.4)	52.3±22.2
VAS latitude decision ≥75	138 (72.6)	91.1±8.6
Modèle de Karasek		
Dimensions		
Job-demand		**22.0±5.0**
Job-demand <21	61 (32.1)	16.0±3.0
Job-demand ≥21	129 (67.9)	25.0±4.0
Latitude decision		**76.7.±8.5**
Latitude decision <70	48 (25.3)	61.9±5.6
Latitude decision ≥70	142 (74.7)	83.8±35.0
Quadrants		
Active	101 (53.2)	
Passive	20 (10.5)	
Tense/job strain	28 (14.7)	
Relaxed	41 (21.6)	

***Tableau 1**. Résultats de l'évaluation du score de Karasek en utilisant le questionnaire à 26 items et en utilisant des échelles visuelles analogiques. Les résultats sont exprimés en moyenne ± déviation standard ou nombre (pourcentage).*

Deuxièmement, il est susceptible de présenter un effet de halo, c'est-à-dire un biais cognitif affectant la perception des répondants. Ceux-ci perçoivent d'entrée de jeu où mènent les questions, et quelles réponses y apporter pour augmenter ou diminuer leur score de latitude décisionnelle, de soutien social, ou encore de demande psychologique. Ainsi ils ne sont plus « libres » dans leurs réponses. Et ce d'autant que

ce questionnaire est si utilisé qu'il est tout à fait envisageable que des salariés l'aient déjà passé, et connaissent malgré eux les questions qui vont suivre. Cet effet de halo peut donc entraîner un biais de classement dans les 4 cadrans. Qui plus est, dans le modèle de Karasek, cet effet de halo est d'autant plus plausible que les items des différentes échelles sont répartis dans l'ordre par dimension mesurée (78). Une autre limite possible est la contagion du stress. En effet, le stress, comme toutes les autres émotions, est contagieux (79). Cette contagion peut se faire entre soignants, mais aussi entre patients et soignants (80).

2.8 Médecine d'urgence et questionnaire de Karasek

Malgré que les professionnels de l'urgence soient une population à haut risque de stress, et malgré le fait que le questionnaire de Karasek soit l'un des gold standard pour évaluer le stress, il n'existait pas au moment de l'étude d'évaluation du stress selon le modèle de Karasek chez les soignants de l'urgence.

3. Impact des gardes de nuit et du stress sur la nutrition

3.1 Synergie entre le travail de nuit et le stress

Selon l'Organisation internationale du travail, le travail de nuit est défini comme "tout travail effectué pendant une période d'au moins sept heures consécutives, comprenant l'intervalle de minuit à 5 heures du matin" (81). En 2020 en Europe, 22 % des hommes et 11 % des femmes travaillaient en horaires postés incluant du travail de nuit (82). Parmi eux, une large proportion de soignants travaille en horaires décalés ou fixes de nuit. Le travail de nuit a de nombreuses conséquences sur la santé avec notamment la perturbation du rythme circadien (83), l'obésité, les maladies cardiovasculaires et

métaboliques (84–88). Fait intéressant, les troubles alimentaires sont également associés à ces pathologies, renforçant potentiellement l'effet synergique entre le travail de nuit et les troubles alimentaires (89).

3.2 Impact du travail de nuit sur la nutrition

De plus, les travailleurs de nuit ont tendance à avoir des habitudes alimentaires plus irrégulières que leurs collègues de jour (90). Cependant, la littérature sur la quantité de nourriture ingérée par les travailleurs de nuit par rapport à ceux de jour n'est pas unanime. En effet, une étude a révélé une consommation alimentaire plus élevée chez les travailleurs de nuit par rapport aux travailleurs de jour (91), tandis que d'autres n'ont pas trouvé de différence significative (92,93). Enfin, certains auteurs ont trouvé un apport énergétique plus faible chez les travailleurs de nuit par rapport aux travailleurs de jour – la diminution semblant être compensée le lendemain (93). Le travail de nuit induit également un conflit entre les horaires de repas diurnes socialement déterminés, les habitudes alimentaires, le rythme biologique de la faim, la satiété et le métabolisme (94,95). Certains résultats ont montré que l'heure et le volume des repas impactent les performances cognitives et la somnolence chez les travailleurs de nuit (96). Eviter les gros repas en début de poste de nuit et opter pour une petite collation pourraient améliorer les performances nocturnes (97). Les soignants travaillant de nuit consomment moins de glucides et de lipides pendant les gardes de nuit que leurs collègues de jour (92,98). De plus, il semble que les principaux apports glucidiques pendant les gardes de nuit comprennent la consommation excessive de sucreries et de boissons sucrées (99–101). Le manque de temps pour manger entraîne une augmentation de la consommation d'aliments froids et de restauration rapide, facteur de risque d'obésité et de maladie cardiovasculaires (100–

104). De plus, il semble que le café/thé et les boissons sucrées soient les boissons majoritairement consommées pendant le travail de nuit et à des doses supérieures à leurs collègues de jour (91,92,105). Enfin, le comportement alimentaire peut être influencé par des critères sociodémographiques tels que l'âge et le sexe, et par des caractéristiques professionnelles telles que l'expérience et la charge de travail (106–108). Il semble que les travailleurs expérimentés et ceux aux horaires décalés, mangent davantage la nuit, mais principalement des collations riches en sucres, en gras et en énergie (109,110). Le travail de nuit induit une augmentation de la consommation d'aliments sucrés et gras, possiblement en réponse au stress chez les mangeurs émotionnels, qui sont le plus souvent des femmes (111,112). Selon la littérature, les travailleurs de nuit des grands centres hospitaliers ont tendance à consommer davantage de restauration rapide car plus facilement accessible et plus pratique à manger (92). Bien que les infirmières aient été largement étudiées, aucune conclusion ne peut être tirée et les preuves épidémiologiques existantes sur la relation entre le travail de nuit des infirmières et leurs habitudes alimentaires sont insuffisantes pour tirer des conclusions définitives (24). En effet, le sujet a souvent exploré les infirmières ou encore plus souvent les industries en Asie avec une population ayant une dépense énergétique très élevée et un niveau socio-économique très bas. La plupart de ces études ont un faible niveau de preuve (échantillons non représentatifs, revues de littérature non systématiques) et sont difficilement transposables dans notre population du fait d'habitudes alimentaires très différentes et d'un niveau de vie élevé (24). Une autre variable potentielle pourrait être le sommeil dont nous n'avons pas étudié l'impact. En effet, la littérature antérieure suggère que les travailleurs de nuit obtiennent moins de sommeil que les travailleurs de jour. Ainsi, si les travailleurs de nuit ont une durée d'éveil plus longue, ils seront plus affamés, et donc plus ingérés

(113). Toutefois, aucune étude n'a jamais été réalisée sur l'impact du travail de nuit sur les apports alimentaires des soignants de l'urgence, ce qui est particulièrement intéressant compte tenu de leurs spécificités.

3.3 Impact du stress sur l'alimentation

L'impact du stress sur l'alimentation est controversé. En effet, alors que le stress aigu est capable d'induire une restriction alimentaire, le stress chronique induira un signal de prise alimentaire offrant ainsi une meilleure réponse aux événements stressants futurs (114). De nombreuses voies physiopathologiques ont été étudiées, notamment l'impact de la ghréline et de la leptine comme biomarqueurs du stress aigu. Deuxièmement, la restriction du sommeil et le rythme nycthéméral perturbé semblent favoriser l'augmentation de l'apport énergétique (24,115). Les soignants de l'urgence sont un parfait exemple pour étudier l'impact des gardes de nuit. En effet, les services sont ouverts 24h/24, 365 jours par an. De plus, les travailleurs de la santé d'urgence travaillent dans des conditions stressantes telles que la surpopulation - manque de lits dans les hôpitaux (10), urgences potentiellement vitales (49), attente d'éventuelles catastrophes (116) avec des conséquences sur les biomarqueurs de stress (14,117). De plus, la disponibilité de nourriture est beaucoup moins importante la nuit par rapport à la journée, surtout dans les hôpitaux. Il s'agit rarement de produits frais mais souvent emballés et réchauffés avec une mauvaise présentation. Or, la préparation et la présentation des aliments semblent influencer la consommation de nourriture scolaire par les élèves et la perception des adultes quant à la qualité des repas scolaires (118).

3.4 Médecine d'urgence, stress, et alimentation

Bien que les professionnels de l'urgence travaillent 24/7, il n'existe pas d'étude ayant évalué l'impact des gardes de nuit sur les apports alimentaires des soignants de l'urgence, ni d'étude prenant en compte les relations complexes entre médecine d'urgence, nutrition, et stress.

4. Greline et Leptine sont les hormones de régulation de l'appétit, mais aussi des potentiels biomarqueurs du stress

4.1 Découverte, synthèse et fonction de la ghréline

La ghréline est un peptide composé de 28 acides aminés découvert en 1999, produite majoritairement par l'estomac. Fait intéressant, cette hormone a été découverte trois ans après son récepteur principal au niveau du système nerveux central induisant une augmentation de l'hormone de croissance (growth-hormone – GH). D'ailleurs, la ghréline est nommée ainsi en lien avec son rôle (Growth Hormone-REleasing peptide, faisant également référence au possible langage ancestral Proto-Indo-Européen dans lequel $g^{h}re$- signifierait grandir (to grow en anglais) (119). D'un point de vue biomoléculaire, la ghréline est le résultat de deux clivages des 117 acides aminés pré-pro-ghréline suivis d'une octanoylation par la Ghréline O-Acyltransférase (GOAT) pour produire la forme active de la ghréline (acyl-ghréline) (120) (Figure 5).

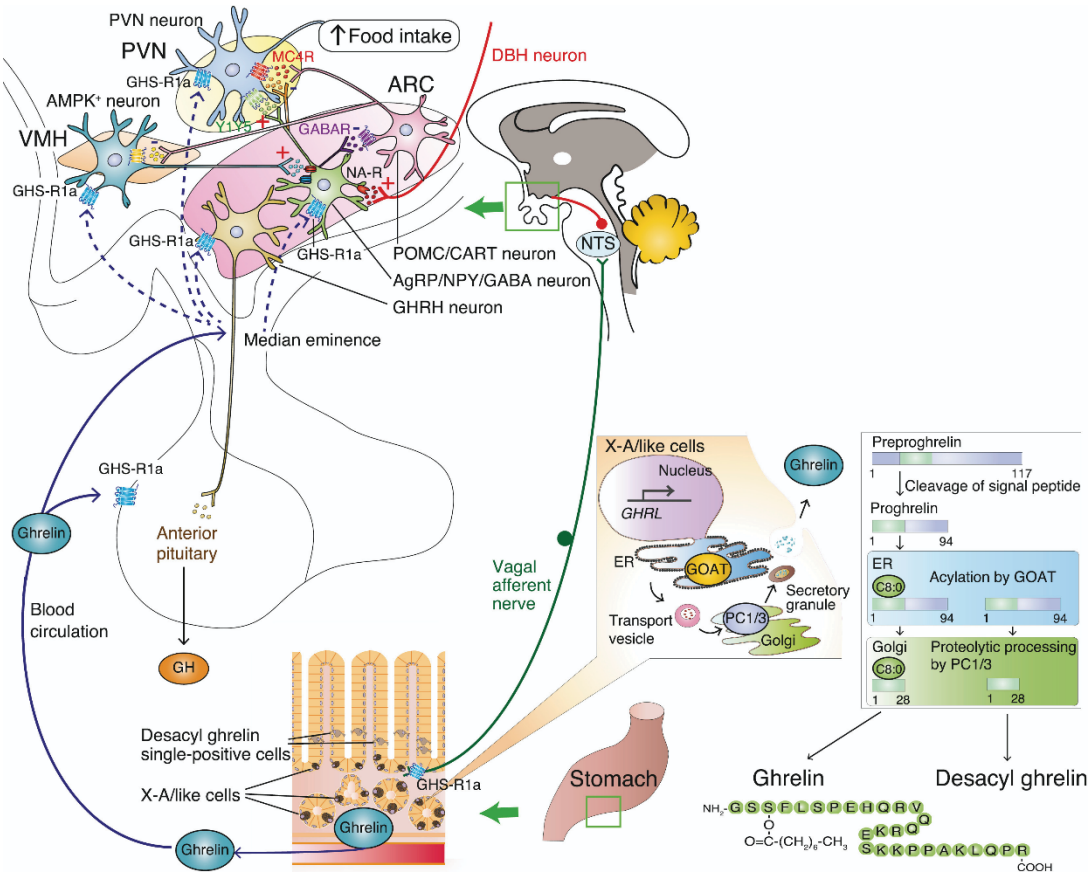

Figure 5. *Synthèse de la ghréline et ses voies de signalisation. D'après Yanagi et al. Cell Metabolism 2018.*

L'acyl-ghréline est connue pour deux effets principaux : 1) équilibrer l'énergie en favorisant la prise alimentaire et la sécrétion d'insuline et d'ACTH (120,121), et 2) la libération d'hormone de croissance (GH) (119). Bien que la ghréline ait de nombreuses fonctions, elle est plus connue comme l'un des principales hormones de régulation de l'appétit, avec un rôle orexigène majeur (122). L'augmentation des niveaux de ghréline participe à l'initiation des repas et favorise les comportements de recherche de nourriture (123). Dans des conditions physiologiques normales, la ghréline présente des variations importantes et immédiates en réponse à un repas, avec une courte demi-vie (<30 minutes) (124–126). Les variations quotidiennes des taux plasmatiques de ghréline montrent une augmentation transitoire durant les périodes pré-prandiales

suivie d'une diminution en post-prandial (127). Il a été proposé que la diminution des taux de ghréline soit déclenchée par l'absorption de nutriments dans l'intestin (124). La ghréline a une réponse aiguë, immédiate et non prolongée à un stimulus, ce qui suggère que l'augmentation des niveaux de ghréline en réponse à un évènement aigu aura une courte durée. La ghréline et la GOAT ne s'expriment pas uniquement dans l'estomac (121). Ils sont également exprimés dans différents tissus tels que le pancréas, l'intestin grêle, l'hypophyse antérieure, le placenta, les lymphocytes, les reins, les gonades, les poumons, le cerveau et l'hypothalamus (128), permettant un relais en cas de gastrectomie. L'expression de l'hypothalamus est médiée par l'horloge circadienne et des facteurs environnementaux tels que le stress. Par ailleurs, la ghréline semble également être impliquée dans la régulation du stress par son action sur l'axe hypothalamo-hypophyso-surrénalien (129).

4.2 Lien entre ghréline et stress

Outre ses multiples fonctions et malgré des résultats contradictoires, la ghréline a été proposée comme biomarqueur du stress, en raison de niveaux plus élevés après un stress aigu (130). Cependant, les mécanismes de cette augmentation ne sont pas encore connus et probablement plurifactoriels. Considérant la rapidité de variation, il semble peu probable que le mécanisme principal soit une augmentation de la production de la pré-pro-ghréline. En revanche, une des possibilités est une augmentation des clivages et/ou de l'octanylation par la GOAT. L'augmentation des taux plasmatiques de ghréline suite à un stress aigu n'étant pas lie à un stimulus alimentaire, d'autres mécanismes de régulation doivent donc s'appliquer. La ghréline a également un rôle à court terme dans la régulation de la santé mentale ; elle est impliquée dans les adaptations à court terme contre la dépression, et dans le contrôle

de l'anxiété après un stress aigu (128). La littérature est rare concernant l'exploration des niveaux de ghréline lors d'un stress physique (131) ou lors d'une combinaison d'un stress physique et mental (132,132). La plupart des études ont utilisé le Trier Social Stress Test (TSST), l'un des outils les plus courants pour induire un stress mental aigu (133). L'augmentation de la ghréline en réponse au stress peut être un mécanisme adaptatif qui peut aider les personnes stressées (129). De plus, stress et obésité étant intrinsèquement liés, il a été suggéré que le stress conduisait à l'obésité via des comportements alimentaires inappropriés potentiellement médiés par la ghréline (134) (Figure 6).

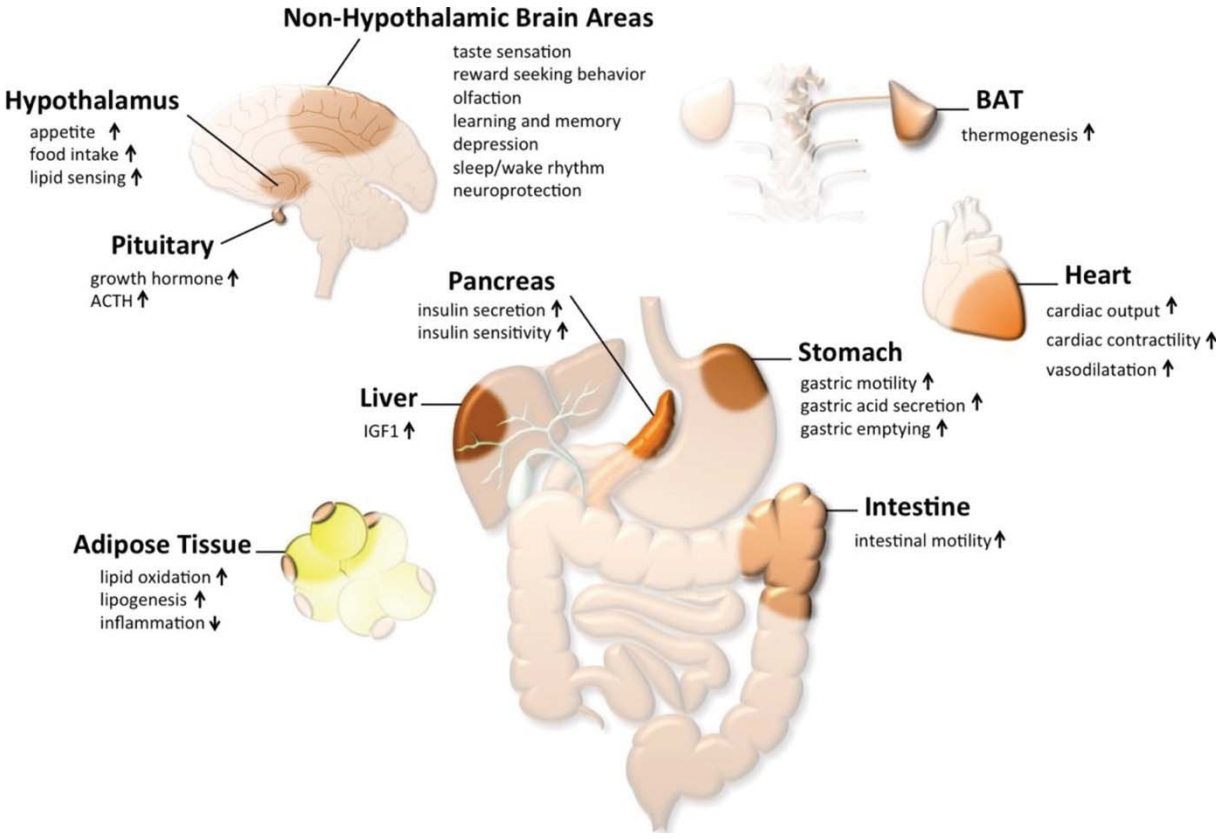

***Figure 6**. Physiologie de la ghréline. Image d'après Anne-Laure Poher et al. Peptides. 2018*

L'étude de la ghréline doit prendre en compte l'indice de masse corporelle. Si une personne en surpoids peut avoir une moindre augmentation des taux de ghréline en

cas de faim (mécanisme adaptatif), il a également été suggéré une augmentation des taux de ghréline dans l'obésité concourant à la majoration de la prise alimentaire et donc de l'obésité elle-même (cercle vicieux). Le stress et l'obésité sont deux problèmes de santé publique intrinsèquement liés (135,136). Il a été proposé que le stress puisse conduire à l'obésité via des comportements alimentaires inappropriés avec une participation active de la ghréline dans la physiopathologie via une réponse non adaptative aux niveaux de ghréline (134). De plus, un véritable cercle vicieux se produit puisque les patients obèses ont un niveau de stress basal plus élevé (137) et les personnes stressées sont celles qui ont le plus de mal à perdre du poids (138). La relation entre obésité et stress a une part biologique importante via les principales hormones de stress régulatrices de l'appétit (leptine, ghréline) (139). Cette relation entre obésité et stress a facilité une recommandation internationale qui suggère de mettre en place des programmes de gestion du stress dans l'obésité pour une perte de poids durable (140). La direction de la relation entre la réponse accrue et prolongée de la ghréline au stress chez les personnes en surpoids et obèses nécessite un examen plus approfondi. Il n'est pas encore possible de déterminer si une réponse plus élevée de la ghréline au stress contribue au développement de l'obésité, ou si les personnes obèses ont développé une réponse accrue de la ghréline à la suite d'une prise de poids. Bien qu'il existe des associations entre les niveaux de ghréline, l'obésité et le stress, les voies causales n'ont pas été établies.

4.3 Découverte, synthèse et fonctions de la leptine

La leptine est un peptide de 167 acides aminés découvert en 1994 (141), dont la majorité est produite par le tissu adipeux blanc mais aussi par d'autres tissus, tels que les ovaires, les glandes mammaires, l'hypophyse, les muscles squelettiques, le tissu

lymphoïde et l'estomac. Son principal effet est sur le système nerveux central (142). Les récepteurs de la leptine sont principalement situés dans le noyau arqué, une partie de l'hypothalamus médio-basal qui produit la pro-opio-mélano-cortine (POMC) (143). La POMC est un précurseur de trois voies principales : l'axe de la mélanocortine, dont le rôle est de réguler l'appétit et le comportement sexuel (144,145); l'axe de l'hormone adrénocorticotrope (ACTH) régulant la sécrétion de glucocorticoïdes principalement impliqués dans la réaction au stress (146); et l'axe de la bêta-endorphine produisant des peptides opioïdes endogènes (146). Sa découverte a changé la vision du tissu adipeux, considéré initialement comme un organe de stockage inactif d'énergie, à un véritable organe endocrinien actif (147). Dans les conditions physiologiques, la leptine a une demi-vie courte – 30 min – avec des variations circadiennes quotidiennes de 18% (142,148). La leptine est majoritairement connue comme l'hormone de satiété, produite par le tissu adipeux avec de faibles niveaux au début du repas et des niveaux élevés après le repas (149). Si l'initiation de la prise alimentaire est médiée par la ghréline, l'insuline et les cannabinoïdes, l'action principale de la leptine se produit après l'initiation du repas (142). Les concentrations sanguines de leptine ne sont pas identiques dans l'ensemble de la population. En effet, les hommes de poids normal semblent avoir des taux de leptine plus faibles que les femmes et les personnes en surpoids (150,151). Outre l'effet de satiété, la leptine joue un rôle actif dans l'homéostasie énergétique, le métabolisme, l'exercice et la fonction neuroendocrinienne (152–154). Cette dernière est centralisée par le récepteur de la leptine situé dans l'hypothalamus (153). De faibles niveaux de leptine peuvent contribuer à l'hyperphagie, à l'hypogonadisme hypogonadotrope et à une diminution de la sécrétion des hormones thyroïdiennes et de croissance (153). La leptine semble également avoir un impact important sur l'homéostasie du glucose en affectant la

sensibilité périphérique à l'insuline indépendamment de ses effets sur la prise alimentaire et le poids (153). Le rôle principal de la leptine est d'arrêter la prise alimentaire via une boucle de rétroaction négative (155). Elle présente des variations nycthémérales. Sa concentration étant la plus faible le jour et la plus élevée la nuit. Plus précisément, le zénith à minuit et le nadir entre 9 h et midi contribuent au maintien du sommeil en inhibant le comportement de prise alimentaire (156). Ce rythme circadien peut être modifié par des critères socio-démographiques tel que l'âge, le sexe et l'indice de masse corporelle (157) (Figure 7).

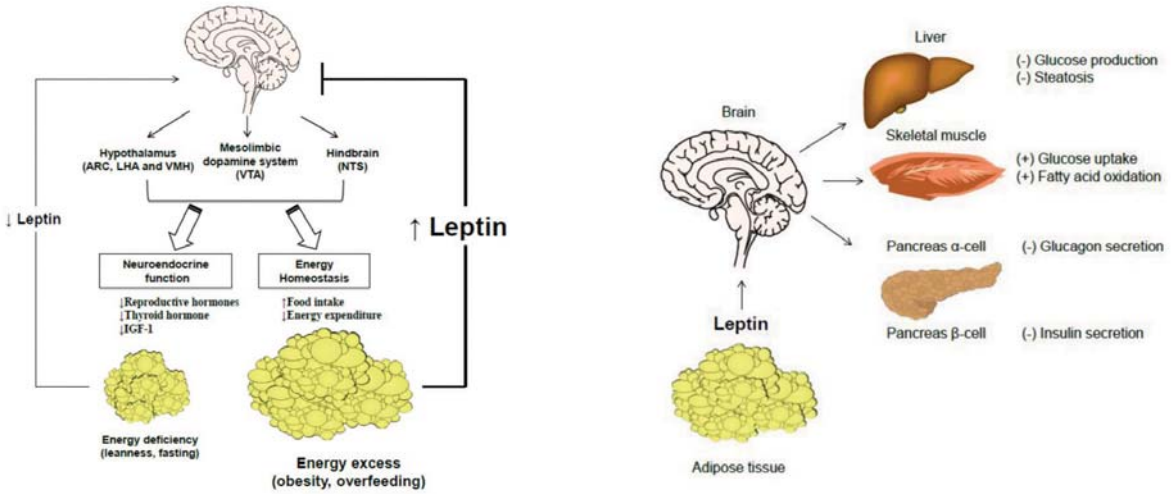

Figure 7. Physiologie de la leptine. D'après Mantzoros et al. Am J Physiol Endocrinol Metab. 2011

4.4 Lien entre leptine et stress

De plus, la leptine a été proposée pour être un biomarqueur du stress aigu, diminuant ses niveaux après un stress aigu. La diminution des niveaux de leptine après un stress aigu peut être un mécanisme adaptatif qui peut aider les gens à répondre au stress. En effet, les événements stressants rendent difficile de rester concentré sur une tâche éventuellement intense qui pourrait nécessiter une grande quantité d'énergie. La

diminution des niveaux de leptine pourrait inciter à augmenter la consommation de nourriture dans l'éventualité où la situation se reproduirait. Il est intéressant de noter que les niveaux de leptine ont besoin de temps pour varier, les niveaux les plus bas étant atteints plus d'une heure après le stress aigu. Cela pourrait s'expliquer par sa demi-vie d'environ 30 minutes, alors que d'autres biomarqueurs ayant une demi-vie plus courte diminuent plus rapidement (158). De plus, la leptine agit principalement sur l'axe hypothalamo-hypophysaire en augmentant la POMC, le précurseur des glucocorticoïdes. La forte relation entre la leptine et les corticoïdes a été prouvée par l'augmentation retardée (6 h) mais durable de la leptine sérique (sur 16 h) après un bolus unique de dexaméthasone administré avant un seul repas copieux (159).

4.5 Lien entre l'obésité, le stress et la leptine

La relation entre l'obésité et le stress est si forte que des propositions de recommandations internationales suggèrent la mise en place de programmes de gestion du stress dans l'obésité pour une perte de poids durable (160,161). Une notion intéressante est la leptinorésistance chez les personnes en surpoids (162). Même s'il existe des prédispositions génétiques à l'obésité induite par l'alimentation, c'est la disponibilité 24 heures sur 24 et 7 jours sur 7 d'une alimentation hypercalorique qui pousse à la suralimentation (163). Un apport alimentaire élevé augmente la production de triglycérides et donc la production de tissu adipeux et par conséquent des niveaux de leptine. Le cercle vicieux se poursuit avec l'apparition d'une résistance cellulaire à la leptine (162). Pour y parvenir, la leptine circulante va augmenter, créant ainsi un nouvel équilibre après l'expansion de la masse grasse. L'augmentation du taux de leptine chez les personnes en surpoids est associée à une diminution du transport de la leptine à travers la barrière hémato-encéphalique. Une boucle de rétroaction

inhibitrice apparaît, entraînant une diminution du signal du récepteur de la leptine. L'augmentation des acides gras libres et la suralimentation chronique semblent induire une lipotoxicité et un stress du réticulum endoplasmique (162). Cette réponse inflammatoire pourrait contribuer d'ailleurs à une réponse physiologique émoussée à la leptine dans l'obésité même si les individus en surpoids ont un niveau de leptine circulant plus élevé tout au long du rythme circadien (135,164). Cependant, les variations quotidiennes chez les personnes en surpoids sont plus faibles que chez les personnes de poids normal. L'amplitude ainsi que la concentration moyenne de leptine sur 24 heures ont augmenté de 280 % et 420 %, respectivement, chez les femmes obèses par rapport aux femmes de poids normal (150). En outre, de nombreux modèles génétiques ont prouvé que l'absence du gène de la leptine induit l'obésité chez l'animal et chez l'homme (165). Pendant plus de cinq décennies, l'équation du bilan énergétique a eu un impact significatif sur la pandémie d'obésité. L'activité physique a considérablement diminué, tandis que la quantité de nourriture et la disponibilité d'aliments à haute teneur calorique ont augmenté (162). L'influence de l'indice de masse corporelle sur la relation entre le stress et la leptine n'est pas linéaire (165). Enfin, les taux de leptine sont influencés par le sexe (166). Plusieurs explications sont possibles et probablement synergiques. Les hommes et les femmes n'ont pas la même répartition du tissu adipeux. Les femmes ont un volume de tissu adipeux viscéral significativement plus faible que les hommes mais un tissu adipeux sous-cutané plus important (166). Or, cette dernière est majoritairement produite dans le tissu adipeux sous cutané, ce dernier produisant plus de leptine que le tissu adipeux viscéral (162). De plus, l'étude du désalignement circadien chez les travailleurs postés a montré que les femmes avaient des niveaux de leptine inférieurs sur 24 heures, tandis que les hommes avaient des niveaux de leptine supérieurs sur 24 heures

lorsqu'ils étaient désalignés (167). Ces résultats pourraient favoriser l'implication de la leptine dans le développement de l'obésité chez les femmes (168).

4.6 Médecine d'urgence, nutrition, et leptine et ghréline comme biomarqueurs du stress

En conclusion, le fait que la leptine et la ghréline soient des biomarqueurs du stress était en débat. Aucune étude n'avait jamais évalué les taux de ghréline et de leptine dans une population de professionnels de l'urgence. Et il n'existait à notre connaissance aucune étude mesurant de façon simultanée les principaux facteurs influençant les taux de ghréline et leptine, à savoir l'alimentation et le stress, mais également des facteurs confondants (sociodémographiques, indice de masse corporelle, etc.).

PROBLEMATIQUE

Nous avons donc démontré la nécessité de répondre à plusieurs problématiques, au travers du protocole de recherche SEEK (Article 1) :

- La mesure du stress des professionnels de l'urgence via l'un des gold standard qu'est le modèle job-demand-control-support de Karasek (Article 2)
- L'étude des apports nutritionnels chez les soignants de l'urgence, et particulièrement l'impact des gardes de nuit sur ces apports (Article 3)
- Démontrer que la ghréline est un biomarqueur du stress (Article 4)
- Démontrer que la leptine est un biomarqueur du stress (Article 5)
- Et enfin, un article de synthèse sur la ghréline et la leptine comme biomarqueurs du stress chez les soignants de l'urgence, en contrôlant les principales variables (stress évalué par le modèle de Karasek, nutrition, gardes de nuit, indice de masse corporelle, et variables sociodémographiques) (Article 6)

ETUDE 1
« Protocol of the study on emergency healthcare workers' responses evaluated by Karasek questionnaire: the SEEK-study protocol »

1. Introduction

Cette première publication a pour but de présenter le protocole de recherche support de cette Thèse. Le postulat de départ est simple. Le stress au travail est un problème de santé publique majeur avec une augmentation de sa prévalence au cours du temps. Les soignants, et surtout les soignants de l'urgence sont particulièrement exposés aux risques psychosociaux, notamment à cause de l'essence même de leur travail conjuguant gardes de jour, gardes de nuit, travail le week-end, prise en charge de détresses vitales et psychologiques, en sous-effectif, avec une surpopulation des services d'urgence pour un manque de lits d'hospitalisation.

D'un point de vue expérimental, il serait impossible de recréer en laboratoire les conditions de stress auxquelles sont soumis les soignants de l'urgence. Il apparaît alors opportun d'étudier leur perception du stress via des modèles de références. Une approche globale holistique intégrant à la fois des mesures subjectives et objectives du stress, et les principaux facteurs confondants, apparait opportun.

Ce protocole a été approuvé par le comité de protection des personnes de Saint-Etienne et enregistré sur la plateforme ClinicalTrial.gov sous le numéro NCT02401607.

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2. Article

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Study Protocol

Protocol of the Study on Emergency Health Care Workers' Responses Evaluated by Karasek Questionnaire: The SEEK-Study Protocol

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Abstract: Background: Stress is a significant public health concern that can be self-evaluated using the job control demands model from Karasek. Emergency health care workers are particularly exposed to stress because of the intrinsic characteristics associated with the job (i.e., life-threatening emergencies, overcrowding, lack of bed spaces). However, these attributes have never been studied using the Karasek model. Methods: An observational, prospective, multicentric study in French Emergency Departments will be conducted using a cohort of emergency health care workers. Four questionnaires before a control day and after a nightshift will be assessed every 5 years in the same emergency departments. Also, the Karasek questionnaire, a sociodemographic questionnaire, the Maslach Burnout Inventory scale, the Hospital Anxiety, Depression Scale, and a food intake questionnaire will be evaluated. Salivary biomarkers (cortisol, immunoglobulin A, lysozyme) will be collected from every emergency health care worker who consents to participating in the study. Conclusion: This study will provide a point of care for the emergency health care workers' stress situation every 5 years. Ethics: This protocol was registered in Clinical Trials under the identification NCT02401607 after the French Ethics Committee's approval.

Keywords: Karasek questionnaire; job demand; job strain; shiftwork; nutrition; emergency physician; stress; job control; biomarkers

1. Background

Chronic stress at work is a significant public health problem increasing morbidity and mortality [1]. Many employees complain about "stress" at work. In the medical field, burnout prevalence near or exceeding 50% has been documented in national studies

conducted in both physicians in training and practicing physicians [2]. This is especially true in the Emergency Departments. Emergency health care workers are a particularly at-risk population. Indeed, their work is a complex interaction between stress due to life-threatening emergencies; overcrowding of the Emergency Department; lack of sleep; bad food repartition before, during, and after shifts; and accumulated fatigue [3]. Health care workers are considered as high-risk group for death by suicide [4]. Although men a higher risk of suicide in the general population, female physicians have higher suicide rates than men [5]. Specialties with a heavy workload, long shifts, and unpredictable hours (associated with sleep deprivation); stress-related situations (life and death emergencies) [6]; and easy access to a means of committing suicide [7] are particularly at risk of suicide [4,8,9]. Emergency health care workers are shift workers with scheduling irregularities regarding hours, duration, and holidays. Shift workers have bad well-being [10] and cardiometabolic risk factors (higher blood pressure [11], higher levels of triglycerides [12], higher risk of obesity [13], higher risk of heart disease [14], and higher metabolic syndrome [15]). Even if quantitative energy intake is the same between nightshift workers and day workers [16], qualitative food choices and habits are different [16]. Shift workers consume more snacks, alcohol, and confectioneries and eat more frequently during the night [17], which possibly hurts circadian regulation [18]. This dysregulation is mainly impacted by the inappropriate secretion of insulin, ghrelin, and leptin [19], leading to diabetes [20]. To our knowledge, no study has evaluated the food intake of emergency physicians before nightshift, during nightshift, and after nightshift.

One way of measuring stress at work is the use of a self-reported psychological questionnaire. Among them, the job control demand model from Karasek is widely used to evaluate psychosocial factors at work [21,22]. It defines job demands and job control as the two broad work-related characteristics present in the environment of most occupations that can be incredibly stressful. Job demands refer to the psychological needs imposed by daily working activities such as mental workload, organizational constraints, and various types of conflicts (i.e., of the role, demands). Job control refers to the lack of decision latitude, specifically the freedom workers can have in realizing their job. Job control is composed of two components: Skill discretion (possibilities to use one's skills) and decision authority (chances of making decisions that can reduce adverse effects of high psychological demands). Workers can perceive both job demand and job control as being low or high. The combination of high job demands and low job control results is called 'job strain.' This situation is the most aversive possible combination. Workers in the 'job strain' configuration are particularly at risk of low well-being [23], burnout [24], and ill-health [25], such as cardiovascular diseases [26,27].

Moreover, the Karasek job strain model is an independent predictor of acute coronary events [28]. Conversely, a combination of low demand and high control results in 'low strain.' The authors proposed an extension of the model in the 1980s to include another dimension: Worksite social support [29]. Support from colleagues and/or from the hierarchy acts as a buffer against complex combinations of job control and demands.

The Karasek job strain model has been assessed in 25,000 workers in the French SUMER study and classified as the main types of occupations [30]. However, no data regarding emergency health care workers' scores at the Karasek questionnaire are available, even though burnout exposure is a well-known problem among health care workers [31,32]. This absence is regrettable as emergency health care workers often need to deal with life-threatening emergencies in a short amount of time, regularly following long shifts [33]. Karasek's questionnaire is supposed to assess a long-term stable perception of work, despite the absence of a study comparing Karasek scores within different conditions in the same participant. It is also essential to explore protective factors that might help alleviate perceived stress and are relatively easy to integrate into medical organizations or daily lifestyle [34].

Regarding biological indicators of stress, several biomarkers of stress have been proposed [33,35,36]. To our knowledge, the relationships between biomarkers of stress and the Karasek job strain model have never been investigated.

We are also interested in finding a precise way to evaluate work stress. Studies have shown contradictory results on biological markers of stress. The present study will use multiple stress markers, allowing for improved and more comprehensive results pertaining to how psychological stress interacts with biological variables.

Cortisol is the historical marker of stress. Nevertheless, several studies have not found modifications in cortisol levels. Thus, no correlations have been demonstrated between secretions of salivary cortisol and stress questionnaires among neonatal health care professionals [37]. Other studies have reported some underlying effects. For example, teaching, a profession with high levels of job stress and burnout, is associated with a significantly higher level of salivary cortisol during workdays versus free days [38].

Among the different biomarkers, our team previously highlighted the potential of salivary dehydroepiandrosterone (DHEA) to assess stress due to its stability (steroid) and its long half-life of 16 h [39]. Related to cortisol, some results have suggested that salivary DHEA levels are modified under stress [40]. Levels of salivary DHEA are also increased in anxiety symptoms [41]. The salivary DHEA's half-life is about 15 h, making it a relatively stable concentration throughout the day, unlike cortisol. Therefore, salivary DHEA is an interesting marker.

Few studies have examined the response of salivary IgA in the case of work-related stress [42]. A recent study described the opposite relationship between stress and salivary IgA levels among healthy volunteers after a psychological stressor [43]. This marker's advantages are its ease of access (saliva) and relatively long half-life (10–15 days), which makes it relatively stable.

Salivary lysozyme has been rarely studied. It does not appear to be modified after acute physical stress on healthy men [44], but studies have found but a negative correlation in university students during their final license exam [45] and in 50 male workers on an assembly line in China [46].

Most biological parameters mentioned here are related to personality questionnaires (locus of control, self-esteem) or perceived health (depression, quality of life, psychosomatic complaints). This will allow us to correlate participants' perceptions of biological modification.

We performed a pilot study with 19 emergency physicians at the Clermont-Ferrand University Hospital. The Karasek questionnaire interview results showed a low decision latitude (59.67 ± 6.44; score below 71) and a high psychological demand (29.39 ± 4.07; score below 20) in this population, illustrating the definition of a stressful work situation (high workload with low autonomy). This state was fortunately balanced by a critical perceived social support (29.94 ± 3.21; score greater than 24). The results demonstrate a perfect illustration of inadequacy between professional demands (taking care of patients regardless of their numbers, varying according to hours and days) and organizational constraints (lack of beds spaces, for example, a situation where decision latitude is nonexistent, generating stress). Our pilot study permits us to situate the emergency physicians on the SUMER study, which lists the mean scores of psychological demands and decision latitude by professional family. This comparison highlights emergency physicians' extraordinary situation, with decision latitude among the lowest and the highest psychological needs. Thus, it becomes interesting to appraise stress in this population through seeking solutions to reduce burnout.

Therefore, the objective of this manuscript was to present the design of a study protocol to examine well-being in emergency health care workers (the SEEK-study). The acronym SEEK is "Study on Emergency physicians' responses Evaluated by Karasek questionnaire". The primary objective is to assess and determine Karasek scores in a large sample size of emergency health care workers. The secondary objectives is to evaluate whether there is a change in work perception both in the short term (on leave and after a nightshift) and long term (with the reproducibility of this study every 5 years). Secondly, we will evaluate

the food intake before, during, and after the nightshift and explore its relationship with Karasek's score and stress biomarkers. We will further explore Karasek's associations with some biomarkers of stress and protective factors.

2. Materials and Methods

2.1. Study Design

Our study will be an observational and prospective study. It will be a multicenter, French study based on the observation of healthy volunteers without invasive sampling in France. We will record different variables and data from the study population without interventions. The study design is described in Figure 1. We will provide repeated measures in the same departments (each measurement time comprising of 24 h, including a nightshift, and 24 h, including a dayshift). We will create a cohort of workers that will be followed every 5 years if they are still working in the Emergency Department. However, we can include new health care workers if needed.

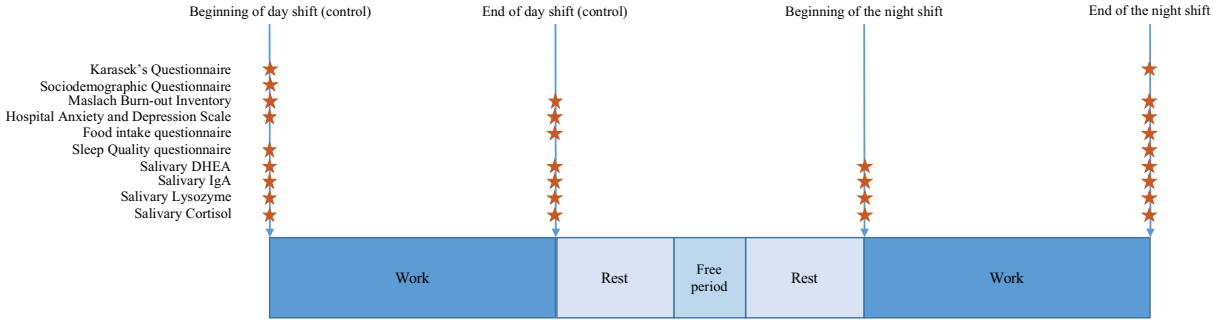

Figure 1. The Study on Emergency physicians' responses Evaluated by Karasek questionnaire (SEEK) protocol.

2.2. Study Settings

According to our pilot study, we evaluate the time required by the participant at about 15 min per phase.

For the first phase, investigators will assess the Karasek's questionnaire, food intake questionnaire, Maslach Burnout Inventory, and Hospital Anxiety Depression Scale (HAD) among Emergency health care workers at the beginning of the control day (around 8:30 am). A sample of saliva in an Eppendorf will be recovered at the same time. Saliva collection will be brought in a cooler to the Institute of Occupational Medicine of Clermont-Ferrand by the end of the day. The samples will be stored at −80 °C. The experimenter will also deliver a pre-stamped envelope for the return of 2 Eppendorf tubes (saliva collection) and questionnaires at the end of the day.

Considering the difficulties of obtaining homogenous planning with all emergency providers, the time passed between the first and the second phase will not be the same between all providers. However, the 2 phases need to be separated by at least 1 week.

For the second phase, investigators will assess the same questionnaires with the saliva collection at the beginning and the end of a 24-hour or 14-hour nightwork session (up to 1 week later). This will permit the evaluation of the relationships between modifications in questionnaire answers and biological responses by comparing results during a control day versus results at the end of a work session, including a nightshift.

The third phase of the SEEK protocol is a longitudinal follow-up. This study design will be reproduced every 5 years in all Emergency Departments. If possible, i.e., if they are already in the same Emergency Department, we will follow-up on the initial cohort. We choose a follow-up of 5 years because it corresponds to the residency program duration in Emergency Medicine in France. We will program 4 sessions for a total of 20 years.

2.3. Ethics and Dissemination

A French Ethics committee (Comité de Protection de Personnes Sud-Est I, CHU Saint-Etienne) approved this study protocol on 3 November 2014, with reference DC-2014-2151. This protocol was registered in ClinicalTrials under the identification NCT02401607.

The results of questionnaires will be coded and managed through ReDCap© software with pseudonymous codification.

2.4. Eligibility Criteria

To fulfill the inclusion criteria, every health care worker will need to over 18 years of age and working in an Emergency Department in France. No requirement of experience is necessary. Healthcare workers will be excluded for refusal of participation, intercurrent pathology with hormones disabilities, impracticability to take the follow-up, psychopathology with depression or anxiety, taking any drugs that modulate inflammation or hormones levels, and pregnancy.

2.5. Recruitment Process

During each part of the study, 120 emergency health care workers will be recruited as participants. During the recruitment phase, all emergency health care workers will individually receive an information letter attached by email. Acceptance or refusal will be given by mail to avoid any subordination effect between the experimenter and the recruited. If they agree, they will have 8 days to sign the consent form to participate in the study. For privacy purposes, the question about their medical history will not be asked by email. Instead, a list of non-inclusion criteria will be given in the information letter. Thus, if any exclusion criteria are present, they can refuse participation without any need for further explanation.

2.6. Outcomes

The primary outcome is the participants' score with respect to the Karasek questionnaire in terms of the 3 dimensions, namely psychological demands, decision latitude, and social support at work.

Secondary outcomes are different biological measures of stress (cortisol concentrations, DHEA-S, salivary IgA, and lysozymes); some psychological questionnaires (see below for details), namely the Maslach Burnout Inventory, the Hospital Anxiety and Depression Scale; and some question about stress (at home, in life, and at work), about sleep quality, and about mental and physical fatigue. Lastly, we will assess food intake using a quantitative and qualitative questionnaire.

3. Results

3.1. Justification of the Sample Size

The number of subjects required justification is based on the ability to recruit participants, namely 120 subjects. Previous studies have shown an acceptance rate above 80% in the emergency health care workers' population; power estimates will be provided based on 100 subjects included. In addition to the expected variability, this type of study can have a fixed margin of error on the estimated sample size (reliability of the sample). Referring to the data of our pilot study, the Karasek questionnaire found low decision latitude (59.67 ± 6.44, 6% higher than 71), a significant psychological burden (29.39 ± 4.07; 94% greater than 20), and high social support (29.94 ± 3.21, 100% above 24), meaning that with at least 100 subjects considered, the error margin will be very satisfying that is respectively ± 1.25, ± 0.8 and ± 0.63. If we consider the different dimensions score as categorical (<> 71 <> 20 and <> 24), accuracy will be $\pm 5\%$ with n = 100.

Furthermore, simulations on secondary objectives can complete this justification. To see a change in the emergency health care workers' work perception during a control day versus the results at the end of a nightshift, 100 subjects will show minimum differences of the order of 2.35, 1.48, and 1.17 for decision latitude dimensions, psychological demand,

and social support, with a type 1 error risk of 5%, a power of 95% and a correlation coefficient of 0.5 (matched condition).

With 100 subjects, and given the assumptions described above, 5 predictors can be explored to identify factors that explain emergency work perception for a power greater than 80% [47].

3.2. Data Collection and Management

Seven questionnaires will be presented to every participant. All psychological assessments will be self-reported.

3.2.1. Karasek Questionnaire

Karasek's questionnaire [21] was French-validated by Brisson et al. in 1998 [48]. The questionnaire includes 26 items measuring the 2 burnout sources: The decision latitude, with 9 items, and psychological job demands, with 9 items. For each item, the subject is asked to respond using a 4-level Likert-type scale. Thus, a high score in the first dimension means that the worker acts autonomously and is less exposed to burnout. Meanwhile, a high score in the second dimension implies that the subject is under a heavy workload, leading to severe psychological stress. Social support, explored by 8 items, acts as a burnout modulator: High social support helps to better tolerate situations linked with burnout emergence. The analysis is based on the median of each factor.

The psychological demand is calculated with the following formula: Q10 + Q11 + Q12 + (5 − Q13) + Q14 + Q15 + Q16 + Q17 + Q18. A score below 20 reflects a low psychological demand. The decision latitude is calculated with the following formula: 4 × Q4 + 4 × (5 − Q6) + 4 × Q8 + 2 × (5 − Q2) + 2 × Q5 + 2 × Q7 +2 × Q1 + 2 × Q3 + 2 × Q9. A score below 71 reflects low decision latitude. Finally, the social support is calculated with the following formula: Q19 + Q20 + Q21 + Q22 + Q23 + Q24 + Q25 + Q26. A score below 24 reflects low social support [22]. In a previous study performed by our team, the Cronbach's alphas for job demands, job control, and social support were 0.58, 0.99, and 0.99, respectively [49].

In summary, the Karasek questionnaire postulates that a work situation generates stress if it combines high psychological demands, low decision latitude, and low social support from the work team or hierarchy. By combining autonomy and demand, 4 broad categories are defined:

- Relaxed work: Low demand, high autonomy
- Passive work: Low demand, low autonomy
- Active work: High demand, high autonomy
- Stressed, tense work: High demand, low autonomy

3.2.2. Maslach Burnout Inventory (MBI) Scale

The MBI scale [50] evaluates 3 different components, giving a burnout evaluation for each component: Emotional exhaustion, depersonalization, and personal accomplishment. Dion and Tessier made a French-translated version of the MBI scale [51]. The scale is composed of 22 items measuring 3 different burnout dimensions: Emotional exhaustion, depersonalization, and personal accomplishment. For each item, the subject is asked to indicate using a 7-point scale the occurrence frequency of the feeling corresponding to a state. Thus, a high score in the first 2 subscales reveals a burnout state. In contrast, a high subscale score on achievement means that the subject feels fulfilled professionally (the achievement subscale is inverted). In a previous study performed by our team in a similar population, analysis of internal consistency yielded a Cronbach's alpha of 0.785, indicating scale reliability [52].

3.2.3. Hospital Anxiety and Depression Scale (HAD) Scale

Zigmond & Snaith's (1983) HAD Scale explores anxiety and depression [53]. It was translated into French by Lépine in 2000 [54]. The scale is composed of 7 items exploring

anxiety symptoms, and 7 others exploring depressive symptoms. Each item is given on a 4 degrees-of-severity scale. Anxiety and depression score ranges from 0 to 21. The generally admitted pathological thresholds score is 8. In a previous study performed by our team in a similar population, the Cronbach's alphas for the components of depression and anxiety were 0.82 and 0.79, respectively [49].

3.2.4. Sociodemographic Report

A unique questionnaire will be used to collect sociodemographic data such as age, sex, weight, height, and marital status. Information about medical history, drugs, and pregnancy (if female) will be collected. A second part of the questionnaire will assess the physical activity (number of hours per week and intensity) and sleep of every health care worker (number of hours and quality assess by a visual analogic scale from worst to best). Others visual analogic scales will assess stress and mental and physical tiredness.

3.2.5. Place of Work

Information about the Emergency Department and hospital such as type of hospital (university or not), number of patients every year, and type of patients (adult, kids, both) will be collected.

3.2.6. Occupational Characteristics

These include seniority (within the hospital, within the Emergency Department, and as an emergency occupation), current position (physician, internship or externship student, nurses, caregivers, cleaners, secretary, hospital porter, other), and type of contract (permanent or temporary). For physicians, these characteristics also include the type of emergency diploma or initial specialty and more details on contracts (professors, senior lecturer, hospital practitioner, assistant).

3.2.7. Food Intake

To study the qualitative and quantitative food intake of emergency health care workers, participants will be given a questionnaire. Three timepoints will be examined—before, during, and after nightshift—and compared to a control day. We will ask participants to complete a 3-day dietary recall that will be explained and detailed to them by a member of the investigation team. We will ask to participants to indicate all the details regarding the food ingested at each meal and in-between meals as precisely as possible. A specialized dietician will provide details in the diary as well as some guidance on how to complete it. Subsequently, the diaries will be reviewed with the participants and the dietitian during a 45-min interview [55]. All data will be pooled and translated in kcal., and the quantity of lipids, carbohydrates, and proteins will be evaluated using the software Nutrilog®.

3.2.8. Biological Samples

Several assays will be performed on the saliva sample. Biological analyses will be conducted by the Institute of Occupational Medicine of the Medical School of Clermont-Ferrand. We will measure salivary cortisol concentrations, DHEA-S, sIgA, and lysozymes. These parameters have been reported in the literature as correlated with the level of stress or workload. Only steroids (cortisol and DHEAS) with good stability will be measured in both samples. Peptides (sIgA and lysozyme) will be measured only during the dayshift (control). The samples made after the work session will be sent by post, which does not guarantee sIgA and lysozyme preservation.

3.3. Data Analysis

Continuous variables will be presented as mean and standard-deviation or median and interquartile range according to the statistical distribution. The normality assumption will be assessed using Shapiro–Wilk test. Categorical variables will be expressed as numbers and associate percentage. The primary analysis will be mainly descriptive and will define

the perception scores of emergency physicians work according to the Karasek questionnaire for each dimension composing the score (decision latitude, psychological demands, and social support), as quantitative and categorical variable. A correlation matrix analysis on quantitative variables (i.e., Karasek questionnaire and other psychological questionnaires) will be conducted using Pearson or Spearman correlation coefficients, in addition to principal component analysis (PCA). The Karasek questionnaire score's evolution, obtained for each dimension, will be tested with a paired two-sample Student's test, or nonparametric Wilcoxon test if necessary. Linear regression models and random-effects models will complete these analyses. These models will permit, with multivariable analyses and covariates' introduction, to seek possible explanatory factors of the Karasek score (a dayshift (control) versus the end of 24 h or shift) and its evolution. The same statistical analysis plan will be used for continuous parameters collected after the dayshift (control) and after the 24-h shift (e.g., all biological samples). For categorical variables, Stuart-Maxwell test will be used. The comparisons for quantitative parameters (e.g., biological data, questionnaires' scores) will be based on Student's *t*-test or nonparametric Mann–Whitney test. The comparisons involving categorical parameters (gender, seniority) will be made with the Chi-squared test or Fisher's exact test. All statistical analyses will be performed as two-sided tests, with a $p < 0.05$ considered as significant. Statistical analyses will be performed using the Stata software (version 16, StataCorp, College Station, TX, USA).

4. Discussion

This protocol seems particularly innovative considering the lack of emergency health care workers in the SUMER study. Indeed, those workers are mainly at risk of burnout [4]. Furthermore, and even if it was not the main objective, the recent actuality with the COVID-19 pandemic showed an increase in the workload for emergency health care workers. Indeed, even in the area with low incidence of first wave of COVID [56], overcrowding is increasing in the Emergency Departments [57]. Furthermore, the 20 years of follow-up will make it possible to assess the impact of local (an increase of the number of workers during shifts, change in the food quality and quantity. . .) and national policy (no more 24-h shifts, security rest after a nightshift) on the well-being of workers. This study will bring important data about emergency health care workers' work perception and stress. No data on the Karasek questionnaire score currently enable u, to compare Emergency Medicine with other medical specialties. Indeed, the SUMER study did not include any emergency health care workers. The SUMER study [30] conducted in France on 25,000 employees in 2002–2003 found that all confounded professions produced average psychological demand scores of 21.5 for men and 21.8 for women, and average decision latitude scores of 71.9 for men and 68.8 for women. The distribution of these four broad categories was Relaxed 29.2%, Passive 25.2%, Active 25.2%, and Tense 20.4%. The SUMER study can be used to identify the psychological demands and decision latitude mean scores by professional family.

Potential Limitations

The psychological questionnaires in this study are self-assessed. Even if those questionnaires are made to avoid bias, it is still possible that responses suffer from variation. As an observational study, we cannot control the 24 h work schedule. Some individuals' sessions might be more demanding than others, thus bringing more important modifications to a biological sample.

5. Conclusions

This project will contribute to an overview of emergency health care workers' conditions. The omission of their place in the SUMER study after the Karasek questionnaire will be corrected. Second, the outcome from this study, repeated every 5 years over 20 years, will provide an insight into whether or not improvements have occurred in the emergency health care working conditions and, if so, how this outcome will influence or impact health care policy. Last, the secondary outcomes will probably give our team the impetus to

improve life quality by increasing quality and quantity of food intake or by the impact of new Emergency Department organization between two measures.

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References

1. Prior, A.; Fenger-Grøn, M.; Davydow, D.S.; Olsen, J.; Li, J.; Guldin, M.-B.; Vestergaard, M. Bereavement, multimorbidity and mortality: A population-based study using bereavement as an indicator of mental stress. *Psychol. Med.* **2018**, *48*, 1437–1443. [CrossRef] [PubMed]
2. West, C.P.; Dyrbye, L.N.; Erwin, P.J.; Shanafelt, T.D. Interventions to prevent and reduce physician burnout: A systematic review and meta-analysis. *Lancet* **2016**, *388*, 2272–2281. [CrossRef]
3. Wong, M.L.; Anderson, J.; Knorr, T.; Joseph, J.W.; Sanchez, L.D. Grit, anxiety, and stress in emergency physicians. *Am. J. Emerg. Med.* **2018**, *36*, 1036–1039. [CrossRef]
4. Dutheil, F.; Aubert, C.; Pereira, B.; Dambrun, M.; Moustafa, F.; Mermillod, M.; Baker, J.S.; Trousselard, M.; Lesage, F.X.; Navel, V. Suicide among physicians and health-care workers: A systematic review and meta-analysis. *PLoS ONE* **2019**, *14*, e0226361. [CrossRef]
5. Lindeman, S.; Läärä, E.; Hakko, H.; Lönnqvist, J. A Systematic Review on Gender-Specific Suicide Mortality in Medical Doctors. *Br. J. Psychiatry* **1996**, *168*, 274–279. [CrossRef]
6. Patterson, P.D.; Weaver, M.D.; Frank, R.C.; Warner, C.W.; Martin-Gill, C.; Guyette, F.X.; Fairbanks, R.J.; Hubble, M.W.; Songer, T.J.; Callaway, C.W.; et al. Association Between Poor Sleep, Fatigue, and Safety Outcomes in Emergency Medical Services Providers. *Prehospital Emerg. Care* **2012**, *16*, 86–97. [CrossRef]
7. Hawton, K.; Clements, A.; Simkin, S.; Malmberg, A. Doctors who kill themselves: A study of the methods used for suicide. *Qjm Int. J. Med.* **2000**, *93*, 351–357. [CrossRef]
8. Feola, A.; Cassandro, P.; Carfora, A.; Petrella, R.; Giordano, C.; Stefanizzi, I.M.; Borriello, R. Suicides in Physicians: Two Cases of Poisoning Involving Fentanyl and Phenobarbital. *Minerva Psichiatr.* **2017**, *8*, 103–109. Available online: https://www.minervamedica.it/en/journals/minerva-psychiatry/article.php?cod=R17Y2017N02A0103 (accessed on 17 March 2021).
9. Feola, A.; Carfora, A.; Mascolo, P.; Petrella, R.; Della Pietra, B.; Campobasso, C.P. Alprazolam-associated death: Suicide or unintentional overdose? *Aust. J. Forensic Sci.* **2021**, *22*, 1–9. [CrossRef]
10. Azmi, M.N.A.S.; Juliana, N.; Teng, M.F.N.I.; Azmani, S.; Das, S.; Effendy, N. Consequences of Circadian Disruption in Shift Workers on Chrononutrition and their Psychosocial Well-Being. *Int. J. Environ. Res. Public Health* **2020**, *17*, 2043. [CrossRef]
11. Riegel, B.; Daus, M.; Lozano, A.J.; Malone, S.K.; Patterson, F.; Hanlon, A.L. Shift Workers Have Higher Blood Pressure Medicine Use, But Only When They Are Short Sleepers: A Longitudinal UK Biobank Study. *J. Am. Heart Assoc.* **2019**, *8*, e013269. [CrossRef]
12. Phoi, Y.Y.; Keogh, J.B. Dietary Interventions for Night Shift Workers: A Literature Review. *Nutriments* **2019**, *11*, 2276. [CrossRef]
13. O'Brien, V.M.; Nea, F.M.; Pourshahidi, L.K.E.; Livingstone, M.B.; Bardon, L.; Kelly, C.; Kearney, J.M.A.; Corish, C. Overweight and obesity in shift workers: Associated dietary and lifestyle factors. *Eur. J. Public Health* **2020**, *30*, 532–537. [CrossRef]
14. Vetter, C.; Devore, E.E.; Wegrzyn, L.R.; Massa, J.; Speizer, F.E.; Kawachi, I.; Rosner, B.; Stampfer, M.J.; Schernhammer, E.S. Association Between Rotating Night Shift Work and Risk of Coronary Heart Disease Among Women. *JAMA* **2016**, *315*, 1726–1734. [CrossRef]
15. Lim, Y.C.; Hoe, V.C.W.; Darus, A.; Bhoo-Pathy, N. Association between night-shift work, sleep quality and metabolic syndrome. *Occup. Environ. Med.* **2018**, *75*, 716–723. [CrossRef]

16. Bonham, M.P.; Bonnell, E.K.; Huggins, C.E. Energy intake of shift workers compared to fixed day workers: A systematic review and meta-analysis. *Chronobiol. Int.* **2016**, *33*, 1086–1100. [CrossRef]
17. Shan, Z.; Li, Y.; Zong, G.; Guo, Y.; Li, J.E.; Manson, J.; Hu, F.B.; Willett, W.C.; Schernhammer, E.S.; Bhupathiraju, S.N. Rotating night shift work and adherence to unhealthy lifestyle in predicting risk of type 2 diabetes: Results from two large US cohorts of female nurses. *BMJ* **2018**, *363*, e4641. [CrossRef] [PubMed]
18. Morris, C.J.; Aeschbach, D.; Scheer, F.A. Circadian system, sleep and endocrinology. *Mol. Cell. Endocrinol.* **2012**, *349*, 91–104. [CrossRef] [PubMed]
19. Bouillon-Minois, J.-B.; Trousselard, M.; Thivel, D.; Gordon, B.; Schmidt, J.; Moustafa, F.; Oris, C.; Dutheil, F. Ghrelin as a Biomarker of Stress: A Systematic Review and Meta-Analysis. *Nutriments* **2021**, *13*, 784. [CrossRef]
20. Morris, C.J.; Purvis, T.E.; Mistretta, J.; Scheer, F.A.J.L. Effects of the Internal Circadian System and Circadian Misalignment on Glucose Tolerance in Chronic Shift Workers. *J. Clin. Endocrinol. Metab.* **2016**, *101*, 1066–1074. [CrossRef] [PubMed]
21. Karasek, R.A. Job Demands, Job Decision Latitude, and Mental Strain: Implications for Job Redesign. *Adm. Sci. Q.* **1979**, *24*, 285–308. [CrossRef]
22. Karasek, R.; Brisson, C.; Kawakami, N.; Houtman, I.; Bongers, P.; Amick, B. The Job Content Questionnaire (JCQ): An instrument for internationally comparative assessments of psychosocial job characteristics. *J. Occup. Health Psychol.* **1998**, *3*, 322–355. [CrossRef]
23. Fan, W.; Moen, P.; Kelly, E.L.; Hammer, L.B.; Berkman, L.F. Job strain, time strain, and well-being: A longitudinal, person-centered approach in two industries. *J. Vocat. Behav.* **2019**, *110*, 102–116. [CrossRef]
24. Durand, A.-C.; Bompard, C.; Sportiello, J.; Michelet, P.; Gentile, S. Stress and burnout among professionals working in the emergency department in a French university hospital: Prevalence and associated factors. *Work* **2019**, *63*, 57–67. [CrossRef] [PubMed]
25. Stansfeld, S.; Candy, B. Psychosocial work environment and mental health—A meta-analytic review. *Scand. J. Work. Environ. Health* **2006**, *32*, 443–462. [CrossRef]
26. Framke, E.; Sørensen, J.K.; Andersen, P.K.; Svane-Petersen, A.C.; Alexanderson, K.; Bonde, J.P.; Farrants, K.; Flachs, E.M.; Hanson, L.L.M.; Nyberg, S.T.; et al. Contribution of income and job strain to the association between education and cardiovascular disease in 1.6 million Danish employees. *Eur. Heart J.* **2019**, *41*, 1164–1178. [CrossRef]
27. Sara, J.D.; Prasad, M.; Eleid, M.F.; Zhang, M.; Widmer, R.J.; Lerman, A. Association Between Work-Related Stress and Coronary Heart Disease: A Review of Prospective Studies Through the Job Strain, Effort-Reward Balance, and Organizational Justice Models. *J. Am. Heart Assoc.* **2018**, *7*, e008073. [CrossRef] [PubMed]
28. Aboa-Eboulé, C.; Brisson, C.; Maunsell, E.; Masse, B.; Bourbonnais, R.; Vézina, M.; Milot, A.; Théroux, P.; Dagenais, G.R. Job Strain and Risk of Acute Recurrent Coronary Heart Disease Events. *JAMA* **2007**, *298*, 1652–1660. [CrossRef]
29. Ganster, D.C.; Fusilier, M.R.; Mayes, B.T. Role of social support in the experience of stress at work. *J. Appl. Psychol.* **1986**, *71*, 102–110. [CrossRef]
30. Niedhammer, I.; Chastang, J.-F.; Levy, D.; David, S.; Degioanni, S.; Theorell, T. Study of the validity of a job-exposure matrix for psychosocial work factors: Results from the national French SUMER survey. *Int. Arch. Occup. Environ. Health* **2008**, *82*, 87–97. [CrossRef]
31. Cocker, F.; Joss, N. Compassion Fatigue among Healthcare, Emergency and Community Service Workers: A Systematic Review. *Int. J. Environ. Res. Public Health* **2016**, *13*, 618. [CrossRef] [PubMed]
32. Hall, L.H.; Johnson, J.; Watt, I.; Tsipa, A.; O'Connor, D.B. Healthcare Staff Wellbeing, Burnout, and Patient Safety: A Systematic Review. *PLoS ONE* **2016**, *11*, e0159015. [CrossRef] [PubMed]
33. Dutheil, F.; Boudet, G.; Perrier, C.; Lac, G.; Ouchchane, L.; Chamoux, A.; Duclos, M.; Schmidt, J. JOBSTRESS study: Comparison of heart rate variability in emergency physicians working a 24-hour shift or a 14-hour night shift—A randomized trial. *Int. J. Cardiol.* **2012**, *158*, 322–325. [CrossRef]
34. Awa, W.L.; Plaumann, M.; Walter, U. Burnout prevention: A review of intervention programs. *Patient Educ. Couns.* **2010**, *78*, 184–190. [CrossRef]
35. Dutheil, F.; Trousselard, M.; Perrier, C.; Lac, G.; Chamoux, A.; Duclos, M.; Naughton, G.; Mnatzaganian, G.; Schmidt, J. Urinary Interleukin-8 Is a Biomarker of Stress in Emergency Physicians, Especially with Advancing Age—The JOBSTRESS* Randomized Trial. *PLoS ONE* **2013**, *8*, e71658. [CrossRef]
36. Lennartsson, A.-K.; Theorell, T.; Kushnir, M.M.; Bergquist, J.; Jonsdottir, I.H. Perceived stress at work is associated with attenuated DHEA-S response during acute psychosocial stress. *Psychoneuroendocrinology* **2013**, *38*, 1650–1657. [CrossRef]
37. Fumagalli, M.; Provenzi, L.; Sorrentino, G.; Ciceri, F.; Fontana, C.; Passera, S.; Moncecchi, M.; Plevani, L.; Laquintana, D.; Borgatti, R.; et al. Self-Report and Biological Indexes of Work-Related Stress in Neonatal Healthcare Professionals: A Repeated-Measures Observational Study. *Adv. Neonatal Care Off. J. Natl. Assoc. Neonatal Nurses* **2021**. [CrossRef]
38. Wettstein, A.; Kühne, F.; Tschacher, W.; La Marca, R. Ambulatory Assessment of Psychological and Physiological Stress on Workdays and Free Days Among Teachers. A Preliminary Study. *Front. Neurosci.* **2020**, *14*, 112. [CrossRef]
39. Leowattana, W. DHEAS as a new diagnostic tool. *Clin. Chim. Acta* **2004**, *341*, 1–15. [CrossRef]
40. Shirotsuki, K.; Izawa, S.; Sugaya, N.; Kimura, K.; Ogawa, N.; Yamada, K.C.; Nagano, Y. Imbalance Between Salivary Cortisol and DHEA Responses Is Associated with Social Cost and Self-perception to Social Evaluative Threat in Japanese Healthy Young Adults. *Int. J. Behav. Med.* **2019**, *27*, 316–324. [CrossRef]

41. Mulligan, E.M.; Hajcak, G.; Crisler, S.; Meyer, A. Increased dehydroepiandrosterone (DHEA) is associated with anxiety in adolescent girls. *Psychoneuroendocrinology* **2020**, *119*, 104751. [CrossRef]
42. Chojnowska, S.; Ptaszyńska-Sarosiek, I.; Kępka, A.; Knaś, M.; Waszkiewicz, N. Salivary Biomarkers of Stress, Anxiety and Depression. *J. Clin. Med.* **2021**, *10*, 517. [CrossRef] [PubMed]
43. Stojanović, N.M.; Randjelović, P.J.; Pavlović, D.; Stojiljković, N.I.; Jovanović, I.; Sokolović, D.; Radulović, N.S. An Impact of Psychological Stress on the Interplay between Salivary Oxidative Stress and the Classic Psychological Stress-Related Parameters. *Oxid. Med. Cell. Longev.* **2021**, *2021*, e6635310. [CrossRef] [PubMed]
44. Allgrove, J.E.; Gomes, E.; Hough, J.P.; Gleeson, M. Effects of exercise intensity on salivary antimicrobial proteins and markers of stress in active men. *J. Sports Sci.* **2008**, *26*, 653–661. [CrossRef] [PubMed]
45. Perera, S.; Uddin, M.; Hayes, J.A. Salivary lysozyme: A noninvasive marker for the study of the effects of stress on natural immunity. *Int. J. Behav. Med.* **1997**, *4*, 170–178. [CrossRef]
46. Yu, S.-F.; Jiang, K.-Y.; Zhou, W.-H.; Wang, S. Relationship between occupational stress and salivary sIgA and lysozyme in assembly line workers. *Chin. Med. J.* **2008**, *121*, 1741–1743. [CrossRef] [PubMed]
47. Harris, R.W.; Willard, G.R. A measure of performance. *Emergency* **1989**, *21*, 42–44. [PubMed]
48. Brisson, C.; Blanchette, C.; Guimont, C.; Dion, G.; Moisan, J.; Vézina, M.; Dagenais, G.R.; Măsse, L. Reliability and validity of the French version of the 18-item Karasek job content questionnaire. *Work Stress* **1998**, *12*, 322–336. [CrossRef]
49. Dutheil, F.; Charkhabi, M.; Ravoux, H.; Brousse, G.; Dewavrin, S.; Cornet, T.; Mondillon, L.; Han, S.; Pfabigan, D.; Baker, J.S.; et al. Exploring the Link between Work Addiction Risk and Health-Related Outcomes Using Job-Demand-Control Model. *Int. J. Environ. Res. Public Health* **2020**, *17*, 7594. [CrossRef]
50. Maslach, C.; Jackson, S.E. *The Maslach Burn-Out Inventory*; Consulting Psychologists Press: Palo Alto, CA, USA, 1986.
51. Dion, G.; Tessier, R. Validation of a French translation of the Maslach Burnout Inventory (MBI). *Can. J. Behav. Sci. Rev. Can. Sci. Comport.* **1994**, *26*, 210–227. [CrossRef]
52. Vukmirovic, M.; Rajovic, N.; Pavlovic, V.; Masic, S.; Mirkovic, M.; Tasic, R.; Randjelovic, S.; Mostic, D.; Velickovic, I.; Nestorovic, E.; et al. The Burnout Syndrome in Medical Academia: Psychometric Properties of the Serbian Version of the Maslach Burnout Inventory—Educators Survey. *Int. J. Environ. Res. Public Health* **2020**, *17*, 5658. [CrossRef]
53. Zigmond, A.S.; Snaith, R.P. The Hospital Anxiety and Depression Scale. *Acta Psychiatr. Scand.* **1983**, *67*, 361–370. [CrossRef] [PubMed]
54. Lépine, J.P.; Godchau, M.; Brun, P.; Lempérière, T. Evaluation of anxiety and depression among patients hospitalized on an internal medicine service. *Ann. Med. Psychol.* **1985**, *143*, 175–189.
55. Tremblay, A.; Dutheil, F.; Drapeau, V.; Metz, L.; Lesour, B.; Chapier, R.; Pereira, B.; Verney, J.; Baker, J.S.; Vinet, A.; et al. Long-term effects of high-intensity resistance and endurance exercise on plasma leptin and ghrelin in overweight individuals: The RESOLVE Study. *Appl. Physiol. Nutr. Metab.* **2019**, *44*, 1172–1179. [CrossRef] [PubMed]
56. Bouillon-Minois, J.-B.; Schmidt, J.; Dutheil, F. SARS-CoV-2 pandemic and emergency medicine: The worst is yet to come. *Am. J. Emerg. Med.* **2020**, *42*, 246–247. [CrossRef] [PubMed]
57. Bouillon-Minois, J.-B.; Raconnat, J.; Clinchamps, M.; Schmidt, J.; Dutheil, F. Emergency Department and Overcrowding during COVID-19 Outbreak; A Letter to Editor. *Arch. Acad. Emerg. Med.* **2021**, *9*, 28.

3. **Conclusion**

Cette première publication donne le cadre des recherches réalisées dans le cadre de cette thèse. Fait intéressant, le protocole a été publié 5 ans après l'accord éthique et le début des inclusions.

ETUDE 2
« Jobstrain of emergency healthcare workers' evaluated by Karasek questionnaire: The SEEK-Study »

1. Introduction

Ce premier article original représente l'essence même du protocole, l'étude du stress chez les soignants de l'urgence. Nous sommes partis du postulat que les soignants de l'urgence sont stressés. Même si cela paraît évident pour quiconque a un jour travaillé dans un service d'accueil des urgences, il était indispensable de le démontrer afin de pouvoir utiliser ces données pour la suite de la thèse. Pour le prouver, nous avons utilisé le modèle « job-demand-control-support » de Karasek – un modèle de questionnaire prouvé et validé dans de nombreuses situations et de nombreux pays qui fait référence en termes de diagnostic de stress au travail. Le modèle de Karasek est basé sur plusieurs éléments. Premièrement la demande psychologique du travail demandé aux soignants. Deuxièmement la latitude décisionnelle dans le cadre de leur travail. Les travailleurs avec une faible latitude décisionnelle et une forte demande psychologique sont en situation de tenson au travail (« jobstrain ») et nécessitent une surveillance accrue. Une troisième dimension est présente dans le modèle de Karasek : le support social. Ce dernier agit comme un facteur protecteur vis à vis des risques psychosociaux chez les travailleurs en situation de jobstrain.

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2. Article

Jobstrain of emergency healthcare workers' evaluated by Karasek questionnaire: The SEEK-Study

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Keywords: Emergency healthcare workers; burnout; public health, mental health

Abstract

Background: Emergency healthcare workers (eHCWs) are particularly at risk of stress, but data using the gold standard questionnaire of Karasek are scarce. We assessed the level of stress of eHCWs, and aimed to compare with general population.

Methods: Cross-sectional nationwide study in French Emergency Departments, using the job-content questionnaire of Karasek, compared with the 25 000 answers in French general population (controls from the SUMER study). Description of job demand, job control and social support were described as well as prevalence of jobstrain and isostrain. Putative factors were searched using mixed-method analysis

Results: 166 eHCWs (37.9±10.5 years old, 42% men) from five French Emergency Department were included: 53 emergency physicians and 104 emergency paramedics, compared to 25 000 workers with other occupations. Job-demand was the highest for physicians (28.3±3.3) and paramedics (25.9±3.8), compared to controls (36.0±7.2) ($p<0.001$). Job-control was the lowest for physicians (61.2±5.8) and paramedics (59.1±6.8), compared to controls (70.4±11.7) ($p<0.001$). Mean social support did not differ between groups (23.6±3.4 for physicians, 22.6±2.9 for paramedics, and 23.7±3.6 for controls). The prevalence of job-strain was massively higher for physicians (95.8%) and paramedics (84.8%), compared to controls (23.9%) ($p<0.001$), as well as for isostrain (45.1% for physicians, 56.8% for paramedics, and 14.3% for controls, $p<0.001$). We did not find any significant impact of sociodemographic on job control, job demand or social support.

Conclusion: eHCWs have a dramatic rate of jobstrain, necessitating urgent promotion of policy to take care of them.

1 Introduction

Stress at work is a main public health concern. In the medical field, half physicians are considered highly stress (1). This is especially true in Emergency Departments (ED) where healthcare workers (HCWs) have a complex interaction between stress due to shift work, fatigue and lack of sleep (2), poor food intake (3), and cardiac strain (4) and life-threatening emergencies in a context of overcrowding (5,6). Currently, the best scale to assess stress level at work is the job-demand-control model (JDC), a self-reported psychological questionnaire, created and validated by Karasek in 1981 (7,8). The JDC model recognizes the importance of daily environmental stressors on long term experience of stress (9). It defines job demand and job control as the two broad work-related characteristics present in the environment of most occupations that could be stressful. Job demand refer to the psychological needs imposed by daily working activities, i.e., mental workload, organizational and time constraints. Job control refers to the latitude of decision and is composed of two components: skill discretion and decision authority. Each worker can perceive both job demand and job control as different levels. Karasek defined the combination of high job demands, and low job control as 'job strain', the most aversive combination, at risk of low well-being (10), burnout (11), and ill-health (12). On the other side, a low job demand and high job control results in 'low strain', but this situation is rare. Since the 80s, another dimension is included in the JDC model, the 'worksite social support'. Indeed, support from colleagues and/or from the hierarchy seems to act as a buffer against complex combinations of job control and demands (13). Iso-strain is defined as job strain with a low social support at work (14). The Job Content Questionnaire (JCQ) (15) derived from Karasek's model and has been developed and validated in several languages. The Karasek job

strain model has been assessed among 25,000 workers in the French SUMER study and classified as the main types of occupations (14,16). However, no or few data regarding emergency HCWs scores at the Karasek questionnaire are available, even though burnout exposure is a well-known problem among them (17,18). It seems that no sociodemographic (sex, age, body mass index, marital status, physical activity) is a protective factor for jobstrain. (19). However, in case of association with "family strain" – family-related stress and familial conflict – women have more depression than men (20).

The main objective of this study was to assess stress levels using Karasek JCD model among emergency HCWs, and to compare with the general population. Secondary objectives were to compare physicians and other providers (defined as paramedical) and to find the impact of sociodemographic on stress levels.

2 Materiel and methods

2.1 Study design

We performed an observational nationwide cross-sectional study. Volunteers emergency HCWs were recruited from French emergency departments. The study design is described in Figure 1. Participants were asked to complete the questionnaire between 6.30 and 9.00 am. We also used data from the SUMER study to compare results from emergency HCWs to other occupations from the general population. (14,16)

2.2 Primary outcome

The primary outcome is the participants' score to the French-validated JCQ questionnaire in the three dimensions – psychological demands, decision latitude, and social support (21). Job-demand and latitude decision making was assessed by the 26 items of the JCQ (nine for both decision latitude and psychological demand and eight for social support). The subject is asked to respond using a 4-level Likert-type scale for each item, ranging from 1 (strongly disagree) to 4 (strongly agree). The decision latitude is calculated with the following formula: 4*Q4 + 4*(5-Q6) + 4* Q8 + 2*(5-Q2) + 2*Q5 + 2*Q7 +2*Q1 + 2*Q3 + 2*Q9. A score below 71 reflects low decision latitude. The psychological demand is calculated with the following formula: Q10 + Q11 + Q12 + (5-Q13) + Q14 + Q15 + Q16 + Q17 + Q18. A score below 20 reflects a low psychological demand. Finally, the social support is calculated with the following formula: Q19 + Q20 + Q21 + Q22 + Q23 + Q24 + Q25 + Q26. A score below 24 reflects low social support (15). In a previous study performed by our team, the Cronbach's alphas for job demands, job control, and social support were 0.58, 0.99, and 0.99, respectively (22). By combining autonomy and demand, four broad categories are defined: Relaxed work: 1) Low demand, high autonomy; 2) Passive work: Low demand, low autonomy; 3) Active work: High demand, high autonomy and 4) Stressed, tense work: High demand, low autonomy. Furthermore, jobstrain is defined as a demand score higher than 21 and a control score less than 70 (16). Add a social support level < 24 define isostrain.

2.3 Secondary outcomes

We collected sociodemographic data such as age, sex, weight, height, kids at home and marital status. Physical activity (in hours per week) and sleep quantity (in hours) and quality using visual analog scale from 0 (bad quality) to 100 (good quality) of every HCWs were asked. We also collected information about the ED and hospital such as type of hospital (university or not). Lastly, seniority (within the ED, and as an emergency occupation). We defined the class "physician" if the

responder was attending, fellow or resident. We defined the class "paramedics" if the responder was nurse, caregiver, cleaner, or administrative job. We studied the impact on job-demand, job-control, social support, jobstrain and isostrain for each following criterion – sociodemographic, seniority, tobacco, coffee or tea, job, night versus day.

2.4 Statistics

No sample size was computed for this purpose as this is an ancillary study of the SEEK- protocol (NCT02401607, (23)), in which 192 subjects were included. We reused those data in order to assess Karasek's scores among eHCW. In this study 157 subjects were included. Study sample is described by frequency and percentage for categorical data and by mean ± standard deviation for continuous data when distribution was normal, or otherwise by median and interquartile range. The normality assumption was assessed graphically and using Shapiro–Wilk test. Comparison between groups (physicians vs paramedics) – considering the subject as statistical unit - were performed using Student's t-test (or Mann and Whitney test when data not normal) for continuous data and using chi^2 test (or Fisher's exact test when appropriate) for categorical data. Analyzes considering the measures (job control, job demand and social support) as statistical unit, considering repeated measures for some subjects, were performed using linear mixed models, with the subject as random effect, firstly in an univariate approach in order to identify characteristics associated with the 3 scores, and then in a multivariable linear mixed model, adjusting for factors statistically highlighted in univariate analysis or clinically relevant. Results are shown as regression coefficients and their 95% confidence interval. For job strain and iso strain outcomes, the process was similar but using logistic mixed model, and results presented as odds ratios and their 95% confidence interval. Statistics were performed using Stata (StataCorp 2019. Stata statistical software: Release 16. College Station, TX: StataCorp LLC.). A French Ethics committee (Comité de Protection de Personnes Sud-Est I, CHU Saint- Etienne) approved this study protocol on 3 November 2014, with reference DC-2014-2151. This protocol was registered in ClinicalTrials under the identification NCT02401607.

3 Results

3.1 Characteristics of population

We recruited 166 emergency HCWs from five French emergency departments, before the COVID-19 pandemic. Nine emergency HCWs were excluded because of pregnancy (n=4) and incomplete data (n=5) (Figure 1). A total of 157 emergency HCWs (53 physicians and 104 paramedics) were analyzed and compared with the 25 000 answers in French general population (controls from the SUMER study).(14,16) Emergency HCWs had a mean age of 37.5±10.5 years old: 35.5±10.5 among physicians and 38.5±10.3 among paramedics. There were 66 (42%) men: 27 (50.9%) men among physicians and 39 (37.5%) men among paramedics. Body mass index was 23.4±3.3 kg/m^2. Physicians had a median seniority of 3.5 [P25-P75: 1.5-10] years in the job and 1.25 [0.5-5] in the ED while paramedics had 10 [4-17] years in the job and 4 [1-11] years in the ED. They drank 3 [2-4.5] cups of coffee or tea per day and performed 3 [1-4] hours of physical activity per week. Table 1 describe all sociodemographic. Twenty-six of them performed the study twice, so we were able to analyze 183 surveys.

	Total n=157	Physician n=53	Paramedics n=104	p-value
Age (years), mean±SD	37.5±10.5	35.5±10.5	38.5±10.3	**0.046**
Men, n (%)	66 (42.0)	27 (50.9)	39 (37.5)	0.11
Physical activity (hours/week), median [IQR]	3 [2-4]	3 [2-5.5]	3 [2-4]	0.71
Body Mass Index (kg/m^2), mean±SD	23.4±3.5	23.3±2.9	23.5±3.8	0.94
Underweight, n (%)	8 (5.2)	2 (3.9)	6 (5.8)	
Normal weight, n (%)	105 (67.7)	37 (71.2)	68 (66.0)	
Overweight, n (%)	37 (23.9)	13 (25.0)	24 (23.3)	
Obesity class 1, n (%)	4 (2.6)	0	4 (3.9)	
Obesity class 2, n (%)	1 (0.7)	0	1 (1.0)	
Seniority (years)				
Job, median [IQR]	6 [3-17]	3.5 [1.5-10]	10 [4-17]	**<0.001**
Department, median [IQR]	3 [1-10]	1.25 [0.5-5]	4 [1-11]	**0.003**
Type of hospital				0.19
General	74 (47.8)	20 (38.5)	54 (52.5)	
University	81 (52.3)	32 (61.5)	49 (47.6)	
Tea-Coffee (cup/shift), median [IQR]	3 [2-4.5]	4 [3-5]	3 [2-4.3]	0.14
Smoker, n (%)	52 (33.1)	15 (28.3)	37 (35.6)	0.36
Sleep at home quantity, (hours), mean±SD	7.3±1.1	7.2±0.9	7.3±1.2	0.99
Sleep at home quality (VAS), mean±SD	68.5±20.3	73.0±19.5	66.3±20.4	0.065
Family situation				0.28
Single-divorced, n (%)	50 (32.1)	20 (37.7)	30 (29.1)	
Married-engaged, n (%)	106 (67.9)	33 (62.3)	73 (70.9)	
Kids at home, n (%)	50 (39.7)	13 (30.2)	37 (44.6)	0.12

159

160 Table 1: Characteristic of the population. 157 eHCWs were included. Results are expressed in mean
161 ± standard deviation or number (percentage) or median [first quartile-third quartile], SD = standard
162 deviation, kg/m2 = kilogram per square meters, VAS = visual analog scale from 0 (badest quality
163 ever) to 100 (best quality ever). Results are significant if $p<0.05$

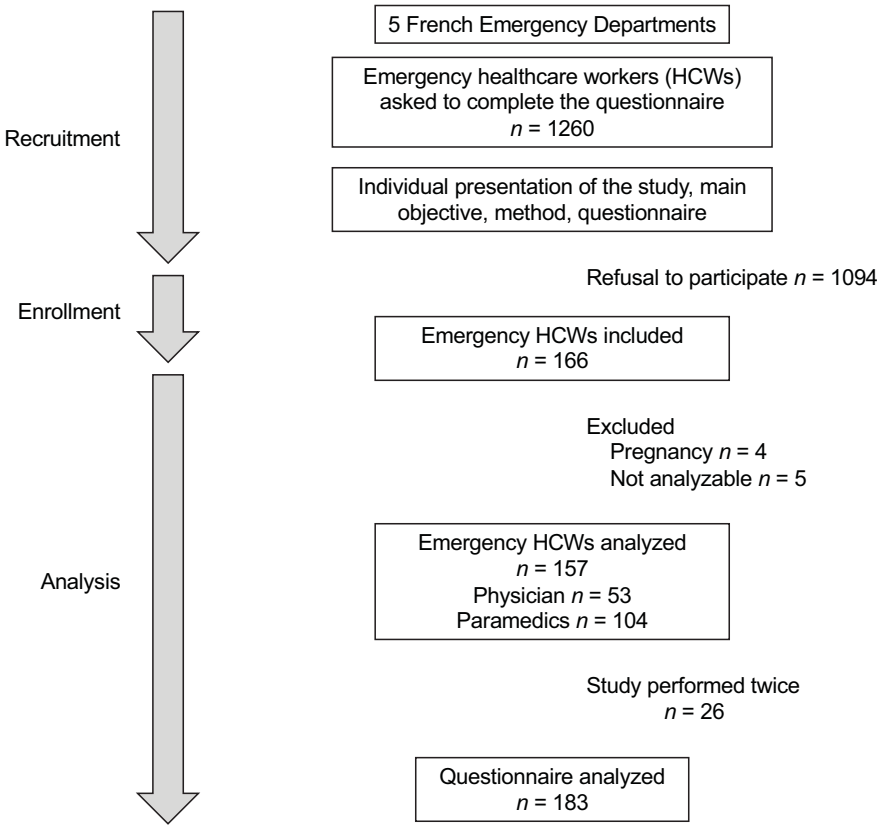


Figure 1. Study design. Among five French Emergency Departments we were able to recruit 192 emergency healthcare workers (HCWs). Nine were excluded because of pregnancy or no data completion. One hundred and eighty-three Karasek survey were analyzed from 157 emergency HCWs.

3.2 Main objective Job Content Questionnaire of Karasek

Job-demand was the highest for physicians (28.3±3.3) and paramedics (25.9±3.8), compared to controls (36.0±7.2) ($p<0.001$). Job-control was the lowest for physicians (61.2±5.8) and paramedics (59.1±6.8), compared to controls (70.4±11.7) ($p<0.001$). Mean social support did not differ between groups (23.6±3.4 for physicians, 22.6±2.9 for paramedics, and 23.7±3.6 for controls) (Figure 2). The prevalence of job-strain was massively higher for physicians (95.8%) and paramedics (84.8%), compared to controls (23.9%) ($p<0.001$), as well as for isostrain (45.1% for physicians, 56.8% for paramedics, and 14.3% for controls, $p<0.001$) (Figure 3, 4 and 5).

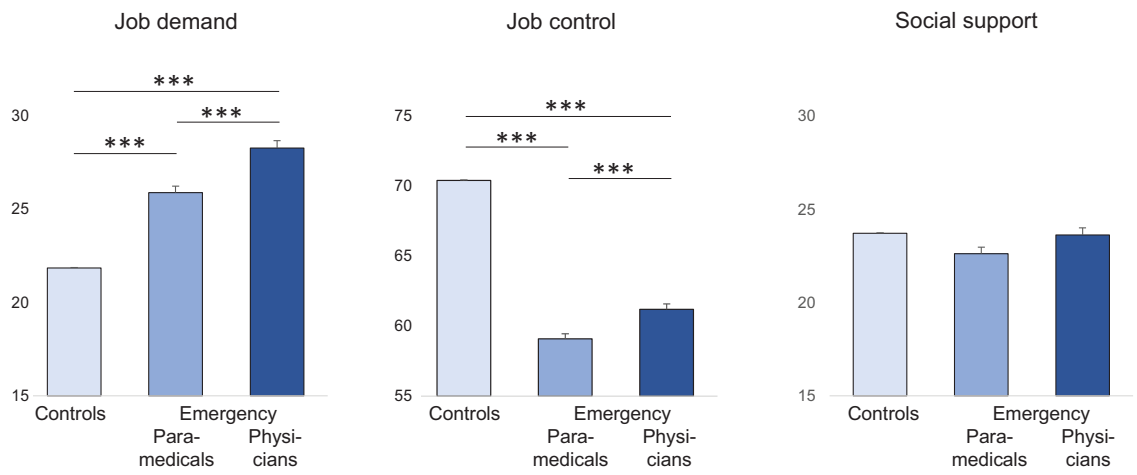


Figure 2. Comparison of job demand, job control, and social between controls (SUMER), paramedics and emergency physicians from emergency departments. ***=p<0.001. Results are significant if p<0.05.

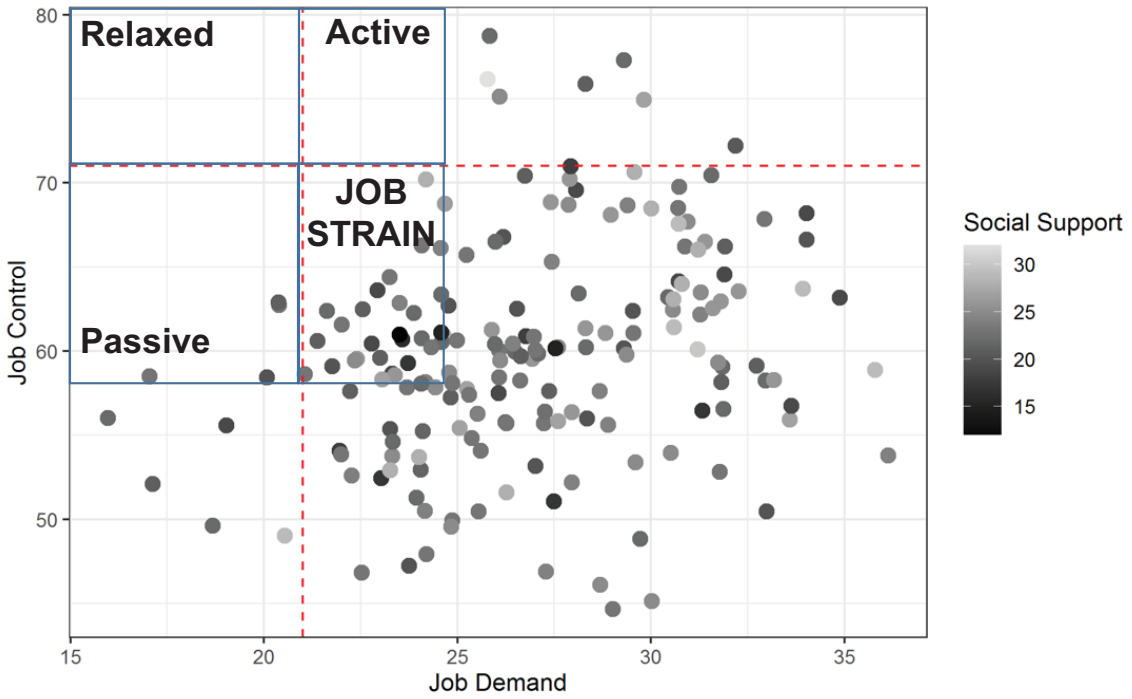
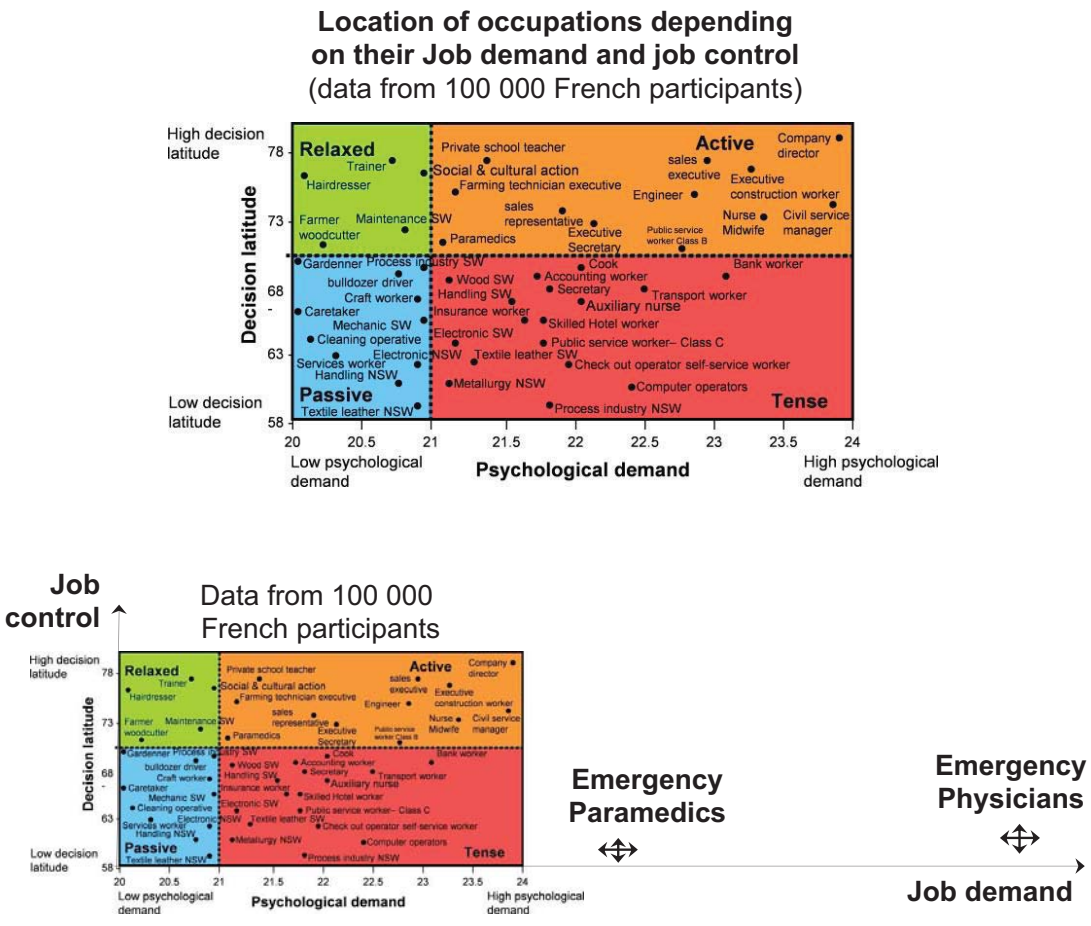


Figure 3. All occupations from SUMER studies (>100 000 French participants) were within the four colored quadrants. Each dot represents an emergency healthcare worker from our study. Darker dots represent a lower social support. Study of the validity of a job-exposure matrix for psychosocial work factors: results from the national French SUMER survey. Int Arch Occup Environ Health 82: 87-97; 15. Niedhammer I, Chastang JF, Gendrey L, David S, Degioanni S (2006) [Psychometric properties of the French version of Karasek's "Job Content Questionnaire" and its scales measuring

188 psychological pressures, decisional latitude and social support: the results of the SUMER]. Sante
189 Publique 18: 413-427



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191 Figure 4. Representation of emergency physician and paramedicals compared to other jobs. Results
192 of other jobs are from the Study of the validity of a job-exposure matrix for psychosocial work
193 factors: results from the national French SUMER survey. Int Arch Occup Environ Health 82: 87-97;
194 15. Niedhammer I, Chastang JF, Gendrey L, David S, Degioanni S (2006) [Psychometric properties
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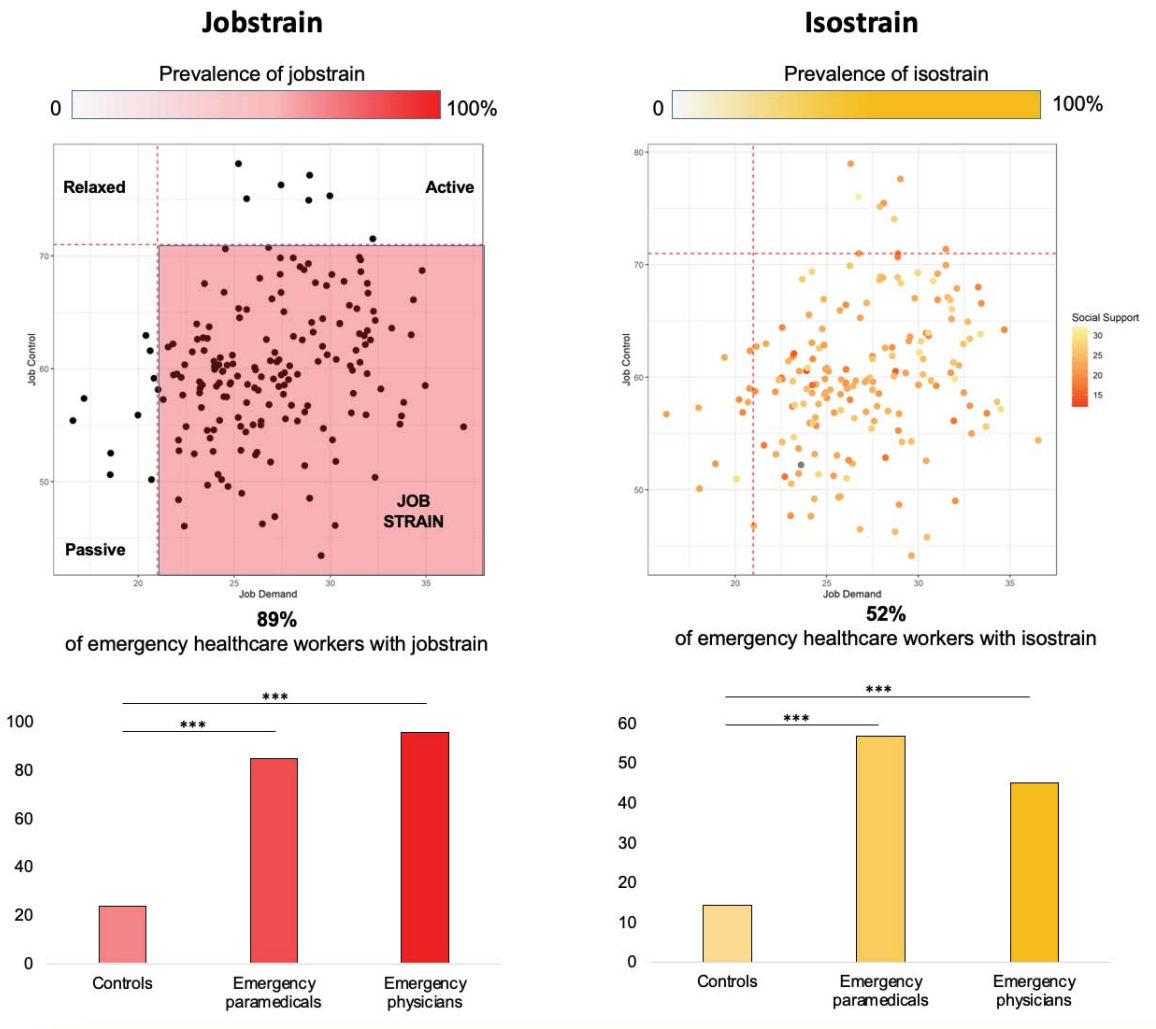

Figure 5. Prevalence of jobstrain and isostrain among our population of emergency healthcare workers. *** = p<0.001. Results are significant if p<0.05. Patients are considered in jobstrain if job demand is > 21 and job control < 70. Patients are considered in isostrain if they have jobstrain and social support < 24.

Variables	Coefficient (95% CI)		p-value
Job control - continuous data			
Age, year	-0.02	(-0.11, 0.08)	0.97
BMI, kg/m2	0.18	(-0.10, 0.47)	0.21
Sex, male	1.47	(-0.53, 3.47)	0.15
Seniority in the ED, year	0.08	(-0.05, 0.21)	0.25
Seniority in the job, year	0.01	(-0.10, 0.10)	0.90
Tobbacco	0.42	(-1.69, 2.52)	0.70
Coffee, tea, cup per day	0.06	(-0.18, 0.30)	0.61
No kids at home vs kids as REF	0.23	(-2.02, 2.48)	0.84
Engaged vs single as REF	1.01	(-1.14, 3.16)	0.36
Physician vs paramedics as REF	1.76	(-0.29, 3.82)	0.093
Job demand - continuous data			
Age, year	0.01	(-0.05, 0.06)	0.80
BMI, kg/m2	-0.14	(-0.30, 0.27)	0.10
Sex, male	-0.80	(-1.97, 0.37)	0.18
Seniority in the ED, year	0.02	(-0.06, 0.10)	0.63
Seniority in the job, year	-0.04	(-0.09, 0.02)	0.17
Tobbacco	0.46	(-0.76, 1.69)	0.46
Coffee, tea, cup per day	-0.03	(-0.17, 0.11)	0.64
No kids at home vs kids as REF	0.87	(-0.42, 2.17)	0.19
Engaged vs single as REF	0.52	(-0.73, 1.77)	0.41
Physician vs paramedics as REF	2.36	(1.20, 3.51)	**<0.001**
Social support - continuous data			
Age, year	0.04	(-0.01, 0.08)	0.11
BMI, kg/m2	-0.04	(-0.17, 0.10)	0.62
Sex, male	0.11	(-0.86, 1.08)	0.82
Seniority in the ED, year	0.04	(-0.03, 0.10)	0.25
Seniority in the job, year	0.02	(-0.03, 0.07)	0.43
Tobbacco	0.87	(-0.14, 1.87)	0.092
Coffee, tea, cup per day	-0.02	(-0.13, 0.09)	0.75
No kids at home vs kids as REF	0.65	(-0.34, 1.64)	0.20
Engaged vs single as REF	0.32	(-0.70, 1.35)	0.53
Physician vs paramedics as REF	0.91	(-0.09, 1.91)	0.075

Variables	Odds Ratio (95% CI)		p-value
Jobstrain			
Age, years	0.97	(0.93, 1.02)	0.23
Body mass index, kg/m2	0.98	(0.86, 1.11)	0.72
Sex, male	0.73	(0.29, 1.86)	0.52
Kids at home vs no kids as REF	1.28	(0.44, 3.74)	0.65
Single vs engaged as REF	1.31	(0.49, 3.51)	0.58
Seniority in the job, years	0.96	(0.92, 0.99)	**0.043**
Seniority in the ED, years	0.96	(0.91, 1.01)	0.13
Tobacco	0.74	(0.29, 1.93)	0.54
Coffe or tea, cup/day	0.89	(0.81, 0.98)	**0.013**
Physician vs paramedics as REF	1.43	(0.54, 3.78)	0.47
Isostrain			
Age, years	0.94	(0.87, 1.01)	0.11
Body mass index, kg/m2	0.91	(0.75, 1.11)	0.38
Sex, male	0.90	(0.23, 3.43)	0.87
Kids at home vs no kids as REF	0.21	(0.04, 1.07)	0.060
Single vs engaged as REF	0.28	(0.06, 1.34)	0.11
Seniority in the job, years	0.96	(0.90, 1.03)	0.30
Seniority in the ED, years	0.99	(0.90, 1.07)	0.75
Tobacco	0.27	(0.06, 1.26)	0.096
Coffe or tea, cup/day	1.00	(0.86, 1.15)	0.98
Physician vs paramedics as REF	0.45	(0.11, 1.83)	0.27

Figure 6. Impact of sociodemographic on quantitative data (job control, job demand, social support) and qualitative data (jobstrain, isostrain). Results about quantitative data are a coefficient and those about qualitative data are in Odds Ratio.

3.3 Impact of sociodemographic

Mixed models showed that physicians have a higher level of job control, job demand but also social support (Figure 5). They were also more in jobstrain compared to paramedic HCWs. Drinking coffee and experience decrease jobstrain (OR=0.89; 0.81 to 0.98 and 0.96, 0.92 to 0.99, respectively). Although not significant, kids seem to be a protective factor of isostrain (OR=0.21, 0.04 to 1.07). We did not find any significant impact of age, BMI, sex, tobacco, coffee or seniority on job control, job demand or social support (Figure 6)

4 Discussion

The main findings were a dramatic rate of jobstrain among emergency HCWs due to an association of high job demand with a low job control. Fortunately, the relatively high social support between emergency HCWs seem to counterbalance their high jobstrain.

4.1 Karasek's model

A recent study proposed to use visual analog scale to be more effective than the long survey (24). According to the SUMER study that assessed Karasek's survey among 25,000 French employees, the French version of the survey has a good validity, especially for job control (16). However, no emergency HCW was included in this study. A high psychological demand is defined by a job-demand higher to 21. Emergency HCWs are therefore in a situation that could be qualify as "non-standard" compared to the French population. Indeed, mean job-demand was 20.99 when we found 26.3. Furthermore, they have a low job-control, i.e., less than 70. French population had a 70.32 level of job-control when our population had a 59.9 level. Finally, the score obtained for the social support item is almost identical between the SUMER study and our population (23.34 vs 23.0). Regarding job strain, we found an extreme score of 89.1% vs 23.9% in the SUMER study (16). Considering that job-strain is a risk factor for musculoskeletal pain (25), coronary heart disease (26,27), type 2 diabetes mellitus (28), cancer (29), depression (30), burnout (31) and mortality (32), our results are alarming but some explanations could be done. Indeed, this feeling of a tense situation at work is probably linked to frequent the number of tense relations with the public, overcrowding, lack of bed available, stressful event, patient's stress, manual handling or even time constraints (4–6). Another explanation is stress contagion. Indeed, stress, like all other emotions is contagious (33). This contagion can be between caregivers, but also between patients and HCWs (34). Considering that consulting in an ED is a stressful event, it could be relevant to adjust HCWs' stress level with patient's level. Furthermore, it seems that physicians can absorbed joy and anger from their colleagues and nurses from leaders, colleagues, and patients. Joy and anger-absorbed were related to physician's exhaustion and cynicism (35).

4.2 All emergency HCWs, but more especially physicians

We compared EPs and other emergency HCWs and we showed that physicians have a higher score of job-demand, job-control but also social support. Furthermore, we found a higher rate of jobstrain and isostrain. Previous studies have showed that nurses have a high cognitive and sensory demands with

a low degree of freedom at work, a lack of autonomy, numerous duties great meaning and commitment to work, less social support and lack of feedback at work (36–38). Although the concept of shared medical decision-making exists since decades, it is poorly used in daily practice between nurses and physicians (39). Indeed, this requires decision-making on a multi-daily basis leading, in the very short term, to a vital stake in the state of health of patients, and this in a context of stress reinforced by the increasingly frequent recourse to justice in the event of a medical error (40). The physician, compared to other emergency HCWs, retains the central role of decision-maker, which can partially explain the obtaining of a higher score versus other emergency HCWs. Furthermore, nurses share the belief that the physician should decide and the patient should rely on his knowledge rather than his own (41). Lastly, some studies found a direct link between physician burnout (which jobstrain is one of the main risk factor) and adverse patient outcomes (42). This known, it increases the stress of the physician, which increase the jobstrain and the vicious circle begins. Although we found a higher rate of isostrain, we also found a higher level of social support among physicians compared to other emergency HCWs. HCWs and especially physicians have a long history of support between them, sometimes considered as confraternity or brotherhood (43,44). Social support can have an important impact on care because it partially mediates the relationship between physician burnout and behavior-based professionalism (45). Furthermore, it is a target to improve quality of life and decrease burnout (46,47).

4.3 Limitations

Our study has some limitations. Questionnaires were filled out by volunteers and a selection bias may have occurred, however the large sample size may limit this bias, as well as the multicentric recruitment (48). As for all questionnaires, self-reported information may over- or under-estimate sensations of job demand, job control, and social support. This study was performed before the COVID pandemic (5,6), limiting heterogeneity between measurements time. However, repetition in the near future of the collection of data may promote a longitudinal follow-up of emergency HCWs. Although the JDC model of Karasek is the gold standard to assess psychosocial risks at work (8), its length makes it difficult to use routinely in daily clinical practice by occupational practitioners and we recently proposed a validation of visual analog scales of job-demand and job-control (24). Unfortunately, we failed to demonstrate the putative influence of some sociodemographic on jobstrain or isostrain, except for the role of seniority within the job that decreased the risk of jobstrain, in accordance with literature (49). We also found that coffee consumption is linked with a lower feeling of jobstrain, which could be explained by the anti-stress properties of caffeine (50).

5 Conclusion

We found a dramatic rate of jobstrain among emergency healthcare workers that could possibly be explained by several factors such as overcrowding, lack of time and shift work. It is now time to take care of our providers if we want to keep them happy at work.

6 Author contribution

Conceptualization, J.-B.B.-M. and F.D.; methodology, J.-B.B.-M., M.T., J.S., and F.D.; formal analysis, A.M.; investigation, M.B., F.M., F.D. and J.S.; data curation, F.D.; writing—original draft preparation, J.-B.B.-M.; writing—review and editing, D.T., M.T., A.M., O.J.A., D.T., U.C.U., M.B., F.M., M.C., G.T.V., M.Z. and C.O.; visualization, J.-B.B.-M, A.M., and F.D. All authors have read and agreed to the published version of the manuscript.

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9 Reference styles

1. West CP, Dyrbye LN, Erwin PJ, Shanafelt TD. Interventions to prevent and reduce physician burnout: a systematic review and meta-analysis. *Lancet* (2016) 388:2272–2281. doi: 10.1016/S0140-6736(16)31279-X

2. Dutheil F, Danini B, Bagheri R, Fantini ML, Pereira B, Moustafa F, Trousselard M, Navel V. Effects of a Short Daytime Nap on the Cognitive Performance: A Systematic Review and Meta-Analysis. *Int J Environ Res Public Health* (2021) 18:10212. doi: 10.3390/ijerph181910212

3. Bouillon-Minois J-B, Thivel D, Croizier C, Ajebo É, Cambier S, Boudet G, Adeyemi OJ, Ugbolue UC, Bagheri R, Vallet GT, et al. The Negative Impact of Night Shifts on Diet in Emergency Healthcare Workers. *Nutrients* (2022) 14:829. doi: 10.3390/nu14040829

4. Dutheil F, Boudet G, Perrier C, Lac G, Ouchchane L, Chamoux A, Duclos M, Schmidt J. JOBSTRESS study: comparison of heart rate variability in emergency physicians working a 24-hour shift or a 14-hour night shift - a randomized trial. *Int J Cardiol* (2012) 158:322–5. doi: 10.1016/j.ijcard.2012.04.141

5. Bouillon-Minois J-B, Schmidt J, Dutheil F. SARS-CoV-2 pandemic and emergency medicine: The worst is yet to come. *Am J Emerg Med* (2020) doi: 10.1016/j.ajem.2020.06.014

6. Bouillon-Minois J-B, Raconnat J, Clinchamps M, Schmidt J, Dutheil F. Emergency Department and Overcrowding During COVID-19 Outbreak; a Letter to Editor. *1* (2021) 9:e28–e28. doi: 10.22037/aaem.v9i1.1167

7. Karasek RA. Job demands, job decision latitude, and mental strain : implications for job redesign. *Adm Sci Q* (1979) 24:285–308.

8. Karasek R, Baker D, Marxer F, Ahlbom A, Theorell T. Job decision latitude, job demands, and cardiovascular disease: a prospective study of Swedish men. *Am J Public Health* (1981) 71:694–705.

9. Theorell T, Karasek RA. Current issues relating to psychosocial job strain and cardiovascular disease research. *J Occup Health Psychol* (1996) 1:9–26.

10. Fan W, Moen P, Kelly EL, Hammer LB, Berkman LF. Job Strain, Time Strain, and Well-Being: A Longitudinal, Person-Centered Approach in Two Industries. *J Vocat Behav* (2019) 110:102–116. doi: 10.1016/j.jvb.2018.10.017

11. Durand A-C, Bompard C, Sportiello J, Michelet P, Gentile S. Stress and burnout among professionals working in the emergency department in a French university hospital: Prevalence and associated factors. *Work* (2019) 63:57–67. doi: 10.3233/WOR-192908

12. Stansfeld S, Candy B. Psychosocial work environment and mental health--a meta-analytic review. *Scand J Work Environ Health* (2006) 32:443–462. doi: 10.5271/sjweh.1050

13. Ganster DC, Fusilier MR, Mayes BT. Role of social support in the experience of stress at work. *J Appl Psychol* (1986) 71:102–10.

14. Niedhammer I, Milner A, Geoffroy-Perez B, Coutrot T, LaMontagne AD, Chastang J-F. Psychosocial work exposures of the job strain model and cardiovascular mortality in France: results from the STRESSJEM prospective study. *Scand J Work Environ Health* (2020) 46:542–551. doi: 10.5271/sjweh.3902

15. Karasek R, Brisson C, Kawakami N, Houtman I, Bongers P, Amick B. The Job Content Questionnaire (JCQ): an instrument for internationally comparative assessments of psychosocial job characteristics. *J Occup Health Psychol* (1998) 3:322–55.

16. Niedhammer I, Chastang J-F, Levy D, David S, Degioanni S, Theorell T. Study of the validity of a job-exposure matrix for psychosocial work factors: results from the national French SUMER survey. *Int Arch Occup Environ Health* (2008) 82:87–97. doi: 10.1007/s00420-008-0311-7

17. Cocker F, Joss N. Compassion Fatigue among Healthcare, Emergency and Community Service Workers: A Systematic Review. *Int J Environ Res Public Health* (2016) 13: doi: 10.3390/ijerph13060618

18. Hall LH, Johnson J, Watt I, Tsipa A, O'Connor DB. Healthcare Staff Wellbeing, Burnout, and Patient Safety: A Systematic Review. *PLoS One* (2016) 11:e0159015. doi: 10.1371/journal.pone.0159015

19. Theorell T, Hammarstrom A, Aronsson G, Traskman Bendz L, Grape T, Hogstedt C, Marteinsdottir I, Skoog I, Hall C. A systematic review including meta-analysis of work environment and depressive symptoms. *BMC Public Health* (2015) 15:738. doi: 10.1186/s12889-015-1954-4

20. Matthews TA, Robbins W, Preisig M, von Känel R, Li J. Associations of job strain and family strain with risk of major depressive episode: A prospective cohort study in U.S. working men and women. *J Psychosom Res* (2021) 147:110541. doi: 10.1016/j.jpsychores.2021.110541

21. Brisson C, Blanchette C, Guimont C, Dion G, Moisan J, Vézina M, Dagenais GR, Masse L. Reliability and validity of the French version of the 18-item Karasek Job Content Questionnaire. *Work Stress* (1998) 12:322–36.

22. Dutheil F, Charkhabi M, Ravoux H, Brousse G, Dewavrin S, Cornet T, Mondillon L, Han S, Pfabigan D, S Baker J, et al. Exploring the Link between Work Addiction Risk and Health-Related Outcomes Using Job-Demand-Control Model. *Int J Environ Res Public Health* (2020) 17: doi: 10.3390/ijerph17207594

23. Bouillon-Minois J-B, Trousselard M, Pereira B, Schmidt J, Clinchamps M, Thivel D, Ugbolue UC, Moustafa F, Occelli C, Vallet G, et al. Protocol of the Study on Emergency Health Care Workers' Responses Evaluated by Karasek Questionnaire: The SEEK-Study Protocol. *Int J Environ Res Public Health* (2021) 18:4068. doi: 10.3390/ijerph18084068

24. Dutheil F, Pereira B, Bouillon-Minois J-B, Clinchamps M, Brousses G, Dewavrin S, Cornet T, Mermillod M, Mondillon L, Baker JS, et al. Validation of Visual Analogue Scales of job demand and job control at the workplace: a cross-sectional study. *BMJ Open* (2022) 12:e046403. doi: 10.1136/bmjopen-2020-046403

25. Amiri S, Behnezhad S. Is job strain a risk factor for musculoskeletal pain? A systematic review and meta-analysis of 21 longitudinal studies. *Public Health* (2020) 181:158–167. doi: 10.1016/j.puhe.2019.11.023

26. Aboa-Eboulé C, Brisson C, Maunsell E, Mâsse B, Bourbonnais R, Vézina M, Milot A, Théroux P, Dagenais GR. Job strain and risk of acute recurrent coronary heart disease events. *JAMA* (2007) 298:1652–1660. doi: 10.1001/jama.298.14.1652

27. Rugulies R, Framke E, Sørensen JK, Svane-Petersen AC, Alexanderson K, Bonde JP, Farrants K, Flachs EM, Magnusson Hanson LL, Nyberg ST, et al. Persistent and changing job strain and risk of coronary heart disease. A population-based cohort study of 1.6 million employees in Denmark. *Scand J Work Environ Health* (2020) 46:498–507. doi: 10.5271/sjweh.3891

28. Li W, Yi G, Chen Z, Dai X, Wu J, Peng Y, Ruan W, Lu Z, Wang D. Is job strain associated with a higher risk of type 2 diabetes mellitus? A systematic review and meta-analysis of prospective cohort studies. *Scand J Work Environ Health* (2021) doi: 10.5271/sjweh.3938

29. Vesterlund GK, Høeg BL, Johansen C, Heitmann BL, E Bidstrup P. Prolonged job strain and subsequent risk of cancer in women - a longitudinal study, based on the Danish Nurse Cohort. *Acta Oncol* (2017) 56:301–306. doi: 10.1080/0284186X.2016.1267399

30. Madsen IEH, Nyberg ST, Magnusson Hanson LL, Ferrie JE, Ahola K, Alfredsson L, Batty GD, Bjorner JB, Borritz M, Burr H, et al. Job strain as a risk factor for clinical depression: systematic review and meta-analysis with additional individual participant data. *Psychol Med* (2017) 47:1342–1356. doi: 10.1017/S003329171600355X

31. Clinchamps M, Auclair C, Prunet D, Pfabigan D, Lesage F-X, Baker JS, Parreira L, Mermillod M, Gerbaud L, Dutheil F. Burnout Among Hospital Non-Healthcare Staff: Influence of Job Demand-Control-Support, and Effort-Reward Imbalance. *J Occup Environ Med* (2021) 63:e13–e20. doi: 10.1097/JOM.0000000000002072

32. Amiri S, Behnezhad S. Job strain and mortality ratio: a systematic review and meta-analysis of cohort studies. *Public Health* (2020) 181:24–33. doi: 10.1016/j.puhe.2019.10.030

33. Peen NF, Duque-Wilckens N, Trainor BC. Convergent neuroendocrine mechanisms of social buffering and stress contagion. *Horm Behav* (2021) 129:104933. doi: 10.1016/j.yhbeh.2021.104933

34. Faessler L, Brodbeck J, Schuetz P, Haubitz S, Mueller B, Perrig-Chiello P. Medical patients' affective well-being after emergency department admission: The role of personal and social resources and health-related variables. *PLoS One* (2019) 14:e0212900. doi: 10.1371/journal.pone.0212900

35. Petitta L, Jiang L, Härtel CEJ. Emotional contagion and burnout among nurses and doctors: Do joy and anger from different sources of stakeholders matter? *Stress Health* (2017) 33:358–369. doi: 10.1002/smi.2724

36. Freimann T, Merisalu E. Work-related psychosocial risk factors and mental health problems amongst nurses at a university hospital in Estonia: a cross-sectional study. *Scand J Public Health* (2015) 43:447–452. doi: 10.1177/1403494815579477

37. Nourollahi-Darabad M, Afshari D, Chinisaz N. Psychosocial Factors Associated With Resilience Among Iranian Nurses During COVID-19 Outbreak. *Front Public Health* (2021) 9:714971. doi: 10.3389/fpubh.2021.714971

38. Ilić IM, Arandjelović MŽ, Jovanović JM, Nešić MM. Relationships of work-related psychosocial risks, stress, individual factors and burnout - Questionnaire survey among emergency physicians and nurses. *Med Pr* (2017) 68:167–178. doi: 10.13075/mp.5893.00516

39. House S, Havens D. Nurses' and Physicians' Perceptions of Nurse-Physician Collaboration: A Systematic Review. *J Nurs Adm* (2017) 47:165–171. doi: 10.1097/NNA.0000000000000460

40. Sabroe I, Mather S, Wilson A, Hall-Flavin DK, Fricker M, Barron LA, Millard C. Error, injustice, and physician wellbeing. *Lancet* (2021) 397:872–873. doi: 10.1016/S0140-6736(21)00512-2

41. Cantaert GR, Van Hecke A, Smolderen K. Perceptions of physicians, medical and nursing students concerning shared decision-making: a cross-sectional study. *Acta Clin Belg* (2021) 76:1–9. doi: 10.1080/17843286.2019.1637487

42. Mangory KY, Ali LY, Rø KI, Tyssen R. Effect of burnout among physicians on observed adverse patient outcomes: a literature review. *BMC Health Serv Res* (2021) 21:369. doi: 10.1186/s12913-021-06371-x

43. Hartling O. [Collegiality, brotherhood and confidentiality]. *Ugeskr Laeger* (2013) 175:1363.

44. Macrae A. The brotherhood of medicine. *Br Med J* (1954) 1:25–27.

45. Song X, Li H, Jiang N, Song W, Ding N, Wen D. The mediating role of social support in the relationship between physician burnout and professionalism behaviors. *Patient Educ Couns* (2021) 104:3059–3065. doi: 10.1016/j.pec.2021.04.025

46. Linos E, Lasky-Fink J, Halley M, Sarkar U, Mangurian C, Sabry H, Linos E, Jagsi R. Impact of Sexual Harassment and Social Support on Burnout in Physician Mothers. *J Womens Health (Larchmt)* (2022) 31:932–940. doi: 10.1089/jwh.2021.0487

47. Velando-Soriano A, Ortega-Campos E, Gómez-Urquiza JL, Ramírez-Baena L, De La Fuente EI, Cañadas-De La Fuente GA. Impact of social support in preventing burnout syndrome in nurses: A systematic review. *Jpn J Nurs Sci* (2020) 17:e12269. doi: 10.1111/jjns.12269

48. Jo D. The interpretation bias and trap of multicenter clinical research. *Korean J Pain* (2020) 33:199–200. doi: 10.3344/kjp.2020.33.3.199

436 49. Dutheil F, Marhar F, Boudet G, Perrier C, Naughton G, Chamoux A, Huguet P, Mermillod M,
437 Saadaoui F, Moustafa F, et al. Maximal tachycardia and high cardiac strain during night shifts
438 of emergency physicians. *Int Arch Occup Environ Health* (2017) doi: 10.1007/s00420-017-
439 1211-5

440 50. Papakonstantinou E, Kechribari I, Sotirakoglou K, Tarantilis P, Gourdomichali T, Michas G,
441 Kravvariti V, Voumvourakis K, Zampelas A. Acute effects of coffee consumption on self-
442 reported gastrointestinal symptoms, blood pressure and stress indices in healthy individuals.
443 *Nutr J* (2016) 15:26. doi: 10.1186/s12937-016-0146-0

444

3. **Conclusion**

Nous avons montré une forte prévalence de soignants de l'urgence en situation de jobstrain et d'isostrain, confirmant notre postulat de départ et des niveaux bien supérieurs à ceux en population générale (étude SUMER).

ETUDE 3
« The negative impact of night shifts on diet in emergency healthcare workers »

1. Introduction

Cet article représente l'objectif principal que je m'étais fixé en commençant ce travail. En effet, comme expliqué dans l'introduction générale, je pense qu'un soignant travaillant la nuit doit toujours avoir à disposition de la nourriture à disposition et à forte valeur énergétique. Or, les frigidaires vides ou contenant de la nourriture à faible valeur nutritive sont monnaie courante. Je souhaitais donc utiliser la science pour prouver l'impact des gardes de nuit sur l'apport calorique ou qualitative des soignants. La méthode des questionnaires n'est certes pas parfaite mais permet de faire une première constatation. En effet, elle est soumise aux interprétations individuelles des quantités ingérées. Cependant, nous avons mis en place des procédures afin de réduire l'écart potentiel en montrant aux participants les tailles de portions et en refaisant la liste de l'ensemble des repas réalisés une fois la journée et le recueil réalisés

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2. Article

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The Negative Impact of Night Shifts on Diet in Emergency Healthcare Workers

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Abstract: Despite the consequences of night-shift work, the diet of night-shift workers has not been widely studied. To date, there are no studies related to food intake among emergency healthcare workers (HCWs). We performed a prospective observational study to assess the influence of night work on the diet of emergency HCWs. We monitored 24-h food intake during a day shift and the consecutive night, and during night work and the daytime beforehand. We analyzed 184 emergency HCWs' food intakes. Emergency HCWs had 14.7% lower (−206 kcal) of their 24-h energy intake during night shifts compared to their day-shift colleagues (1606.7 ± 748.2 vs. 1400.4 ± 708.3 kcal, $p = 0.049$) and a 16.7% decrease in water consumption (1451.4 ± 496.8 vs. 1208.3 ± 513.9 mL/day, $p = 0.010$). Compared to day shifts, night-shift had 8.7% lower carbohydrates, 17.6% proteins, and 18.7% lipids. During the night shift the proportion of emergency HCWs who did not drink for 4 h, 8 h and 12 h increased by 20.5%, 17.5%, and 9.1%, respectively. For those who did not eat for 4 h, 8 h and 12 h increased by 46.8%, 27.7%, and 17.7%, respectively. A night shift has a huge negative impact on both the amount and quality of nutrients consumed by emergency healthcare workers.

Keywords: nutrients; work; well-being; quality of life; prevention; public health

1. Introduction

According to the International Labor Organization, night work is defined as "all work which is performed during a period of not less than seven consecutive hours, including the interval from midnight to 5 a.m." [1]. In 2020 in Europe, 22% of men and 11% of women worked on shifts that included night work [2], including healthcare workers (HCWs) [2,3].

Night work has many health consequences, from disturbance of the circadian rhythm [4], to obesity and cardiometabolic disorders [5–10]. Interestingly, eating disorders are also associated with those pathologies, potentially enhancing the synergistic effect between night work and eating disorders [11]. Additionally, night-shift workers tend to have more irregular eating habits than their day colleagues [12]. Night work also induces a conflict between socially determined diurnal mealtimes, eating habits, the biological rhythm of hunger, satiety, and metabolism [13,14]. Some findings showed that meal timing and meal size have an impact on cognitive performance and subjective sleepiness among night-shift workers. Some programs proposed to avoid large meals during the beginning of a night shift and to opt for a small snack to improve performance during the night [15]. Lastly, eating behavior can be influenced by sociodemographic criteria such as age and gender [16], and by occupational characteristics such as experience [16] and workload [17,18]. Although nurses have been widely studied, no conclusion can be made and the existing epidemiological evidence on the relationship between night-shift work of nurses and their dietary habits is inadequate to draw any definite conclusions [19]. Emergency HCWs are a perfect example for studying the impact of night shifts [20]. Indeed, emergency departments (ED) are open 24 h a day, 365 days a year. Furthermore, emergency HCWs are working under stressful conditions such as overcrowding—lack of beds in hospitals [20], life-threatening emergencies [21], the wait for possible disasters [22] with consequences on biomarkers of stress [23,24]. Furthermore, the availability of food is much less important during the night compared to the day in a hospital. It is rarely fresh but often packaged reheated food with a bad presentation. However, food preparation and presentation appears to influence student consumption of school food and adult perception of school meal quality [25]. Given that emergency HCWs work under the time pressure of urgent care, they must both take care of patients and themselves i.e., finding the time to eat and drink. To the best of our knowledge, there are no studies that assessed the influence of night work on the diet among the population of emergency HCWs, nor in relation to their occupational characteristics.

Therefore, the main objective of our study was to assess the influence of night work on the diet of emergency HCWs. Secondary objectives were to study the impact of sociodemographic, and occupational characteristics on the diet of emergency HCWs.

2. Materials and Methods

2.1. Study Design

We performed a prospective nationwide observational study in five French hospitals—two university hospitals and three non-university hospitals. The main inclusion criterion was to work as an emergency HCW. Exclusion criteria were refusal to participate and pregnancy. This study is part of the SEEK protocol [20,22]. We obtained the ethical approval from Ethics Committee South-East I (DC-2014-2151) and the protocol was registered on ClinicalTrials.gov as number NCT02401607. Each participant had their food intake monitored twice over 24 consecutive hours: (1) during a day shift (from 8:30 a.m. to 6:30 p.m.) + the night (no work, 6:30 p.m. to 8.30 a.m.), and (2) during a rest day (from 8:30 a.m. to 6:30 p.m.) and a night shift (6:30 p.m. to 8:30 a.m.) (Figure 1). Participants also had to complete a questionnaire on their sociodemographic characteristics.

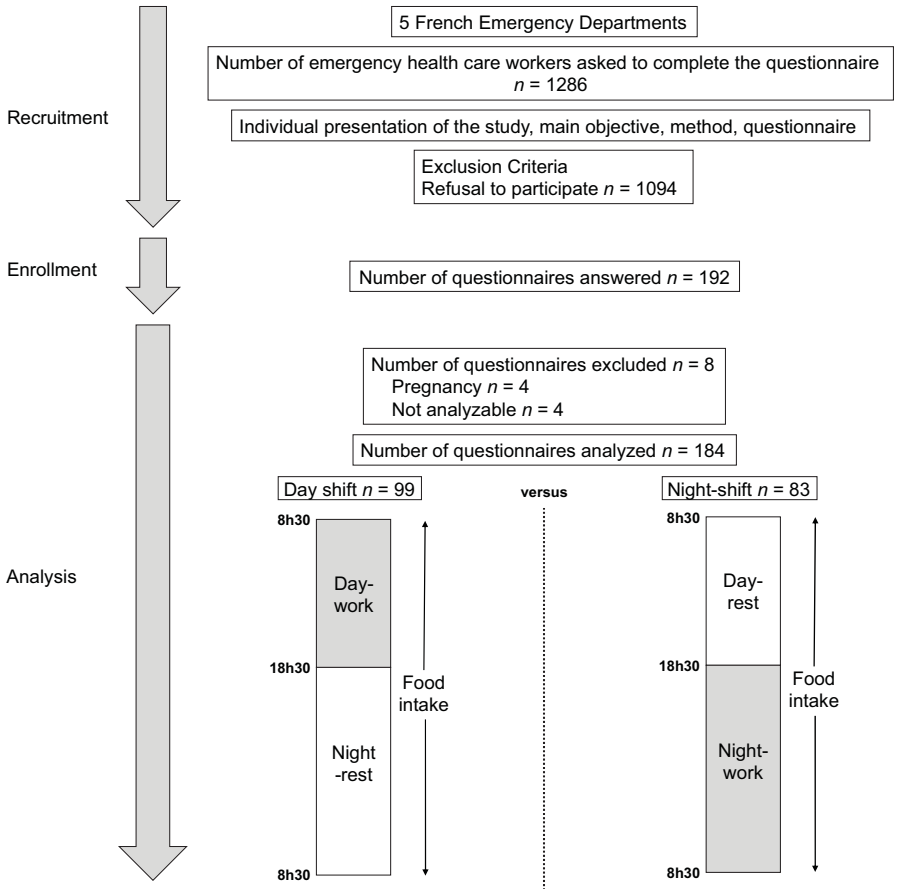

Figure 1. Study design. Among five French emergency departments we were able to recruit 192 emergency health care workers. Eight were excluded because of pregnancy or no data completion. Food intake was studied for 99 emergency health care workers during a day shift and 83 during a night shift.

2.2. Outcomes

Participants were asked to complete a 24-h dietary recall that was explained to them by a member of the investigation team. The participants were asked to indicate as precisely as possible all the details regarding the food ingested at each meal and in-between meals. The diaries were reviewed afterward with the participants during a dedicated interview. We next used Nutrilog® (version 3.2, Nutrilog, Marans, France), a diet and nutrition software for health care professionals, to translate participants' answers on nutrients intake using nutrition table Ciqual® on this software [26]. We retrieved total energy intake (kcal), glucids (grammes and % energy intake, and sugar), lipids (grammes and % energy intake, and simple, mono- and poly-unsaturated fatty acids), protids (grammes and % energy intake), calcium, cholesterol, fibres, and water. We further looked at time of intake and more specifically we calculated number of emergency HCWs that did not eat or drink for more than 4, 8, and 12 consecutive hours.

Participants had also to complete a short questionnaire to retrieve their sociodemographic (age, gender, marital status) and work characteristics (occupation, job seniority, and setting—university hospital or not).

2.3. Statistics

The main judgment criterion was food intake as quantitative variables. From personal experience and observation in a preliminary non-published study among 10 emergency

HCWs, there is at least a 20 ± 20% decrease in food intake during a night shift compared to a day shift, because of the increased working demands during a night shift due to fewer staff. Using this difference as the main outcome, we calculated that a sample size of 10 participants allowed a statistical power greater than 80% with an alpha level less than 5%.

Statistical procedures were performed with Stata software (v17, College Station, TX, USA). Quantitative variables were expressed as mean ± standard deviation (SD), and qualitative variables were expressed as number (%). The Gaussian distribution for each food intake variable was assessed by a Shapiro–Wilk test. Mean levels of each 24 h food intake variable were compared between night and day shifts using Wilcoxon (signed rank) tests. Association between food intake, sociodemographic (age, gender, marital status) and work characteristics (occupation, job seniority, and setting—university hospital or not), were assessed using Chi2 for categorical variables, and Spearman correlations for quantitative variables. The influence of shift condition, sociodemographic and work characteristics with each food intake variable were further assessed using univariate regressions—linear regressions for quantitative variables (coefficient and 95 confidence intervals—95% CI) and logistic regression for qualitative variables (odds ratio and 95% CI). Significance was set at the $p < 0.05$ level.

3. Results

We included 192 emergency HCWs from five hospitals. Four emergency HCWs were excluded because pregnancy and four for incomplete data. In total, we analyzed 184 emergency HCWs (Figure 1). Table 1 presents sociodemographic characteristics of the participants.

Table 1. Sociodemographic characteristics. SD = standard deviation, n = number of participants, cm = centimeters, kg = kilograms, kg/m^2 = kilogram per square meter.

	All	**Male**	**Female**
	***n* = 184**	***n* = 81**	***n* = 103**
Age, years	37.2 ± 10.2	37.8 ± 10.4	36.8 ± 10.1
Body Mass Index, kg/m^2	23.2 ± 3.9	24.3 ± 3.8	22.3 ± 3.7
Family situation			
Married/in couple	127 (69%)	57 (71.3%)	70 (68.0%)
Single	56 (30.4%)	23 (28.7%)	33 (32.0%)
Missing data	1 (0.6%)	1 (1.2%)	-
Children			
No children	86 (46.7%)	40 (49.4%)	46 (44.7%)
≥1 children	63 (42.3%)	27 (33.3%)	36 (34.8%)
Missing data	34 (18.4%)	14 (17.3%)	21 (20.4%)
Seniority, years			
As a provider	10.5 ± 10	10.5 ± 9.6	10.6 ± 10.4
In the hospital	9.9 ± 9.8	9.0 ± 9.0	10.6 ± 10.3
In the emergency department	6.4 ± 10	5.6 ± 6.5	6.9 ± 8.3

3.1. Main Objective: Impact of Night Shift on Alimentation

3.1.1. Quantitative Data

The night shift group of emergency HCWs reported a 14.7% (−206 kcal) lower 24-h energy intake compared to the day shift group (1606.7 ± 748.2 vs. 1400.4 ± 708.3 kcal, $p = 0.049$). Compared to day shifts, there were a 8.7% decrease among the night shift group of carbohydrates (178.8 ± 81.5 vs. 163.3 ± 86.0 g/day, $p = 0.120$), 17.6% of proteins (80.6 ± 30.3 vs. 66.4 ± 36.4 g/day, $p < 0.001$), 18.7% of lipids (75.1 ± 35.9 vs. 61.13 ± 32.7 g/day, $p = 0.030$), 18.2% of simple fatty acids (31.8 ± 16.1 vs. 26.0 ± 13.4 g/day, $p = 0.056$), 19.1% of monounsaturated fatty acids (25.6 ± 14.2 vs. 20.7 ± 14.2 g/day, $p = 0.049$), 20.9% of polyunsaturated fatty acids (7.7 ± 4.8 vs. 6.13 ± 4.5 g/day, $p = 0.050$),

13.9% of calcium (665.6 ± 249.3 vs. 573.3 ± 297.9 mg/day, $p = 0.049$), 12.5% of cholesterol (318.7 ± 238.9 vs. 278.7 ± 243.0 mg/day, $p = 0.161$), 11.7% of fiber (15.8 ± 7.1 vs. 13.9 ± 8.2 g/day, $p = 0.171$) and 16.7% of water consumption (1451.4 ± 496.8 vs. 1208.3 ± 513.9 mL/day, $p = 0.010$). (Table 2 and Figure 2).

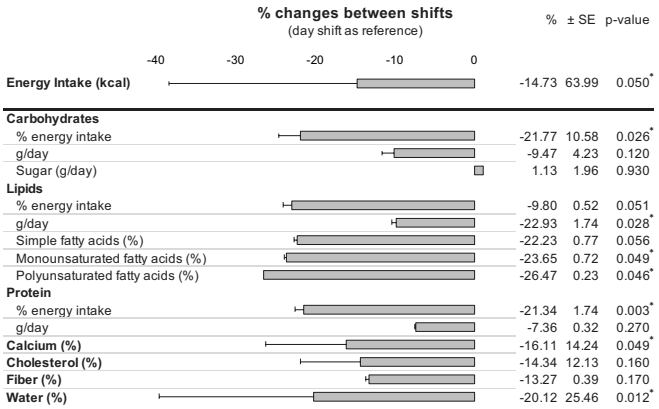

Figure 2. Food intake variations between night and day shifts. Differences in total energy intake, carbohydrates, lipids, protein, calcium, cholesterol, fiber, and water consumptions between day and night shifts among 184 questionnaires. Differences expressed in percentage with day shift as reference. Results: a night shift induces a decrease of all components related to daily ingesta except on sugar. SE standard error; *p*-value with * are significant (if <0.05).

Table 2. Impact of night shift on energy intake and water consumption among emergency health care workers. Kcal = kilocalories, g = gram, mg = milligrams, mL = milliliter, *p*-value with * are significant (if <0.05).

	All	**Day-Shift**	**Night-Shift**	**Comparisons between Shifts**
	***n* = 184**	***n* = 101**	***n* = 83**	***p*-Value**
Energy Intake (kcal)	1523.1 ± 737.0	1606.7 ± 748.2	1400.4 ± 708.3	0.049 *
Carbohydrates (g/day)	172.1 ± 83.5	178.8 ± 81.5	163.3 ± 86.0	0.120
Lipids (g/day)	69.1 ± 35.1	75.1 ± 35.9	61.13 ± 32.7	0.030 *
Simple fatty acid	29.3 ± 15.4	31.8 ± 16.1	26.0 ± 13.4	0.056
Monounsaturated fatty acid	23.4 ± 14.4	25.6 ± 14.2	20.7 ± 14.2	0.049 *
Polyunsaturated fatty acid	7.0 ± 4.7	7.7 ± 4.8	6.13 ± 4.5	0.050 *
Protein (g/day)	74.5 ± 33.7	80.6 ± 30.3	66.4 ± 36.4	<0.001 *
Cholesterol (mg/day)	301.3 ± 240.5	318.7 ± 238.9	278.7 ± 243.0	0.161
Fiber (g/day)	15.0 ± 7.6	15.8 ± 7.1	13.9 ± 8.2	0.171
Calcium (mg/day)	625.5 ± 274.2	665.6 ± 249.3	573.3 ± 297.9	0.049 *
Water (mL/day)	1345.8 ± 516.6	1451.4 ± 496.8	1208.3 ± 513.9	0.010 *

3.1.2. Qualitative Data

Overall during shifts, there were 38% of emergency HCWs who did not drink for 4 h, 19% for 8 h, and 5% for 12 h; and 46% who did not eat for 4 h, 27% for 8 h, and 9% for 12 h. More specifically, the night shift group of emergency HCWs reports a proportion of participants who did not drink for 4 h, 8 h and 12 h increased by 20.5% (50.0% vs. 29.5%, $p = 0.015$), 17.5% (29.3% vs. 11.5%, $p = 0.009$), and 9.1% (10.3% vs. 1.3%, $p = 0.018$) respectively. Similarly, the proportion of emergency HCWs who did not eat for 4 h, 8 h and 12 h was higher in the night shift group by 46.8% (72.4% vs. 25.6%, $p < 0.001$), 27.7% (43.1% vs. 15.4%, $p < 0.001$), and 17.7% (19.0% vs. 1.3%, $p < 0.001$) (Table 2 and Figure 3) respectively.

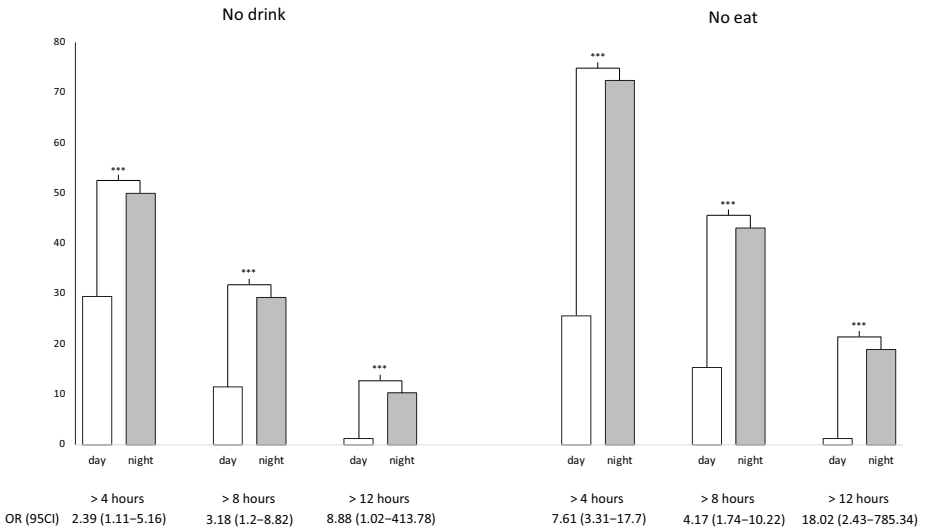

Figure 3. Risk of no-intakes for emergency health care workers during shifts. Percentage of participants declaring not drinking/not eating, over 4-, 8-, or 12-h during night- and day-shifts. A total of 136 questionnaires were analyzed. Odds ratio (OR) was used to access the impact of nightshifts using day-shifts as reference. 95% CI = 95% confidence intervals; *** represent *p*-value which are all <0.018 (significant if <0.05).

3.2. Regression Analysis

3.2.1. Quantitative Variables

Energy intake is significantly lower among females compared to males (coefficient = 340.1, 95% CI 107.5 to 572.7, $p = 0.004$) and among non-university hospitals compared to university hospitals (378.5, 143.9 to 613.1, $p = 0.002$). Consumption of lipids was decreased by night work (−3.34, −6.59 to −0.09, $p = 0.04$), and increased by age (0.19, 0.04 to 0.35, $p = 0.02$), and in workers who were single (3.80, 0.36 to 7.24, $p = 0.03$). Simple fatty acid consumption was decreased by night work (−5.22, −10.34 to 0.1, $p = 0.051$), and increased with age (0.27, 0.02 to 0.52, $p = 0.023$). Cholesterol consumption increased with age (4.78, 1.21 to 8.34, $p = 0.009$), male (75.8, 1.71 to 149.8, $p = 0.04$), and seniority (5.03, 0.27 to 9.80, $p = 0.038$). Night work did not statistically influence other nutrition variables (Figure 4 and Appendix A).

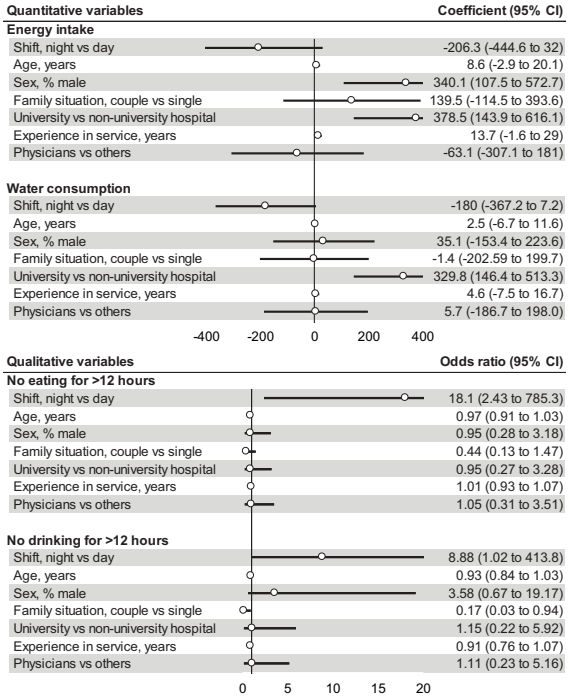

Figure 4. Univariate analysis that found a strong tendency on the impact of night shifts on energy intake, water consumption. Coefficient up to 0 induce a positive impact of the variable (right side of the reference line). Negative coefficient induce a negative impact of the variable (left side of the reference line); 95% CI: 95% confidence interval.

3.2.2. Qualitative Variables

Night shifts triggered a rise in the risk of not drinking for more than 4 h, 8 h and 12 h by 2.4 (OR = 2.39, 95% CI 1.11 to 5.16, $p = 0.015$), 3.2 (3.18, 1.20 to 8.82, $p = 0.009$) and 8.9 (8.88, 1.04 to 413.8, $p = 0.018$) respectively compared to day shifts. Furthermore, night shifts increased the risk of not eating for more than 4 h, 8 h and 12 h by 7.6 (7.61, 3.31 to 17.7, $p < 0.001$), 4.2 (4.17, 1.74 to 10.22, $p < 0.001$) and 18 (18.0, 2.43 to 785.3, $p < 0.001$), respectively, (Figures 3 and 4, and Appendix A). Except for night shift, the regression analysis did not find any impact on sociodemographic, location of work or seniority.

4. Discussion

We demonstrated that nightshift has a negative impact on both the amount and quality of nutrients intake among emergency HCWs. Furthermore, 27% of emergency HCWs do not have time to eat during more than 8 consecutive hours of the night shifts, and they do not even have time to drink for nearly one fifth of them. Main other influencing variables were seniority and location of centers.

4.1. The Negative Impact of Night Shift on Food Intake

Emergency HCWs working during a night shift have a slighter 24-h energy intake compared to those working during a day shift, but also compared to daily recommended diet [27]. Literature is not consistent about these results. Although we did not find any study about the impact of night shifts among emergency physicians, there is some among nurses with controversial results. Some found a lower energy intake among night workers versus day workers [28,29] while others did not find any significant differences [30–32]; however, another study found higher food intake among night workers versus day workers [33]. Although we do not study the energy intake the day after the shift, it seems that this low

food intake is compensated for on the day of recovery after work [29]. We can explain this low food intake in our study. First, emergency HCWs are subjected to daily stress due to overcrowding of EDs [34], lack of beds available in the hospital, and life-threatening emergencies [35,36]. However, the impact of stress on eating is controversial. Indeed, while acute stress is able to induce dietary restriction, chronic stress will induce food intake signal thus providing a better response to future stressful events [37]. Many pathophysiological pathways have been studied, especially the impact of ghrelin and leptin as biomarkers of acute stress [38–40]. It would be interesting to study those biomarkers among emergency HCWs. Secondly, sleep restriction and disturbed nychthemeral rhythm promote increased energy intake [19,41].

4.2. The Amount and Quality of Nutrient Intake and Shifts

The quality and choice of food during the night shift differs from the day shift [19]. This could induce restrictive behavior. Our results are in accordance with this. Indeed, emergency HCWs eat fewer carbohydrates and lipids during night shifts than their daytime colleagues [28,42]. Those results are also in agreement with the literature. Furthermore, it seems that the main carbohydrate intake during night shifts include the excessive consumption of sweets and sugary drinks [43–45]. Concerning lipids, night workers, and especially permanent night-shift workers, are at risk of dyslipidemia [9]. However, in our study, emergency HCWs eat less lipid and fat during night shifts than during day shifts. This is in line with literature [28,29,43]. Another possible explanation is the lack of time to eat during both day and night shifts. It seems that this lack of time leads to an increase in consumption of cold foods and fast foods [31,44,45], which predisposes individuals to obesity and cardiovascular disorders [46,47]. We also showed a low protein consumption during night shifts—type of position held, overwork and the quality of sleep are risk factors for low protein consumption [27,47]. Our results showed a low consumption of water consumed by emergency HCWs. Some of them do not even consume fluids during the entire night shift, i.e., during more than 12 h [28,48]. It seems that coffee/tea and sugary drinks are the preferred drinks mostly consumed during night work [28,33,49].

4.3. Other Influencing Variables

We showed a link between age, emergency HCWs' position held and the consumption of lipids, fat, and cholesterol. The more experience they have, the more lipids, fat, and cholesterol they consume. This is in line with a study that shows that eating behavior is influenced by seniority, and age [50]. It seems that experienced workers, with staggered schedules, eat more during the night, but mainly snacks rich in sugar, fat, and energy [50,51]. We also found that males have a higher energy, cholesterol, and protein intake, but also are less able to spend more than 4 h without eating. This finding is not in agreement with the literature. Indeed, night work induces an increase in the consumption of sugary and fatty foods, possibly in response to stress among emotional eaters, who are most often women [52,53]. University hospitals are larger than non-university hospitals, so we could imagine that emergency HCWs have less time to eat because ED is more overcrowded. However, we found that working in a large health center would have a positive influence on the diet of emergency HCWs. According to the literature, night workers in large hospital centers tend to consume more "junk food", which is easily accessible and more convenient to eat [28]. Our study is the first to examine the influence of night work on the diet of emergency physicians. Indeed, the subject often explored nurses or even more often industries in Asia with a population having a very high energy expenditure and a very low socio-economic level. Most of these studies have a low level of evidence (non-representative samples, unsystematic literature reviews) and are difficult to transpose in our population due to very different eating habits and high standards of living [19]. Another potential variable could be the sleep that we did not study the impact of. Indeed, previous literature suggests that night-shift workers obtain less sleep compared to day-shift workers.

Thus, if night-shift workers have a longer duration awake, they will be hungrier, and so more intake [54].

4.4. Limitations

Our study has some limitations. Firstly, the analyses of the dietary data were not necessarily done in the same subjects for day and night as we had more day shifts and fewer night shifts. Secondly, we worked on questionnaires that utilized self-reported information that may have contained some imprecision in the description of the food portions consumed as well as over- or under-declarations on the part of the participants completing the questionnaires. Although our data were collected via a self-assessment questionnaire with self-reported responses, the general methodological quality of our study was good and the risk of bias across participants was reduced through the use of a validated scale presented to every emergency HCW before the beginning of the data collection session. Another limitation is that we did not study the impact of cognition. Indeed, the impact on memory in case of a decrease of attentiveness or responsiveness could impact negatively the ability to fill in the questionnaire. By and large, while quality assurance protocols were put in place for the data collection process, it was difficult to micro-manage the different centers. Lastly, strict inclusion criteria were applied in order to extract data from a targeted population of emergency HCWs and thus answer our research questions. Continuous monitoring of food intake may be relevant and mandatory in future research. On the other hand, few studies consider the diet of emergency HCWs, and when this is the case, it concerns nurses [55]. Our study is therefore the first to look at the nutrition of emergency physicians during night shifts. Unfortunately, we did not study the food intake the day following the night shift. We previously showed that a night shift has a prolonged effect on some outcomes such as biomarkers of stress [23,24]. Further studies assessing the food intake during rest after a night shift could be relevant. Finally, very few studies have looked at the impact of night work on emergency physicians [24]. It would, therefore, be interesting to conduct more prospective and interventional studies to try to explore all the underlying mechanisms and subsequently put in place health-promotion and/or preventive strategies.

5. Conclusions

We showed that emergency healthcare workers working during nightshift have a lower amount and quality of nutrient intake. They seem to eat less and less healthily. Furthermore, sometimes some emergency HCWs go for long hours without eating. One fifth of them do not even drink for more than 8 consecutive hours of night shifts. Further studies assessing the food intake during rest after night shifts could be relevant. Preventive policies should target those workers.

Author Contributions: Conceptualization, J.-B.B.-M. and F.D.; methodology, J.-B.B.-M., J.S., G.B., and F.D.; formal analysis, S.C.; investigation, J.-B.B.-M., F.D. and J.S.; data curation, F.D.; writing—original draft preparation, J.-B.B.-M.; writing—review and editing, D.T., É.A., O.J.A., U.C.U., R.B., G.T.V. and M.T.; visualization, C.C. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee South-East I of France, for studies involving humans.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: All relevant data are in this manuscript.

Acknowledgments: To all emergency health care workers that were involved in this manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

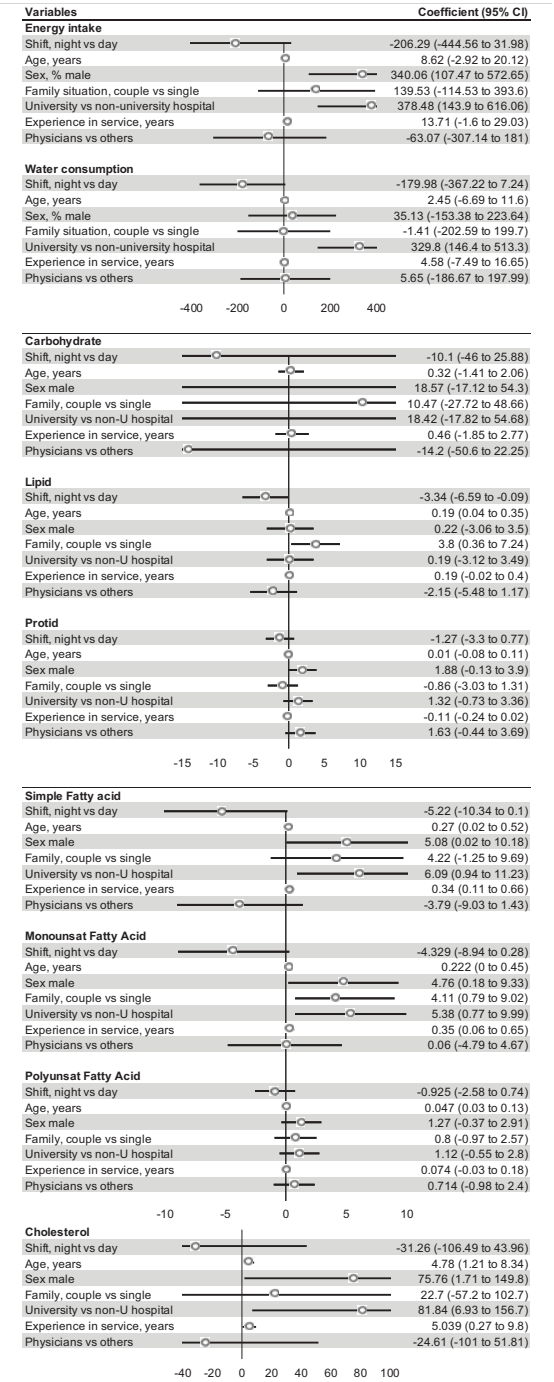

Figure A1. Univariate analysis that found a strong tendency on the impact of night shift on energy intake, water consumption, carbohydrate, lipid, protids, simple fatty acid, monounsaturated fatty acid, polyunsaturated fatty acid and cholesterol. Coefficient up to 0 induces a positive impact of the variable (right side of the reference line). Negative coefficient induces a negative impact of the variable (left side of the reference line); 95% CI: 95% confidence interval. Other significant results are described in the results part.

25. O'Neill, M.; Mujahid, M.; Hutson, M.; Fukutome, A.; Robichaud, R.; Lopez, J. Investing in Public School Kitchens and Equipment as a Pathway to Healthy Eating and Equitable Access to Healthy Food. *J. Sch. Health* **2020**, *90*, 492–503. [CrossRef]
26. Tremblay, A.; Clinchamps, M.; Pereira, B.; Courteix, D.; Lesourd, B.; Chapier, R.; Obert, P.; Vinet, A.; Walther, G.; Chaplais, E.; et al. Dietary Fibres and the Management of Obesity and Metabolic Syndrome: The RESOLVE Study. *Nutrients* **2020**, *12*, 2911. [CrossRef]
27. Nutrient Recommendations: Dietary Reference Intakes (DRI). Available online: https://ods.od.nih.gov/HealthInformation/Dietary_Reference_Intakes.aspx (accessed on 19 November 2021).
28. Reeves, S.L.; Newling-Ward, E.; Gissane, C. The Effect of Shift-work on Food Intake and Eating Habits. *Nutr. Food Sci.* **2004**, *34*, 216–221. [CrossRef]
29. Sahu, S.; Dey, M. Changes in Food Intake Pattern of Nurses Working in Rapidly Rotating Shift. *Al Ameen J. Med. Sci.* **2011**, *4*, 9.
30. Naghashpour, M.; Amani, R.; Nematpour, S.; Haghighizadeh, M.H. Dietary, Anthropometric, Biochemical and Psychiatric Indices in Shift Work Nurses. *Food Nutr. Sci.* **2013**, *4*, 1239–1246. [CrossRef]
31. Tada, Y.; Kawano, Y.; Maeda, I.; Yoshizaki, T.; Sunami, A.; Yokoyama, Y.; Matsumoto, H.; Hida, A.; Komatsu, T.; Togo, F. Association of Body Mass Index with Lifestyle and Rotating Shift Work in Japanese Female Nurses. *Obesity* **2014**, *22*, 2489–2493. [CrossRef]
32. Beebe, D.; Chang, J.J.; Kress, K.; Mattfeldt-Beman, M. Diet Quality and Sleep Quality among Day and Night Shift Nurses. *J. Nurs. Manag.* **2017**, *25*, 549–557. [CrossRef]
33. Ramin, C.; Devore, E.E.; Wang, W.; Pierre-Paul, J.; Wegrzyn, L.R.; Schernhammer, E.S. Night Shift Work at Specific Age Ranges and Chronic Disease Risk Factors. *Occup. Environ. Med.* **2015**, *72*, 100–107. [CrossRef] [PubMed]
34. Xu, H.G.; Johnston, A.N.B.; Greenslade, J.H.; Wallis, M.; Elder, E.; Abraham, L.; Thom, O.; Carlström, E.; Crilly, J. Stressors and Coping Strategies of Emergency Department Nurses and Doctors: A Cross-Sectional Study. *Australas. Emerg. Care* **2019**, *22*, 180–186. [CrossRef] [PubMed]
35. Bouillon-Minois, J.-B.; Schmidt, J.; Dutheil, F. SARS-CoV-2 Pandemic and Emergency Medicine: The Worst Is yet to Come. *Am. J. Emerg. Med.* **2020**, *42*, 246–247. [CrossRef] [PubMed]
36. Bouillon-Minois, J.-B.; Raconnat, J.; Clinchamps, M.; Schmidt, J.; Dutheil, F. Emergency Department and Overcrowding During COVID-19 Outbreak; a Letter to Editor. *Arch. Acad. Emerg. Med.* **2021**, *9*, e28. [CrossRef]
37. Bremner, J.D.; Moazzami, K.; Wittbrodt, M.T.; Nye, J.A.; Lima, B.B.; Gillespie, C.F.; Rapaport, M.H.; Pearce, B.D.; Shah, A.J.; Vaccarino, V. Diet, Stress and Mental Health. *Nutrients* **2020**, *12*, 2428. [CrossRef] [PubMed]
38. Bouillon-Minois, J.-B.; Trousselard, M.; Thivel, D.; Gordon, B.A.; Schmidt, J.; Moustafa, F.; Oris, C.; Dutheil, F. Ghrelin as a Biomarker of Stress: A Systematic Review and Meta-Analysis. *Nutrients* **2021**, *13*, 784. [CrossRef]
39. Bouillon-Minois, J.-B.; Trousselard, M.; Thivel, D.; Benson, A.C.; Schmidt, J.; Moustafa, F.; Bouvier, D.; Dutheil, F. Leptin as a Biomarker of Stress: A Systematic Review and Meta-Analysis. *Nutrients* **2021**, *13*, 3350. [CrossRef]
40. Dutheil, F.; de Saint Vincent, S.; Pereira, B.; Schmidt, J.; Moustafa, F.; Charkhabi, M.; Bouillon-Minois, J.-B.; Clinchamps, M. DHEA as a Biomarker of Stress: A Systematic Review and Meta-Analysis. *Front. Psychiatry* **2021**, *12*, 688367. [CrossRef]
41. St-Onge, M.-P.; Pizinger, T.; Kovtun, K.; RoyChoudhury, A. Sleep and Meal Timing Influence Food Intake and Its Hormonal Regulation in Healthy Adults with Overweight/Obesity. *Eur. J. Clin. Nutr.* **2019**, *72*, 76–82. [CrossRef]
42. Geliebter, A.; Gluck, M.E.; Tanowitz, M.; Aronoff, N.J.; Zammit, G.K. Work-Shift Period and Weight Change. *Nutrition* **2000**, *16*, 27–29. [CrossRef]
43. Roskoden, F.C.; Krüger, J.; Vogt, L.J.; Gärtner, S.; Hannich, H.J.; Steveling, A.; Lerch, M.M.; Aghdassi, A.A. Physical Activity, Energy Expenditure, Nutritional Habits, Quality of Sleep and Stress Levels in Shift-Working Health Care Personnel. *PLoS ONE* **2017**, *12*, e0169983. [CrossRef]
44. Han, K.; Choi-Kwon, S.; Kim, K.S. Poor Dietary Behaviors among Hospital Nurses in Seoul, South Korea. *Appl. Nurs. Res. ANR* **2016**, *30*, 38–44. [CrossRef] [PubMed]
45. Almajwal, A.M. Stress, Shift Duty, and Eating Behavior among Nurses in Central Saudi Arabia. *Saudi Med. J.* **2016**, *37*, 191–198. [CrossRef] [PubMed]
46. Elizabeth, L.; Machado, P.; Zinöcker, M.; Baker, P.; Lawrence, M. Ultra-Processed Foods and Health Outcomes: A Narrative Review. *Nutrients* **2020**, *12*, 1955. [CrossRef]
47. Jia, P.; Luo, M.; Li, Y.; Zheng, J.-S.; Xiao, Q.; Luo, J. Fast-Food Restaurant, Unhealthy Eating, and Childhood Obesity: A Systematic Review and Meta-Analysis. *Obes. Rev. Off. J. Int. Assoc. Study Obes.* **2021**, *22* (Suppl. 1), e12944. [CrossRef] [PubMed]
48. Heath, G.; Dorrian, J.; Coates, A. Associations between Shift Type, Sleep, Mood, and Diet in a Group of Shift Working Nurses. *Scand. J. Work. Environ. Health* **2019**, *45*, 402–412. [CrossRef]
49. Bilski, B. Influence of shift work on the diet and gastrointestinal complains among nurses. A pilot study. *Med. Pract.* **2006**, *57*, 15–19.
50. Morikawa, Y.; Miura, K.; Sasaki, S.; Yoshita, K.; Yoneyama, S.; Sakurai, M.; Ishizaki, M.; Kido, T.; Naruse, Y.; Suwazono, Y.; et al. Evaluation of the Effects of Shift Work on Nutrient Intake: A Cross-Sectional Study. *J. Occup. Health* **2008**, *50*, 270–278. [CrossRef]
51. Dietary Behavior and Its Relation with Lifestyle, Rotating Work Shifts and Job Satisfaction among Nurses of Ain Shams University Hospitals. *Egypt. J. Community Med.* **2016**, *34*, 75–86. [CrossRef]
52. Grzymisławska, M.; Puch, E.A.; Zawada, A.; Grzymisławski, M. Do Nutritional Behaviors Depend on Biological Sex and Cultural Gender? *Adv. Clin. Exp. Med.* **2020**, *29*, 165–172. [CrossRef]

53. Dutheil, F.; Chaplais, E.; Vilmant, A.; Courteix, D.; Duche, P.; Abergel, A.; Pfabigan, D.M.; Han, S.; Mobdillon, L.; Vallet, G.T.; et al. Stress Management in Obesity during a Thermal Spa Residential Programme (ObesiStress): Protocol for a Randomised Controlled Trial Study. *BMJ Open* **2019**, *9*, e027058. [CrossRef] [PubMed]
54. Santa Cecília Silva, A.A.; Lopes, T.D.V.C.; Teixeira, K.R.; Mendes, J.A.; de Souza Borba, M.E.; Mota, M.C.; Waterhouse, J.; Crispim, C.A. The Association between Anxiety, Hunger, the Enjoyment of Eating Foods and the Satiety after Food Intake in Individuals Working a Night Shift Compared with after Taking a Nocturnal Sleep: A Prospective and Observational Study. *Appetite* **2017**, *108*, 255–262. [CrossRef] [PubMed]
55. Nicholls, R.; Perry, L.; Duffield, C.; Gallagher, R.; Pierce, H. Barriers and Facilitators to Healthy Eating for Nurses in the Workplace: An Integrative Review. *J. Adv. Nurs.* **2017**, *73*, 1051–1065. [CrossRef] [PubMed]

3. **Conclusion**

Nous avons confirmé notre hypothèse initiale que les soignants de l'urgence consomment moins de nourriture lors d'une garde de nuit par rapport à une garde de jour. Cependant, nous avons également constaté que l'apport calorique est insuffisant lors d'une garde de jour aussi. De plus, nous avons constaté que certains soignants passent la garde entière (de jour ou de nuit) sans manger ni boire, ce qui n'est pas déontologiquement acceptable. Nous avons donc décidé depuis de sensibiliser les soignants à la nutrition et au nécessaire bénéfice de boire et de manger suffisamment lors d'une garde.

ETUDE 4 & 5 :

« Ghrelin as a biomarker of stress: a systematic review and meta-analysis »

et

« Leptin as a biomarker of stress: a systematic review and meta-analysis »

1. Introduction

Une fois que nous avons prouvé que les soignants sont stressés et qu'ils ont un impact important du travail aux urgences, majoré la nuit, sur leur nutrition, nous devions prouver que les hormones de régulation de l'appétit sont des biomarqueurs de stress. Pour se faire, nous avons fait rapidement un tour de revue de littérature mais aucune étude de grande ampleur et statistiquement positive n'était présente. Nous avons alors décidé de réaliser une revue systématique de la littérature avec méta-analyse. Initialement nous souhaitions réaliser une seule étude pour la ghréline et la leptine. Cependant, les variations de la ghréline et de la leptine étaient inversées, la logique pas forcément si logique et surtout chaque article (la méta-analyse sur la leptine et celle sur la ghréline) dépassait déjà largement le nombre de mots autorisés dans les instructions aux auteurs des différentes revues potentielles. Nous avons également décidé de se limiter au stress aigu afin de ne pas mélanger les messages. Nous avons exclu l'impact d'un stress chronique sur les taux de ghréline et de leptine car les problématiques sont encore plus complexes (leptinorésistance etc).

Les deux articles ont donné lieu à une publication dans la revue Nutrients (IF 6.706).

2. Article

« Ghrelin as a biomarker of stress »

nutrients

MDPI

Review

Ghrelin as a Biomarker of Stress: A Systematic Review and Meta-Analysis

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Abstract: Introduction: Ghrelin is an orexigenic hormone which favors food-seeking behavior and has been postulated to be a biomarker of stress. We conducted a systematic review and meta-analysis on the evolution of ghrelin levels following acute stress. Methods: The PubMed, Cochrane Library, Embase, and ScienceDirect databases were searched for studies reporting ghrelin levels before and after acute stress in humans. Results: We included ten studies for a total of 348 patients. Acute stress (intervention) was always in a laboratory. Acute stress was psychological (Trier Social Stress Test), physical, or mixed (cold pressure test). The overall meta-analysis demonstrated an increase in ghrelin after the stress intervention (ES = 0.21, 95CI 0.09 to 0.34) compared with baseline levels. Stratification by time demonstrated an acute increase in ghrelin levels in the five minutes immediately following the initiation of stress (0.29, 0.10 to 0.48) but without any difference after. Obese individuals had a more significant (ES = 0.51, 95CI 0.18 to 0.84) and prolonged increase in ghrelin levels for up to 45 min compared with non-obese individuals who had a significant increase only five minutes after stress. Moreover, the ghrelin levels increased in response to stress with BMI (coefficient 0.028, 0.01 to 0.49; $p = 0.013$) and decreased with the time after the stress intervention (coefficient -0.007, −0.014 to −0.001; $p = 0.025$). Conclusion: Ghrelin is a biomarker of stress, with a short-term increase following acute stress. Obese individuals have both a higher and prolonged response, emphasizing the link between obesity and stress.

Keywords: appetite; anxiety; metabolism; public health; mental health

1. Introduction

Psychosocial stress has been known as a major public health problem for more than 30 years [1]. Identifying acute stressful events with objective measures is growing in interest in physiology and preventive medicine [2]. Biomarkers of stress may help to assess specific working conditions and develop preventive strategies for stress management that can be evaluated. Despite the most common biomarkers of stress derived from the hypothalamic–pituitary–adrenal axis being associated with the physiological stress response [3], other biomarkers have been proposed. Ghrelin is a 28-amino-acid peptide discovered in 1996,

most commonly known as one of the main appetite regulation hormones, with an orexigenic role [4]. Increased ghrelin levels influence meal initiation and food-seeking behavior [5]. However, besides its multiple functions and despite conflicting results, ghrelin has been suggested to be a biomarker of stress [4], due to increased levels following acute stress. Under normal physiological conditions, ghrelin exhibits high and immediate variations in response to a meal [6], with a short circulating half-life of less than half an hour [7,8]. Ghrelin has an acute, immediate, and non-prolonged response to a stimulus, suggesting that the increase in ghrelin levels in response to acute stress may have a short duration. However, the results are equivocal concerning the ghrelin response to acute stress. To our knowledge, no meta-analysis to date has examined the effects of acute stress on ghrelin levels. Moreover, stress and obesity are intrinsically linked [9]. Stress has been suggested to lead to obesity via inappropriate eating behaviors [10]. Therefore, we hypothesized that obese individuals will exhibit a larger response in ghrelin levels following acute stress. Understanding the possible impact of ghrelin in the biological relationship between obesity and stress may help to determine an efficient preventive strategy.

Thus, we aimed to conduct a systematic review and meta-analysis to demonstrate that ghrelin could be a biomarker of acute stress, with a short-term increase following acute stress, and that the ghrelin response may be greater in obese individuals compared with normal-weight individuals.

2. Materials and Methods

2.1. Literature Search

We searched PubMed, Cochrane Library, Embase, and ScienceDirect with the following keywords, "ghrelin" and "stress", on 15 September 2020, for all articles describing our primary outcome variable—i.e., the measurement of ghrelin levels before and after acute stress—with or without a control group. We chose to use broad keywords to retrieve all possible articles. The search was not limited to specific years, languages, or regions. Additionally, reference lists of all publications that met the inclusion criteria were manually searched to identify any further studies that were not found with the electronic search, as well as reference lists from reviews. We excluded studies on animals and patients with psychiatric disorders. Two authors (J.-B.B.-M. and M.T.) conducted all literature searches, collated the abstracts, and separately reviewed the abstracts, and based on the selection criteria, decided the suitability of the articles for inclusion. A third author (F.D.) was asked to review the articles where consensus on suitability was debated. All the authors then examined the eligible articles. The search strategy is presented in Figure 1.

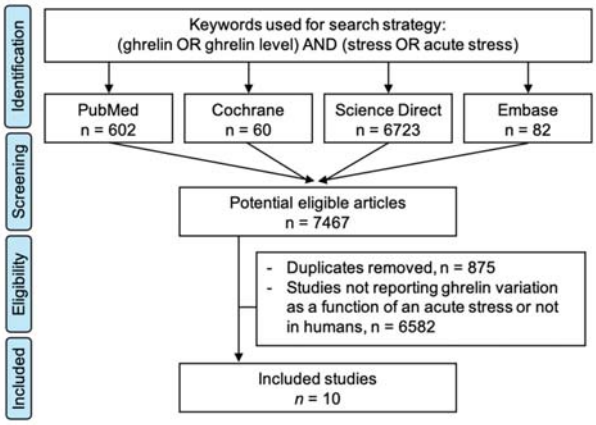

Figure 1. Search strategy.

2.2. Quality of Assessment

We used the Newcastle Ottawa Scale (NOS) [11] to evaluate the quality of the included articles. The NOS was developed to assess the quality of studies based on three types of biases: bias of selection, bias of comparability, and bias of exposure. Those three items were evaluated through eight items or sub-items, with one point given when the study fulfilled the criteria. The maximal score was eight, which was then converted into a percentage.

2.3. Statistical Considerations

The statistical analysis was conducted using Stata software (version 16, StataCorp, College Station, TX, USA). The ghrelin levels were summarized for each study sample and reported as the mean and the standard-deviation (SD) before and after the acute stress. Random effects meta-analyses (DerSimonian and Laird approach) were conducted when data could be pooled. p values less than 0.05 were considered statistically significant. We described our results by calculating the effect size (ES, standardized mean differences as SMD) of ghrelin levels from before and after acute stress. A positive ES denotes an increase in ghrelin levels. A scale for ES has been suggested with 0.8 reflecting a large effect, 0.5 a moderate effect, and 0.2 a small effect. In particular, we conducted three main meta-analyses stratified by time after the withdrawal of the stress: a global meta-analysis with all participants, a meta-analysis with only normal-weight individuals, and a meta-analysis with only obese individuals. All the articles included reported several measurement times of ghrelin levels following acute stress. All the meta-analyses were stratified by time after stress. The number of stratifications was determined by the number of studies within each stratification. For example, the main meta-analysis was stratified on four time measures: <5 min, 5–15 min, 15–45 min, and >45 min. Heterogeneity in the study results was evaluated by examining forest plots, and confidence intervals (CI), and by using formal tests for homogeneity based on the I^2 statistic, which is the most common metric for measuring the magnitude of between-study heterogeneity and is easily interpretable. I^2 values range between 0% and 100% and are typically considered low at <25%, modest at 25–50%, and high at >50%. For rigor, funnel plots of these meta-analyses were used to search for potential publication biases. In order to verify the strength of the results, further meta-analyses were then conducted, excluding studies that were not evenly distributed around the base of the funnel. We also tried to compute a meta-analysis stratified on the type of sampling (blood, saliva, etc.) or the type of stress.

Meta-regression analyses were conducted to explore the influence of the study or the participants' characteristics on the standardized mean differences. The following characteristics were considered when available: age, sex of the participants (male versus female), body mass index (BMI) and other sociodemographic variables, characteristics of the acute stress (duration, type of stress), and the time of sampling. Results were expressed as regression coefficients and 95%CI.

3. Results

The initial search retrieved 6631 putative articles (60 in the Cochrane Library, 651 in PubMed, 82 in Embase, and 6723 in ScienceDirect). The removal of duplicates and the use of the selection criteria reduced the number of articles reporting the evaluation of ghrelin level in blood or saliva to ten articles for the systematic review [12–21] and nine for the meta-analysis—with one study not reporting the number of participants [15] (Figure 1). All all articles were written in English.

3.1. Quality of Articles and Study Designs

Using the NOS criteria, all of the ten included studies had a score of >6 and considered high-quality (Figure 2). All the studies were cohort studies without blind assessment and mentioned ethical approval.

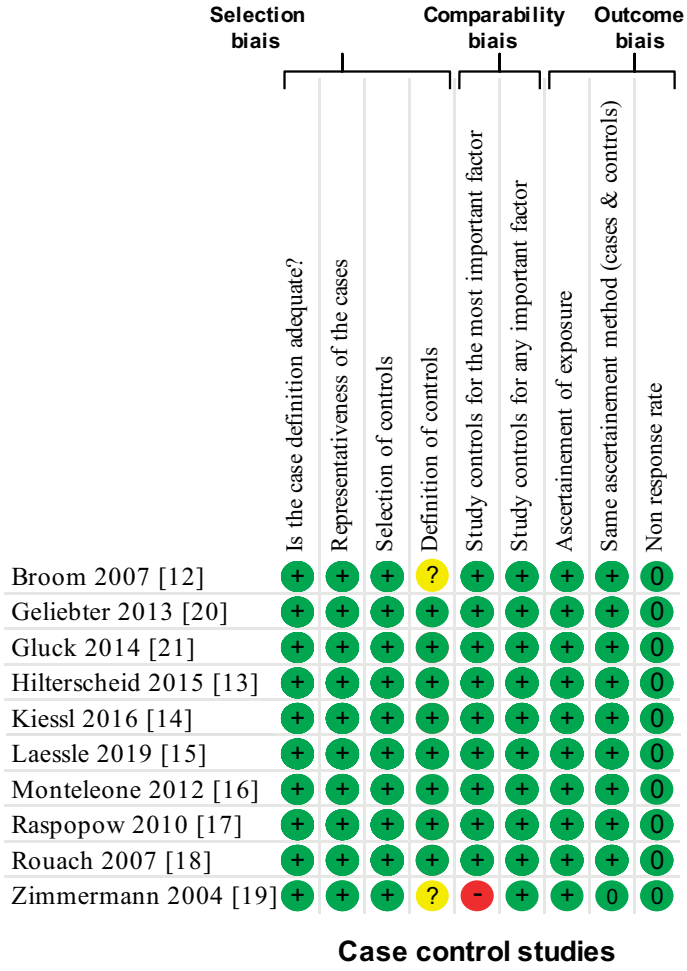

Figure 2. Methodological quality of included articles using the Newcastle–Ottawa Quality Assessment Scale. Yes: +; no: -; cannot say: ?; not applicable: NA.

3.2. Inclusion and Exclusion Criteria

All of the participants were adults. One study included participants who were physically active or involved in competitive sports [12], two recruited only overweight women [20,21], two recruited obese and normal-weight women [14,18], and five recruited healthy individuals [13,15–17,19], men [13,16] and women [15–17] (Table 1). Participants were recruited via advertisements sent to University campuses [12,13,15], from an online poll [17], from the local newspaper [14,20,21], and from a clinic [18]; two studies did not specify recruitment procedures [16,19]. Most studies [13–21] shared the same exclusion criteria based on clinical eating disorders (in the past or present), acute medical illnesses, a regular medications that could influence hormone levels, and current or prior substance-related or other psychiatric disorders. Two studies with overweight individuals excluded those with recent dieting or an unstable body weight—i.e., a variation of 5% over the past three months [20,21]. One study did not describe the exclusion criteria [12].

Table 1. Descriptive characteristics of the included studies (all the studies had baseline measures of ghrelin levels, i.e., before stress).

Study	Country	Study Design	Population			Stress		Ghrelin Assessment		
			Characteristics	Men (*n*)	Women (*n*)	Type	Duration (min)	Time after Stress (min)	Fluid	Technique
Broom 2007 [12]	UK	Non-RCT	Training and controls	18	0	Physical (1 h at 75% VO_2max)	60	2 measures: 0, 60	Blood	RIA
Geliebter 2014 [20]	USA	Non-RCT	Overweight women	0	17	Cold pressure test	2	6 measures: 0, 5, 15, 30, 45, 60	Blood	RIA
Gluck 2018 [21]	USA	Non-RCT	Overweight women	0	10	Cold pressure test	2	7 measures: 0, 2, 5, 15, 30, 45, 60	Blood	RIA
Hilterscheid 2015 [13]	Germany	Non-RCT	Women	0	27	Mental (TSST)	10	3 measures: 0, 30, 60	Blood	ELISA
Kiessl 2016 [14]	Germany	Non-RCT	Obese and normal-weight	0	85	Mental (TSST)	15	3 measures: 0, 30, 60	Blood	ELISA
Laessle 2018 [15]	Germany	Non-RCT	Women	0	48	Mental (TSST)	15	3 measures: 0, 30, 60	Blood	Not reported
Monteleone 2012 [16]	Italy	Non-RCT	Healthy women	0	10	Mental (TSST)	15	5 measures: 0, 10, 25, 40, 60	Saliva	ELISA
Raspopow 2012 [17]	Canada	Non-RCT	Women	0	48	Mental (TSST)	15	4 measures: 0, 10, 20, 30	Blood	RIA
Rouach 2007 [18]	Israël	Non-RCT	Obese and normal-weight	6	10	Mental (TSST)	15	5 measures: 0, 15, 35, 50, 75	Blood	RIA
Zimmermann 2006 [19]	Germany	Non-RCT	Healthy men	9	0	Mental (TSST)	15	5 measures: 0, 20, 35, 50, 65	Blood	RIA

CPT: Cold Pressor Test; ELISA: Enzyme-linked-immunosorbent-assay; RCT: Randomized Controlled Trial; RIA: Radio-immuno-assay; TSST: Trier Social Stress Test; UK: United Kingdom; USA: United States of America.

3.3. Population

Sample sizes ranged from 9 [19] to 85 [14] (Table 1). We included a total of 305 patients. Ages ranged from 19.3 ± 2.0 years [17] to 50.2 ± 12.1 years [18]. One study did not specify the mean age, but only that age was between 18 and 30 [14]. Sex was reported in all studies: seven studies recruited only women [13–17,20,21], one recruited both men and women [18], and two only men [12,19]. In total, 22% of the included participants were men. Body Mass Index (BMI) ranged from 21.2 ± 2.0 [18] to 35.5 ± 4.6 kg/m^2 [20]. No studies reported smoking, alcohol consumption, or leisure physical activity.

3.4. Outcome and Aim of the Studies

The main objective of all of the included studies was to assess the effect of acute stress instigated in a laboratory on ghrelin levels (and other hormones).

3.5. Type of Stress

Seven studies used the Trier Social Stress Test [13–19]. This procedure combines social stress (public speech] with mental stress (arithmetic under time pressure) and is a validated tool to provoke psychobiological stress responses. Two studies used the Cold Pressor Test [20,21], i.e., the immersion of the non-dominant hand up to the wrist in a rectangular-shaped container of 0 °C ice-water for 2 min. One study used a physical stressor (maximum oxygen uptake treadmill running test) [12] (Table 1).

3.6. Method of Sampling for Markers Analysis

Nine studies measured ghrelin levels in blood [12–15,17–21] and one in saliva [16] (Table 1). All the studies included in the meta-analysis gave details on the method of sampling and analysis. The blood samples were collected in EDTA treated tubes and immediately centrifuged to yield plasma for hormone determinations. The plasma was frozen between −20 °C [12] and −80 °C [19] until laboratory analysis. Concentrations were determined by radio-immuno-assay (RIA) [12,17–21] or enzyme-linked-immunosorbent-assay (ELISA) [13,14]. All studies also reported an inter-assay and intra-assay coefficient, ranging from 3.2% [20,21] to 12% [18], and from 1.91% [13] to 8% [17], respectively.

3.7. Meta-Analyses of Ghrelin Variation Depending on Time after Acute Stress

The overall meta-analysis of nine studies (41 groups) demonstrated an increase in ghrelin levels after the stress intervention (ES = 0.21, 95CI 0.09 to 0.34) compared with the baseline levels. Stratification by time demonstrated an increase in ghrelin levels in the 5 min following the stress intervention (0.29, 0.10 to 0.48) but there was no statistical difference between 5 and 15 min (0.22, −0.04 to 0.48), between 15 and 45 min (0.40, −0.08 to 0.88), and after 45 min (0.04, −0.18 to 0.26) (Figure 3).

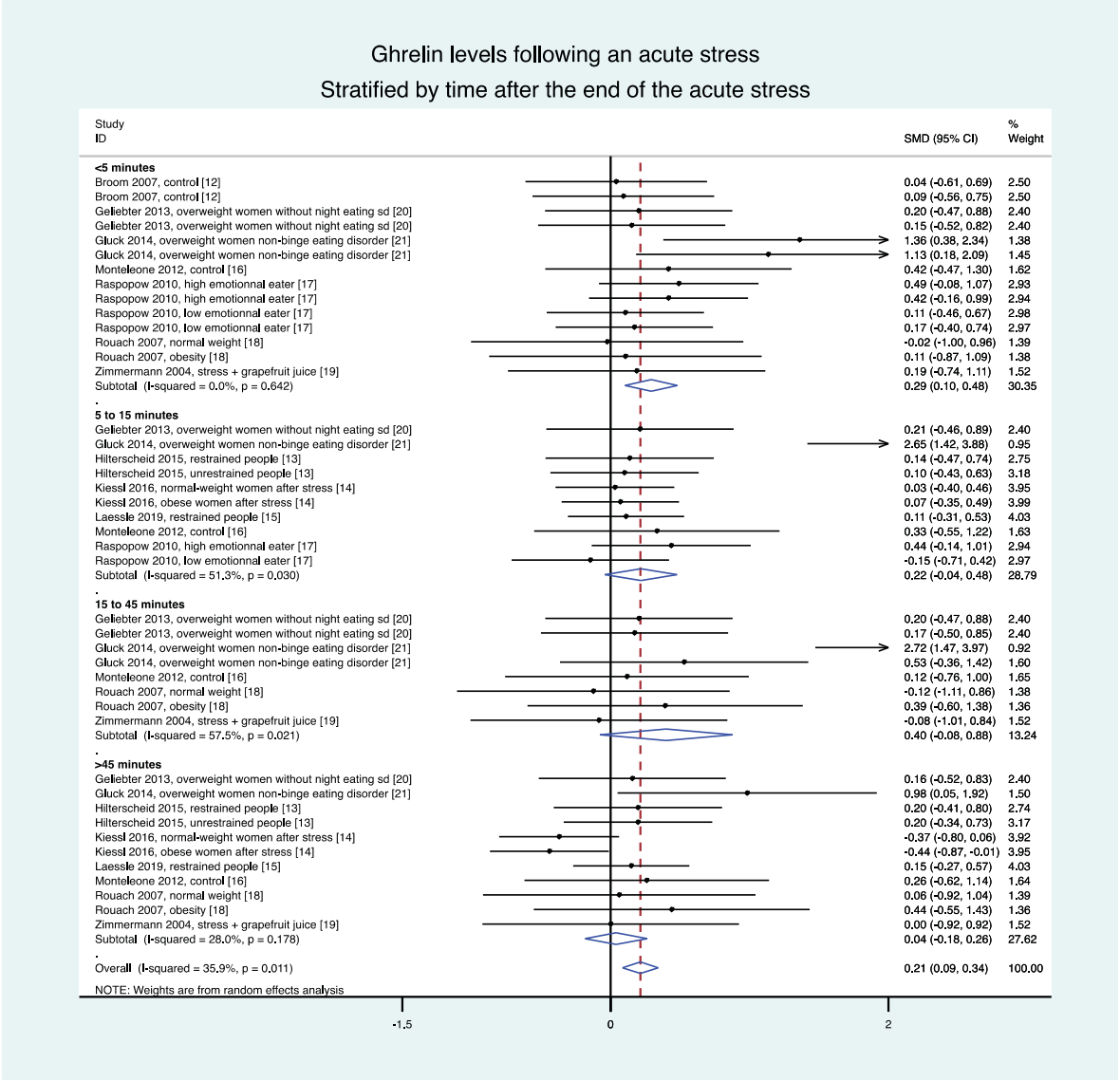

Figure 3. Meta-analysis of ghrelin levels following acute stress compared to baseline levels, stratified by time after the initiation of the acute stress intervention.

3.8. Meta-Analyses in Normal-Weight Population Were Based on Eight Studies (28 Groups)

Stratification by time demonstrated an increase in ghrelin levels in the 5 min following the stress intervention (0.23, 0.01 to 0.45) but without a difference between 5 and 45 min (0.10, −0.09 to 0.28) and after 45 min (0.02, −0.20 to 0.24), nor in overall results (0.11, −0.01 to 0.23) (Figure 4).

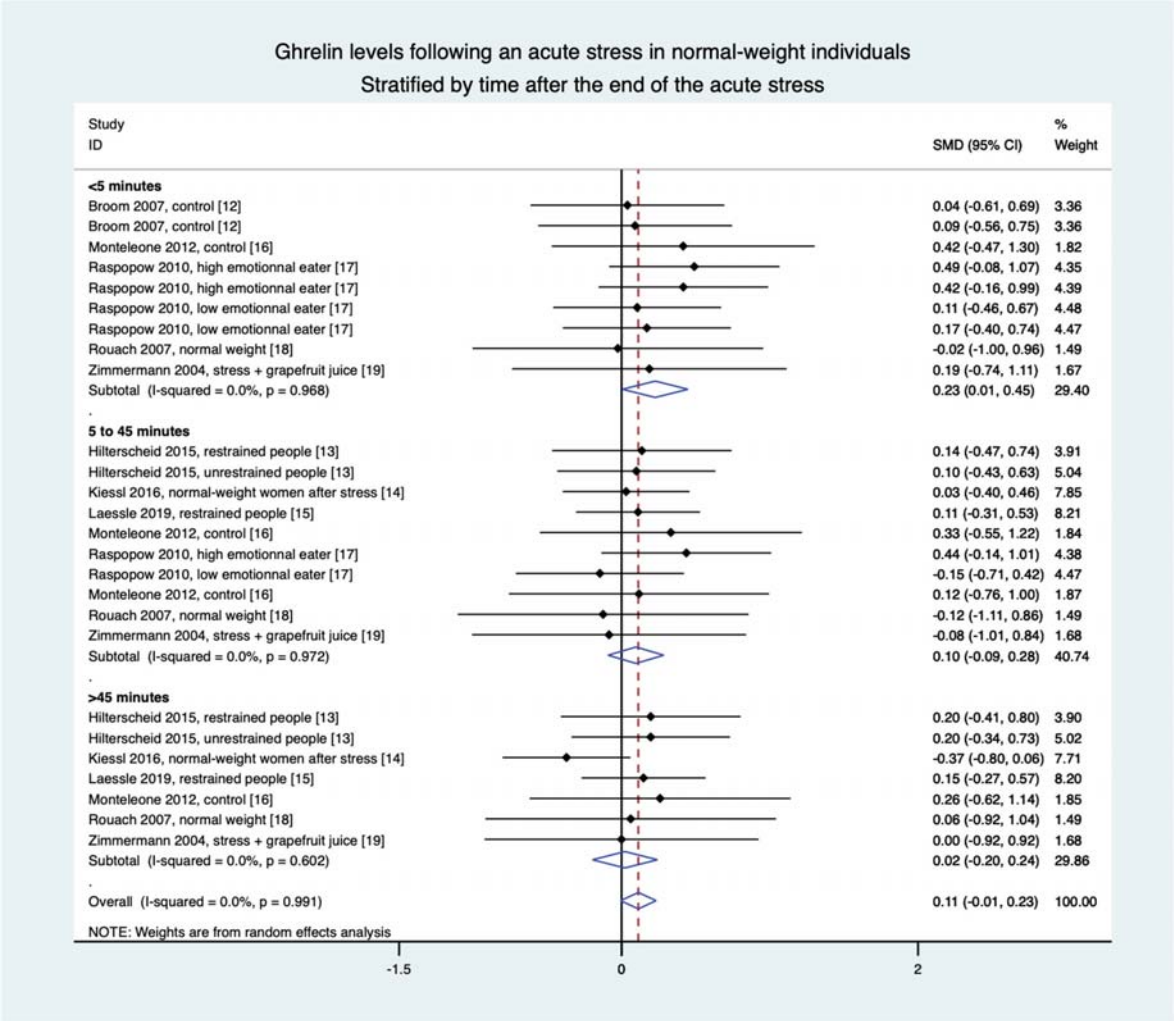

Figure 4. Meta-analysis of ghrelin levels after acute stress compared to baseline levels in the normal-weight population, stratified by time after the initiation of the acute stress intervention.

3.9. Meta-Analyses in Overweight Individuals Based on Four Studies (15 Groups)

Stratification by time demonstrated an increase in ghrelin levels in the 5 min following the stress intervention (0.52, 0.03 to 1.02), between 5 and 45 min (0.71, 0.15 to 1.27), and in the overall results (0.51, 0.18 to 0.84). The only non-significant difference was after 45 min (0.19, −0.44 to 0.82) (Figure 5).

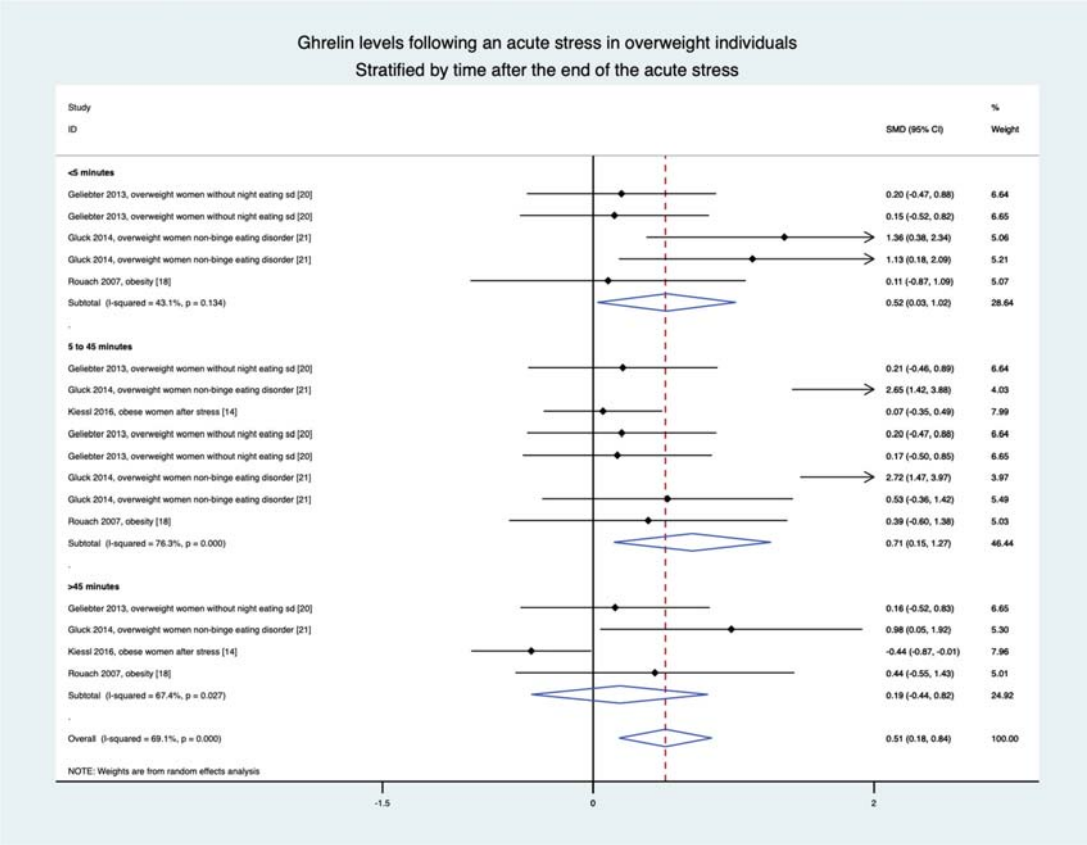

Figure 5. Meta-analysis of ghrelin levels after acute stress compared to baseline levels in the overweight population, stratified by time after the initiation of the acute stress intervention.

3.10. Meta-Regressions and Sensitivity Analysis

Levels of ghrelin after stress increased with BMI (ES = 0.026, 95CI 0.004 to 0.48). Ghrelin levels decreased with time after the stress intervention (−0.007, −0.014 to −0.001). Sociodemographic variables (age, sex) did not influence the level of ghrelin, nor did the duration of stress or time of sampling (Figure 6). A sensitivity analysis demonstrated similar results after the exclusion of studies that were not evenly distributed around the funnel plot (Figure 7). Insufficient data precluded further analyses by type of stress (mental, physical, or both) or by type of sampling (blood, saliva, etc.).

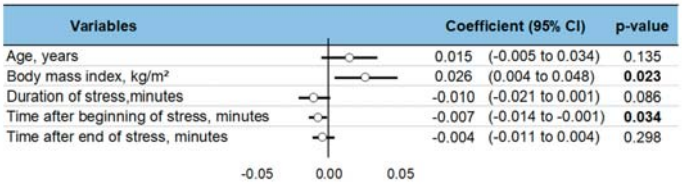

Figure 6. Meta-regressions—i.e., factors influencing changes in ghrelin levels following acute stress. Each variable's effect on the outcome is represented in the forest-plot by a dot on a horizontal line. The circles represent the coefficient for each variable, and the length of each line around the dots represents their 95% confidence interval (95CI). The black solid vertical line represents the null estimate (with a value of 0). Horizontal lines that cross the null vertical line represent non-significant variables on the outcome. Bold *p*-value are significant.

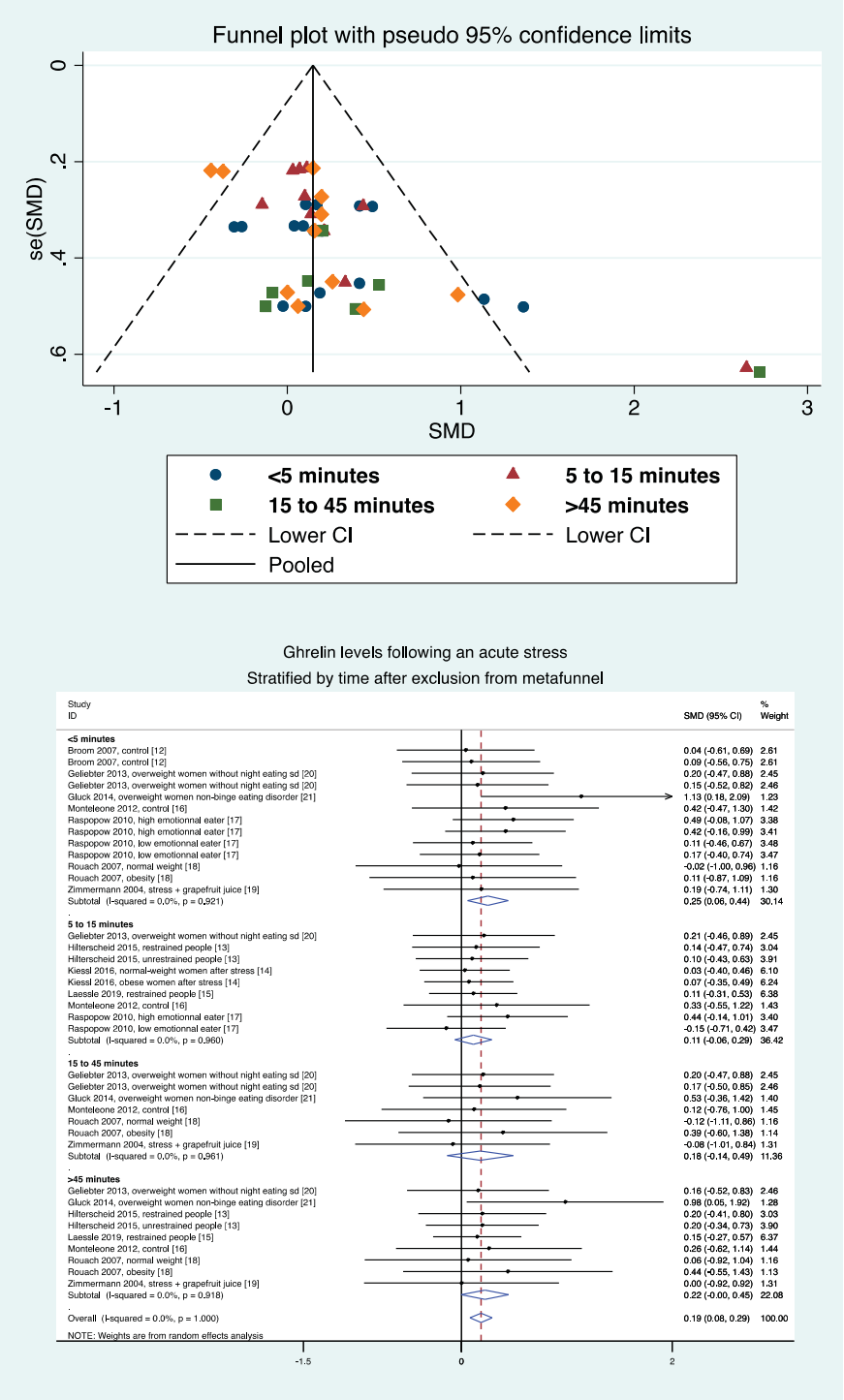

Figure 7. Metafunnel and meta-analysis of ghrelin levels after acute stress compared to baseline levels after exclusion from the metafunnel, stratified by time after the initiation of the acute stress intervention.

4. Discussion

The main findings were that ghrelin is a biomarker of stress, with a short-term increase following an acute stress intervention. Moreover, overweight and obese individuals had an extended response compared to normal-weight individuals, demonstrating the link between obesity and stress.

4.1. Ghrelin as a Biomarker of Stress

The active form of ghrelin (acyl-ghrelin) is a 28-amino-acid peptide discovered in 1996 [22], with multiple functions [23] but is mainly an appetite-regulating hormone produced by the stomach [24] whish acts on the central nervous system [25]. Very interestingly, we demonstrated that acyl-ghrelin is also a biomarker of stress that increases following exposure to a stress environment. Acyl-ghrelin is known for two main effects: (1) balancing energy by promoting food intake [26,27] and secreting of insulin [28] and ACTH, and (2) release of growth hormone (GH) [23,29]. The increase in ghrelin in response to stress can be an adaptive mechanism that may help people with stress [30]. Moreover, high ghrelin levels seem to influence the learning process and memory [31,32]. From a biomolecular point of view, ghrelin is the result of two cleavages from the 117-amino-acids pre-pro-ghrelin [33] followed by an octanoylation by the Ghrelin O-Acyltransferase (GOAT) to produce the active form of ghrelin (acyl-ghrelin). Despite demonstrating an increase in active ghrelin levels following acute stress, the mechanisms of the increase are not yet known, i.e., an increase of the production of the pre-pro-ghrelin, an increase of the cleavages, and/or an increase of the GOAT octanylation. Lastly, contrary to common thoughts, ghrelin and GOAT are not only expressed in the stomach [25,34]. They are also expressed in different tissues such as the pancreas, small-intestine, anterior pituitary gland, placenta, lymphocyte, kidney, gonads, lung, brain, and hypothalamus [24,25]. Hypothalamus expression is mediated by the circadian clock and environmental factors such as stress.

4.2. Acute Response to Acute Stress Intervention

We demonstrated that ghrelin levels had a short-term increase in response to acute stress, with high levels immediately after the stressful event and then a gradual decrease. This could be explained in part by its short half-life of between 10 and 31 min [7,8]. Therefore, ghrelin can be considered a biomarker of acute stress, such as catecholamines, heart rate variability, or cytokines [35,36]. Moreover, ghrelin is also implicated in the regulation of stress through its action on the hypothalamic-pituitary-adrenal axis [30]. Physiologically, the main role of ghrelin is for meal initiation and food-seeking behavior [6]. Daily variations of plasma ghrelin levels show transient increase in pre-prandial periods followed by a decrease in post-prandial periods [37,38]. The decrease has been proposed to be triggered by absorption of nutrients within the intestine [39]. However, the decrease in plasma ghrelin levels following acute stress cannot be linked with meal stimulus, so other mechanisms of regulation should apply. Ghrelin also has a short-term role in the regulation of mental health; it is implicated in short-term adaptations against depression, and in the control of anxiety after acute stress [30].

4.3. Ghrelin Levels and Characteristics of Stress

In our meta-analysis, ghrelin levels globally increased with whichever the type of stress was involved (physical, mental, or both). Even if there was no statistical difference between the types of stress, the literature is scarce regarding the exploration of ghrelin levels during physical stress [12] and both physical and mental stress [20,21]. Most of the studies included in our meta-analysis used the (Trier Social Stress Test) TSST, one of the most common tools to induce acute mental stress. Even though a dose-response relationship has been demonstrated between the duration or the type of stress and some biomarkers of stress, we failed to demonstrate a dose-response relationship between the duration of stress and ghrelin levels. Moreover, none of the nine included studies reported such relations. A limited number of studies with physical stress precluded further analyses. However,

studies of other biomarkers suggest a larger increase when both physical and mental stress is induced [20]. In our meta-analyses, as well as in literature, sociodemographic variables (age, sex) did not influence ghrelin levels. However, larger increases in cytokines have been reported in older individuals under stressful conditions [40]. Lastly, even if insufficient data precluded further analyses, blood sampling is commonly reported as being a better way to assess stress compared with saliva or urine sampling [41].

4.4. A prolonged Response in Overweight and Obese Individuals

Even though a positive effect size was identified for the overall population, there is a difference between normal-weight and overweight people. Indeed, the normal-weight population's effect size was small and only significant during the first five minutes. This could impact our conclusions on the overall meta-analysis and possibly reduce the generalization of our results. In contrast, we showed a higher and longer increase in ghrelin levels in the overweight patients than in the normal-weight patients, in accordance with the literature [42]. Moreover, we demonstrated that levels of ghrelin after stress increased with BMI. Stress and obesity are two public health issues [43,44] that are intrinsically linked [9]. It has been proposed that stress can lead to obesity via inappropriate eating behaviors [10] through a non-adaptive response to ghrelin levels [9]. In addition, obesity is a major stress factor [45]. Stressed people are those who have the greatest difficulties losing weight [46]. The relationship between obesity and stress is biological via the main stress hormones regulating appetite (leptin, ghrelin) [47,48]. This relationship between obesity and stress facilitated an international recommendation that suggests implementing stress management programs in obesity for a sustainable weight loss [49]. The direction of the relationship between the heightened and prolonged ghrelin response to stress in overweight and obese individuals requires further consideration. It is not yet possible to determine if a higher ghrelin response to stress contributes to the development of obesity, or if obese individuals have developed a heightened ghrelin response as a result of weight gain. The results from our studies therefore have implications to use ghrelin as a screening tool to identify people at risk of obesity. Although associations between ghrelin levels, obesity and stress exist, causal pathways have not been established [50,51]. The biological pathways of ghrelin response to acute stress are yet to be fully understood [52], and therefore the biological explanations of a greater ghrelin response following acute stress in obese individuals are also lacking.

4.5. Limitations

Our study has some limitations. Noon of the included studies had a randomized controlled design. Moreover, blinding interventions were deemed infeasible. Though there were similarities between the inclusion criteria, they were not identical. Limiting our meta-analysis to studies sharing precisely the same inclusion and exclusion criteria was not possible due to the limited data. All of the studies were monocentric, limiting the generalizability of our results. However, our selection of articles was rigorous, and few studies were outliers considering meta-funnels. The low I^2 to the attested homogeneity between the studies. Moreover, the homogeneity of the data precluded further sensitivity analysis of the different methods for measuring ghrelin levels (ELISA and RIA), stressors (TSST, sport, and CPT), and sampling (blood and saliva). The high I^2 (69.1%) for meta-analysis in obese individuals might limit the generalization. However, we demonstrated a positive effect of BMI in our meta-regression.

5. Conclusions

Ghrelin is a biomarker of stress, with a short-term increase following acute stress. Obese individuals have both a higher and prolonged response, emphasizing the link between obesity and stress. Appetite regulation testing warrants further investigation for use as part of weight management strategies, especially in overweight/obese individuals.

Author Contributions: J.-B.B.-M. conceived and designed the analysis. J.-B.B.-M., M.T. and F.D. conducted the systematic literature search. D.T., J.S. and F.M. corrected the manuscript. J.-B.B.-M., C.O., B.A.G. and F.D. wrote the manuscript. All authors gave final approval for the eligibility of all articles included in the analysis and provided critical revision of the article. J.-B.B.-M. and F.D. analysed the data. J.-B.B.-M. and F.D. wrote the first draft of the manuscript and were responsible for the integrity of the data analysis. All authors have read and agreed to the published version of the manuscript.

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References

1. Graham, N.M.H. Psychological stress as a public health problem: How much do we know? *Community Health Stud.* **1988**, *12*, 151–160. [CrossRef]
2. Buzgoova, K.; Balagova, L.; Marko, M.; Kapsdorfer, D.; Riecansky, I.; Jezova, D. Higher perceived stress is associated with lower cortisol concentrations but higher salivary interleukin-1beta in socially evaluated cold pressor test. *Stress* **2020**, *23*, 248–255. [CrossRef]
3. Woda, A.; Picard, P.; Dutheil, F. Dysfunctional stress responses in chronic pain. *Psychoneuroendocrinology* **2016**, *71*, 127–135. [CrossRef] [PubMed]
4. Bali, A.; Jaggi, A. An Integrative Review on Role and Mechanisms of Ghrelin in Stress, Anxiety and Depression. *Curr. Drug Targets* **2016**, *17*, 495–507. [CrossRef]
5. Hansson, C.; Shirazi, R.H.; Näslund, J.; Vogel, H.; Neuber, C.; Holm, G.; Anckarsäter, H.; Dickson, S.L.; Eriksson, E.; Skibicka, K.P. Ghrelin Influences Novelty Seeking Behavior in Rodents and Men. *PLoS ONE* **2012**, *7*, e50409. [CrossRef] [PubMed]
6. Cummings, D.E. Ghrelin and the short- and long-term regulation of appetite and body weight. *Physiol. Behav.* **2006**, *89*, 71–84. [CrossRef] [PubMed]
7. Akamizu, T.; Takaya, K.; Irako, T.; Hosoda, H.; Teramukai, S.; Matsuyama, A.; Tada, H.; Miura, K.; Shimizu, A.; Fukushima, M.; et al. Pharmacokinetics, safety, and endocrine and appetite effects of ghrelin administration in young healthy subjects. *Eur. J. Endocrinol.* **2004**, *150*, 447–455. [CrossRef] [PubMed]
8. Nagaya, N.; Kojima, M.; Uematsu, M.; Yamagishi, M.; Hosoda, H.; Oya, H.; Hayashi, Y.; Kangawa, K. Hemodynamic and hormonal effects of human ghrelin in healthy volunteers. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2001**, *280*, R1483–R1487. [CrossRef]
9. Dutheil, F.; Chaplais, E.; Vilmant, A.; Courteix, D.; Duche, P.; Abergel, A.; Pfabigan, D.M.; Han, S.; Mobdillon, L.; Vallet, G.T.; et al. Stress management in obesity during a thermal spa residential programme (ObesiStress): Protocol for a randomised controlled trial study. *BMJ Open* **2019**, *9*, e027058. [CrossRef] [PubMed]
10. Sinha, R.; Jastreboff, A.M. Stress as a Common Risk Factor for Obesity and Addiction. *Biol. Psychiatry* **2013**, *73*, 827–835. [CrossRef] [PubMed]
11. Stang, A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur. J. Epidemiol.* **2010**, *25*, 603–605. [CrossRef] [PubMed]
12. Broom, D.R.; Stensel, D.J.; Bishop, N.C.; Burns, S.F.; Miyashita, M. Exercise-induced suppression of acylated ghrelin in humans. *J. Appl. Physiol.* **1985**, *102*, 2165–2171. [CrossRef] [PubMed]
13. Hilterscheid, E.; Laessle, R. Stress-induced release of GUT peptides in young women classified as restrained or unre-strained eaters. *Eat. Weight Disord. Stud. Anorex. Bulim. Obes.* **2015**, *20*, 435–439. [CrossRef]
14. Kiessl, G.R.R.; Laessle, R.G. Stress does not affect ghrelin secretion in obese and normal weight women. *Eat. Weight Disord. Stud. Anorex. Bulim. Obes.* **2017**, *22*, 79–84. [CrossRef]
15. Laessle, R.; Hilterscheid, E. Stress-Induced Release of Eating-Related Hormones in Young Women Classified as Re-strained and Unrestrained Eaters. *Neuropsychobiology* **2019**, *78*, 27–30. [CrossRef] [PubMed]
16. Monteleone, P.; Tortorella, A.; Scognamiglio, P.; Serino, I.; Monteleone, A.M.; Maj, M. The Acute Salivary Ghrelin Response to a Psychosocial Stress Is Enhanced in Symptomatic Patients with Bulimia Nervosa: A Pilot Study. *Neuropsychobiology* **2012**, *66*, 230–236. [CrossRef]
17. Raspopow, K.; Abizaid, A.; Matheson, K.; Anisman, H. Psychosocial stressor effects on cortisol and ghrelin in emotional and non-emotional eaters: Influence of anger and shame. *Horm. Behav.* **2010**, *58*, 677–684. [CrossRef]
18. Rouach, V.; Bloch, M.; Rosenberg, N.; Gilad, S.; Limor, R.; Stern, N.; Greenman, Y. The acute ghrelin response to a psychological stress challenge does not predict the post-stress urge to eat. *Psychoneuroendocrinology* **2007**, *32*, 693–702. [CrossRef]
19. Zimmermann, U.S.; Buchmann, A.; Steffin, B.; Dieterle, C.; Uhr, M. Alcohol administration acutely inhibits ghrelin secre-tion in an experiment involving psychosocial stress. *Addict Biol.* **2007**, *12*, 17–21. [CrossRef] [PubMed]
20. Geliebter, A.; Carnell, S.; Gluck, M.E. Cortisol and ghrelin concentrations following a cold pressor stress test in over-weight individuals with and without Night Eating. *Int. J. Obes.* **2005**, *37*, 1104–1108. [CrossRef]
21. Gluck, M.E.; Yahav, E.; Hashim, S.A.; Geliebter, A. Ghrelin Levels After a Cold Pressor Stress Test in Obese Women With Binge Eating Disorder. *Psychosom. Med.* **2014**, *76*, 74–79. [CrossRef]

22. Howard, A.D.; Feighner, S.D.; Cully, D.F.; Arena, J.P.; Liberator, P.A.; Rosenblum, C.I.; Hamelin, M.; Hreniuk, D.L.; Palyha, O.C.; Anderson, J.; et al. A receptor in pituitary and hypo-thalamus that functions in growth hormone release. *Science* **1996**, *273*, 974–977. [CrossRef]
23. Kojima, M.; Hosoda, H.; Date, Y.; Nakazato, M.; Matsuo, H.; Kangawa, K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature* **1999**, *402*, 656–660. [CrossRef]
24. Sakata, I.; Yang, J.; Lee, C.E.; Osborne-Lawrence, S.; Rovinsky, S.A.; Elmquist, J.K.; Zigman, J.M. Colocalization of ghrelin O-acyltransferase and ghrelin in gastric mucosal cells. *Am. J. Physiol. Endocrinol. Metab.* **2009**, *297*, E134–E141. [CrossRef] [PubMed]
25. Ueberberg, B.; Unger, N.; Saeger, W.; Mann, K.; Petersenn, S. Expression of Ghrelin and its Receptor in Human Tissues. *Horm. Metab. Res.* **2009**, *41*, 814–821. [CrossRef]
26. Kim, M.S.; Yoon, C.Y.; Jang, P.G.; Park, Y.J.; Shin, C.S.; Park, H.S.; Ryu, J.W.; Pak, Y.K.; Park, J.Y.; Lee, K.U.; et al. The Mitogenic and Antiapoptotic Actions of Ghrelin in 3T3-L1 Adipocytes. *Mol. Endocrinol.* **2004**, *18*, 2291–2301. [CrossRef] [PubMed]
27. Baldanzi, G.; Filigheddu, N.; Cutrupi, S.; Catapano, F.; Bonissoni, S.; Fubini, A.; Malan, D.; Baj, G.; Granata, R.; Broglio, F.; et al. Ghrelin and des-acyl ghrelin inhibit cell death in cardiomyocytes and endothelial cells through ERK1/2 and PI 3-kinase/AKT. *J. Cell Biol.* **2002**, *159*, 1029–1037. [CrossRef] [PubMed]
28. Broglio, F.; Arvat, E.; Benso, A.; Gottero, C.; Muccioli, G.; Papotti, M.; Lely, A.J.V.D.; Deghenghi, R.; Ghigo, E. Ghrelin, a natural GH secretagogue produced by the stomach, induces hyperglycemia and reduces insulin secretion in humans. *J. Clin. Endocrinol. Metab.* **2001**, *86*, 5083–5086. [CrossRef]
29. Kojima, M.; Kangawa, K. Ghrelin: Structure and Function. *Physiol. Rev.* **2005**, *85*, 495–522. [CrossRef]
30. Spencer, S.J.; Xu, L.; Clarke, M.A.; Lemus, M.; Reichenbach, A.; Geenen, B.; Kozicz, T.; Andrews, Z.B. Ghrelin regulates the hypothalam-ic-pituitary-adrenal axis and restricts anxiety after acute stress. *Biol. Psychiatry* **2012**, *72*, 457–465. [CrossRef] [PubMed]
31. Diano, S.; Farr, S.A.; Benoit, S.C.; McNay, E.C.; Da Silva, I.; Horvath, B.; Gaskin, F.S.; Nonaka, N.; Jaeger, L.B.; Banks, W.A.; et al. Ghrelin controls hippocampal spine synapse density and memory performance. *Nat. Neurosci.* **2006**, *9*, 381–388. [CrossRef] [PubMed]
32. Atcha, Z.; Chen, W.-S.; Ong, A.B.; Wong, F.-K.; Neo, A.; Browne, E.R.; Witherington, J.; Pemberton, D.J. Cognitive enhancing effects of ghrelin receptor agonists. *Psychopharmacology* **2009**, *206*, 415–427. [CrossRef] [PubMed]
33. Hosoda, H.; Kojima, M.; Mizushima, T.; Shimizu, S.; Kangawa, K. Structural divergence of human ghrelin. Identification of multiple ghrelin-derived molecules produced by post-translational processing. *J. Biol. Chem.* **2003**, *278*, 64–70. [CrossRef]
34. Sakata, I.; Nakamura, K.; Yamazaki, M.; Matsubara, M.; Hayashi, Y.; Kangawa, K.; Sakai, T. Ghrelin-producing cells exist as two types of cells, closed- and opened-type cells, in the rat gastrointestinal tract. *Peptides* **2002**, *23*, 531–536. [CrossRef]
35. Dutheil, F.; Boudet, G.; Perrier, C.; Lac, G.; Ouchchane, L.; Chamoux, A.; Duclos, M.; Schmidt, J. JOBSTRESS study: Comparison of heart rate variability in emergency physicians working a 24-hour shift or a 14-hour night shift—A randomized trial. *Int. J. Cardiol.* **2012**, *158*, 322–325. [CrossRef]
36. Dutheil, F.; Trousselard, M.; Perrier, C.; Lac, G.; Chamoux, A.; Duclos, M.; Naughton, G.; Mnatzaganian, G.; Schmidt, J. Urinary Interleukin-8 Is a Biomarker of Stress in Emergency Physicians, Especially with Advancing Age—The JOBSTRESS* Randomized Trial. *PLoS ONE* **2013**, *8*, e71658. [CrossRef]
37. Bellone, S.; Rapa, A.; Vivenza, D.; Castellino, N.; Petri, A.; Me, E.; Broglio, F.; Prodam, F.; Ghigo, E.; Bona, G. Circulating ghrelin levels as function of gender, pubertal status and adiposity in childhood. *J. Endocrinol. Investig.* **2002**, *25*, RC13–RC15. [CrossRef] [PubMed]
38. Cummings, D.E.; Purnell, J.Q.; Frayo, R.S.; Schmidova, K.; Wisse, B.E.; Weigle, D.S. A pre-prandial rise in plasma ghrelin lev-els suggests a role in meal initiation in humans. *Diabetes* **2001**, *50*, 1714–1719. [CrossRef]
39. Williams, D.L.; Cummings, D.E.; Grill, H.J.; Kaplan, J.M. Meal-Related Ghrelin Suppression Requires Postgastric Feedback. *Endocrinology* **2003**, *144*, 2765–2767. [CrossRef]
40. Donato, A.J.; Morgan, R.G.; Walker, A.E.; Lesniewski, L.A. Cellular and molecular biology of aging endothelial cells. *J. Mol. Cell. Cardiol.* **2015**, *89 Pt B*, 122–135. [CrossRef]
41. Steckl, A.J.; Ray, P. Stress Biomarkers in Biological Fluids and Their Point-of-Use Detection. *ACS Sens.* **2018**, *3*, 2025–2044. [CrossRef]
42. Cui, H.; López, M.; Rahmouni, H.C.K. The cellular and molecular bases of leptin and ghrelin resistance in obesity. *Nat. Rev. Endocrinol.* **2017**, *13*, 338–351. [CrossRef]
43. Quine, L. Workplace bullying in NHS community trust: Staff questionnaire survey. *BMJ* **1999**, *318*, 228–232. [CrossRef] [PubMed]
44. Dutheil, F.; Lac, G.; Le Sourd, B.; Chapier, R.; Walther, G.; Vinet, A.; Sapin, V.; Verney, J.; Ouchchane, L.; Duclos, M.; et al. Different modalities of exercise to reduce visceral fat mass and cardiovascular risk in metabolic syndrome: The RESOLVE randomized trial. *Int. J. Cardiol.* **2013**, *168*, 3634–3642. [CrossRef] [PubMed]
45. Foss, B.; Dyrstad, S.M. Stress in obesity: Cause or consequence? *Med. Hypotheses* **2011**, *77*, 7–10. [CrossRef]
46. Robinson, E.B.; Hunger, J.M.; Daly, M.J. Perceived weight status and risk of weight gain across life in US and UK adults. *Int. J. Obes.* **2015**, *39*, 1721–1726. [CrossRef] [PubMed]
47. Haleem, D.J. Investigations into the involvement of leptin in responses to stress. *Behav. Pharmacol.* **2014**, *25*, 384–397. [CrossRef]

48. Schellekens, H.; Finger, B.C.; Dinan, T.G.; Cryan, J.F. Ghrelin signalling and obesity: At the interface of stress, mood and food reward. *Pharmacol. Ther.* **2012**, *135*, 316–326. [CrossRef]
49. Isasi, C.R.; Parrinello, C.M.; Jung, M.M.; Carnethon, M.R.; Birnbaum-Weitzman, O.; Espinoza, R.A.; Penedo, F.J.; Perreira, K.M.; Schneiderman, N.; Sotres-Alvarez, D.; et al. Psychosocial stress is associated with obesity and diet quality in Hispanic/Latino adults. *Ann. Epidemiol.* **2015**, *25*, 84–89. [CrossRef]
50. Bremner, J.D.; Moazzami, K.; Wittbrodt, M.T.; Nye, J.A.; Lima, B.B.; Gillespie, C.F.; Rapaport, M.H.; Pearce, B.D.; Shah, A.J.; Vaccarino, V. Diet, Stress and Mental Health. *Nutrients* **2020**, *12*, 2428. [CrossRef]
51. Sominsky, L.; Spencer, S.J. Eating behavior and stress: A pathway to obesity. *Front. Psychol.* **2014**, *5*. [CrossRef] [PubMed]
52. Tomiyama, A.J. Stress and Obesity. *Annu. Rev. Psychol.* **2019**, *70*, 703–718. [CrossRef] [PubMed]

3. Article

« Leptin as a biomarker of stress »

nutrients

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Review

Leptin as a Biomarker of Stress: A Systematic Review and Meta-Analysis

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Abstract: Background: Leptin is a satiety hormone mainly produced by white adipose tissue. Decreasing levels have been described following acute stress. Objective: To conduct a systematic review and meta-analysis to determine if leptin can be a biomarker of stress, with levels decreasing following acute stress. Methods: PubMed, Cochrane Library, Embase, and ScienceDirect were searched to obtain all articles studying leptin levels after acute stress on 15 February 2021. We included articles reporting leptin levels before and after acute stress (physical or psychological) and conducted random effects meta-analysis (DerSimonian and Laird approach). We conducted Meta-regressions and sensitivity analyses after exclusion of groups outside the metafunnel. Results: We included seven articles—four cohort and three case-control studies—(28 groups) from 27,983 putative articles. Leptin levels decreased after the stress intervention (effect size = −0.34, 95%CI −0.66 to −0.02) compared with baseline levels, with a greater decrease after 60 min compared to mean decrease (−0.45, −0.89 to −0.01) and in normal weight compared to overweight individuals (−0.79, −1.38 to −0.21). There was no difference in the overweight population. Sensitivity analyses demonstrated similar results. Levels of leptin after stress decreased with sex ratio—i.e., number of men/women—(−0.924, 95%CI −1.58 to −0.27) and increased with the baseline levels of leptin (0.039, 0.01 to 0.07). Conclusions: Leptin is a biomarker of stress, with a decrease following acute stress. Normal-weight individuals and women also have a higher variation of leptin levels after stress, suggesting that leptin may have implications in obesity development in response to stress in a sex-dependent manner.

Keywords: anxiety; appetite; mental health; metabolism; public health

1. Introduction

Psychosocial stress is a significant public health concern [1–3] with substantial consequences, such as burnout [4], anxiety [5], depression [6], and suicide [7]. Stressed people also have more cardiovascular diseases [8], eating disorders [9], and are more overweighted or obese [10]. Identifying stressful events is an important research topic in medicine because it can lead to policies for prevention. Although the literature has proposed many

biomarkers of stress [11–13], none is ubiquity, and the majority of those depend on the hypothalamic–pituitary–adrenal axis [14]. Leptin is a 167-aminoacid peptide mainly expressed in white adipose tissue (WAT) [15]. Its discovery changed the view of WAT from a superficial tissue responsible for energy deposit to an active endocrine organ [16]. Leptin is commonly known as a satiety hormone produced by WAT with low levels during the meal initiation and high levels after the meal [15]. Leptin blood levels are not the same in all individuals. Indeed, normal-weight people and men seem to have lower levels of leptin [17,18]. Besides the satiety effect, leptin plays an active role in energy homeostasis [19], metabolism [20], exercise [21], and neuroendocrine function [20]. This neuroendocrine function is centralized by receptor of leptin in the hypothalamic. Low leptin levels contribute to of hyperphagia, hypogonadotropic hypogonadism, and suppression of thyroid and growth hormone (GH) levels [20]. Leptin seems to also have an important impact on glucose homeostasis. Indeed, it seems to affect peripheral insulin sensitivity via central nervous system mechanisms independent of its effects on food intake and weight [20].

Furthermore, it has been proposed to be a biomarker of acute stress, decreasing its levels after acute stress. In physiological conditions, leptin has a short-term half-life—30 min—with 18% daily circadian variations [22,23]. To our knowledge, no meta-analysis to date has examined the effects of acute stress on leptin levels. Secondly, a strong link is present between stress and obesity because of destructive eating behaviors [24].

Thus, we aimed to conduct a systematic review and meta-analysis to determine if leptin levels could be a relevant biomarker of acute stress, with a decrease following the acute stress, and compare the response in leptin levels between overweight and normal-weight individuals.

2. Materials and Methods

2.1. Literature Search

PubMed, Cochrane Library, Embase, and ScienceDirect databases were searched on 15 February 2021, with the following keywords "leptin" OR "ob protein" OR "ob gene product" OR "obesity factor" OR "obese gene product" OR "obese protein" AND "anxiety" OR "anxious" OR "stress" OR "mood" OR "emotion" (detailed search strategy, Appendix A). The use of broad keywords aimed to be as exhaustive as possible. Articles needed to describe our primary outcome variable, i.e., the measurement of leptin levels before and after acute stress with or without a control group. We did not limit our search to specific years, languages, or regions, but studies on animals and patients with psychiatric disorders were excluded. Reference lists from reviews and articles retrieved from our search were explored to identify any further studies. Two authors (JBB and MT) conducted searches, collated and separately reviewed the abstracts, and decided the suitability of the articles for inclusion. A third author (FD) reviewed the articles where consensus on appropriateness was debated. All authors then examined the eligible articles. The search strategy is presented in Figure 1.

2.2. Data Collection

The data collected included first author's name, publication year, study design, country, aims and outcomes of included articles, sample size, age, sex, characteristics of stress (type, duration), characteristics of measurement (time of measurement, type of fluid, technic of measurement), leptin levels, and putative adjustment/explaining factors (such as body mass index (BMI), insulinoresistance, smoking, or leisure physical activity).

2.3. Quality of Assessment

The Newcastle Ottawa Scale (NOS) for cohort studies and the NOS for case-control studies were used to assess the quality of the included articles based on three types of bias (selection, comparability, and exposure) [25]. The maximal score was eight—one point per question.

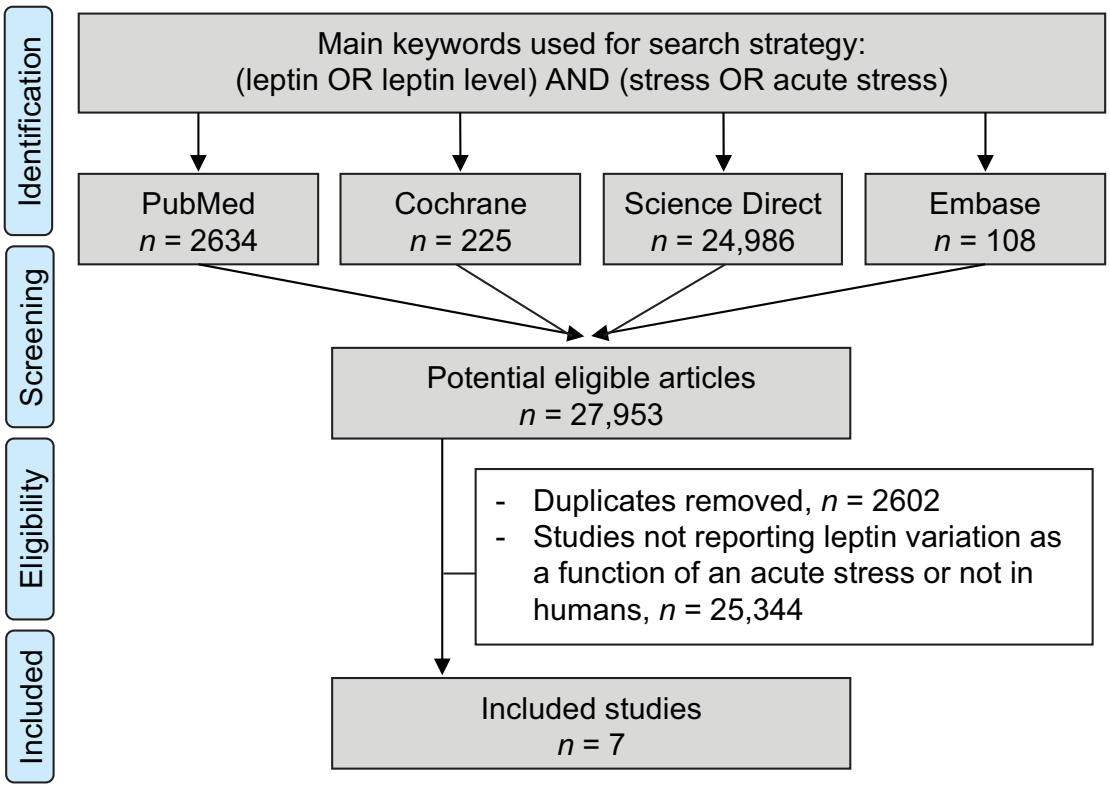

Figure 1. Search strategy.

2.4. Statistical Consideration

We used Stata software (version 16, StataCorp, College Station, TX, USA) to conduct the statistical analysis. Random effects meta-analyses (DerSimonian and Laird approach) were conducted on leptin levels before and after acute stress [26]. Results were expressed as effect size (ES), with a negative ES denoting a decrease in leptin levels. An ES at 0.8 reflects a large effect, 0.5 a moderate effect, and 0.2 a small effect. Specifically, we conducted meta-analysis stratified on time after the stress and a meta-analysis stratified by weight—overweight (BMI > 25) versus normal-weight people considering number of articles in each group. We stratified all meta-analysis by time after stress. We determined the stratification time to every 30 min according to the leptin half-life (25 ± 5 min). Sensitivity analyses were conducted after excluding studies that were not evenly distributed around the base of the funnel-plot and to search for potential publication bias. Heterogeneity between studies was also evaluated using I^2 statistic. I^2 is easily interpretable with values ranging between 0% and 100%: $I^2 < 25\%$ reflects a low heterogeneity, $25 < I^2 < 50\%$ reflects a modest heterogeneity, and $I^2 > 50\%$ reflects a high heterogeneity. We also conducted a meta-analysis by type of stress when feasible.

We also conducted meta-regression analyses to explore the influence of putative explaining factors, such as age, sex of participants, BMI and other sociodemographic variables, characteristics of the acute stress (duration, type of stress), and time of sampling. We expressed results as regression coefficients and 95% CI. *p*-value less than 0.05 were considered statistically significant.

3. Results

The initial search retrieved 27,983 putative articles (108 in the Cochrane Library, 2634 in PubMed, 108 in Embase, and 24,986 in ScienceDirect). Removal of duplicates and use of

the selection criteria—i.e., human study, at least one measure before acute stress and one after the end of the stressful event, approval of an Institutional Review Board or an Ethic Committee—reduced the number of articles reporting the evaluation of leptin level in the blood to seven articles [27–33] for the systematic review and meta-analysis (Figure 1). All articles were written in English.

3.1. Quality of Articles and Study Designs

Using the NOS criteria, all the seven included studies had a score of >6 and were considered high quality (Figure 2). Three studies were case-control studies [29,32,33] without blind assessment, and four were cohort studies [27,28,30,31]. All studies mentioned an ethical approval.

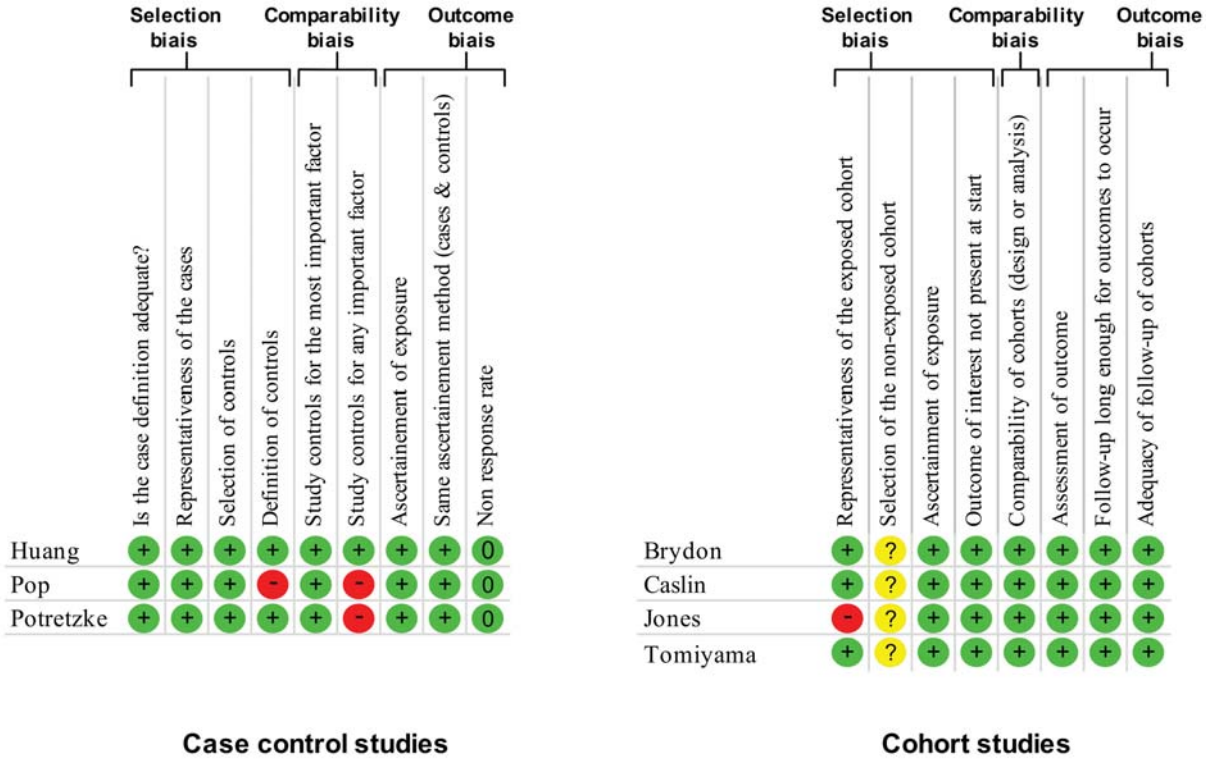

Figure 2. Methodological quality of included articles using Newcastle—Ottawa Quality Assessment Scale Yes, +; No, −; Cannot say, ?; Not applicable, N/A; 0, percentage of non-response.

3.2. Inclusion and Exclusion Criteria of Included Articles

All participants were adults and were considered "healthy" by investigators, i.e., without any current infectious diseases or a history of autoimmune, endocrine (with a particular mention of diabetes), inflammatory, or neurological disorders. Furthermore, women were not pregnant and could not be lactating. Participants were excluded if they took medication that could interfere with leptin, such as corticosteroids, antibiotics, or anti-inflammatories. The studies were performed in three countries: the United Kingdom [27], the United States of America [28–31,33], and Romania [32]. Two studies recruited only healthy women (one included all ages [27] and the second only postmenopausal [30]). Two studies recruited healthy normal and overweight men [28,29]. One study recruited healthy smokers who were asked to be abstainers for four weeks [33]. If they succeeded, they were classified as abstainers but were classified as relapsers if they failed. Two studies recruited healthy volunteers comparing normal-weight and overweight individuals in one study [32] and

insulin-resistant and insulin-sensitive ones in the other [31]. The separation between insulin-resistant or insulin-sensitive individuals was made after a quantitative insulin-sensitivity check index [34] (QUICKI) with a cut-off point of <0.33 to have insulin resistance and >0.33 to have normal insulin sensitivity (Table 1).

Table 1. Characteristics of included studies.

Study	Country	Study Design	Population			Stress		Leptin Assessment		
			Characteristics	Men *n*	Women *n*	Type	Duration (Minutes)	Time after Stress (Minutes)	Fluid	Technique
Brydon 2008	UK	Cohort	Healthy women	0	67	Mental	10	2 measures: 0 and 45	Blood	ELISA
Caslin 2015	USA	Cohort	Healthy normal and overweight men	20	0	Mental	20	2 measures: 30 and 120	Blood	ELISA
Huang 2014	USA	Case control	Healthy normal and overweight men	20	0	Mental	20	2 measures: 0 and 60	Blood	ELISA
Jones 2016	USA	Cohort	Healthy insulin-resistant and insulin-sensitive volunteers	0	60	Mental (TSST)	13	3 measures: 0, 15, and 90	Blood	RIA
Pop 2010	Romania	Case control	Healthy normal and overweight volunteers	42	37	Physical (VO_2 max)	12.5	1 measure: 30	Blood	ELISA
Potrezke 2014	USA	Case control	Healthy smokers (relapsers and abstainers)	22	14	Mental	24	4 measures: 0, 30, 46, and 76	Blood	ELISA
Tomiyama 2012	USA	Cohort	Healthy postmenopausal women	0	40	Mental (TSST)	10	3 measures 0, 50, and 90	Blood	ELISA

3.3. Population

We included a total of 322 participants, and the sample size ranged from 20 [28,29] to 79 [32]. Mean age ranged between 21.2 ± 0.8 [28] to 62.0 ± 6.0 years [30]. Sex was reported in all studies. Three studies recruited only women [27,30,31], two only men [27,28], and two both sexes [32,33]. We included a total of 104 men (32.3%) and 218 women (67.7%). All studies reported body mass index (BMI), ranging from 22 kg/m^2 [28] to 38 kg/m^2 [29]. Three studies used BMI to create groups, i.e., normal weight and overweight [27,29,32]. One study used the capacity to abstain from smoking for four weeks to create groups, i.e., abstainers and relapsers [33]. Only two studies reported height and weight [28,29] and only three the percentage of body fat [26–28]. Only one study reported smoking [27], waist circumference [27], leisure physical activity [33], HbA1c [27], and insulin resistance [31] and glycemia, LDL, HDL, and triglyceride levels [32].

3.4. Main Outcome of Studies

The main outcome of all studies included in our meta-analysis was the effect of acute stress on the variation of leptin blood levels (and possibly other hormones, such as cortisol [27–31,33], IL-6 [27–29,31], IL-1Ra [27,28], insulin [31], LDL-HDL [32], and adiponectin [31,32]).

3.5. Type of Stress

All studies described the procedure of the stressful event. Six studies used mental stress and one physical stress. Three studies [27,30,31] used the Tried Social Stress Test—a validated tool to provoke psychobiological stress responses composed of a combination which consists of a 3-min preparation period, a 5-min free speech, and a 5-min mental arithmetic task in front of 2–3 audience members. Two studies used a computer-based mental task previously validated as stressful [35]. Patients were presented with a colour-word on the screen, which was written in a different colour font. Simultaneously, the computer said a third colour, while the subjects were required to identify the font colour in which the word was presented. A new colour-word was given every second for 2 min. Following the Stroop colour-word task, subjects were presented with a three-digit number

from which they were required to randomly subtract either 3, 7, 8, or 13. Auditory feedback was given by the program when participants entered an incorrect answer. The mental arithmetic task continued for 2 min. This 4-min cycle of two stressors occurred five times for a total of 20 min. Prior to the start of the task, subjects were instructed to work as accurately and quickly as possible and informed that their scores would be recorded. In addition, an investigator stayed in the room. [28,29]. One study used only public speaking. The public speaking challenge entailed participants composing and delivering three 4-min speeches focusing on three scenarios. The three scenarios were presented in a counterbalanced order. In one scenario, participants were presented with a controversial social issue and were asked to introduce their positions and defend them. In another scenario, participants were given an article about an issue of general interest and were asked to construct a presentation based on this article. In a third scenario, participants were asked to imagine a hypothetical situation where they were being accused of shoplifting [33]. The last one used physical stress on a cycle ergometer during the time needed to obtain VO_2 max. All participants were submitted to symptom-limited, maximal stress testing on a cycloergometer, according to classical protocols. Mean effort was 103 ± 27 Ws, and mean duration 12.5 ± 3 min [32].

3.6. Time of Procedure

Three studies were performed during the beginning of the morning—between 7:30 a.m. and 8:30 a.m. [28–30]—and three during the beginning of the afternoon—between noon and 2:30 p.m. [27,31,33]. One did not mention when the study was performed [36].

3.7. Method and Time of Sampling

All studies measured leptin levels in blood. All studies included except one [32] gave details on the method of sampling and analysis. Blood samples were collected in EDTA-treated tubes and immediately centrifuged to yield plasma for hormone determinations. Concentrations were determined by radio-immuno-assay (RIA) [30,31] or enzyme-linked-immunosorbent-assay (ELISA) [27–29,32,33]. Three studies also reported inter-assay and intra-assay coefficient, ranging from 5% [28] to 12% [27] and from 6.6% [30] to 10% [27,28], respectively. All studies measured leptin levels within the two hours following the end of the acute stress.

3.8. Meta-Analysis of Leptin Variation

The overall meta-analysis of seven studies (28 groups) demonstrated a decrease in leptin levels after the stress intervention (effect size = −0.34, 95% CI −0.66 to −0.02, I^2 86.7%) compared with the baseline levels. Stratification by time showed a non-statistically significant decrease in leptin levels in the 30 min (−0.38, −1.24 to 0.48) and between 30 and 60 min following the stress intervention (−0.16, −0.42 to 0.10) as well as a significant decrease after 60 min (−0.45, −0.89 to −0.01) (Figure 3). Stratification by weight classification showed a significant decrease in leptin levels in the normal-weight population, i.e., BMI < 25 kg/m^2 (−0.79, −1.38 to −0.21). There was no difference in the overweight population, i.e., BMI > 25 kg/m^2 (−0.04, −0.41 to 0.32) (Figure 4). Stratification by type of stress was not salient for physical activity, as it was only reported in one study. There was a tendency (p = 0.054) for a decrease in leptin levels following an acute mental stress (−0.35, −0.70 to 0.01). This could be explained by the low number of studies (n = 6 after exclusion), which increase the 95% confidence interval from −0.66; −0.02 to −0.70; 0.01).

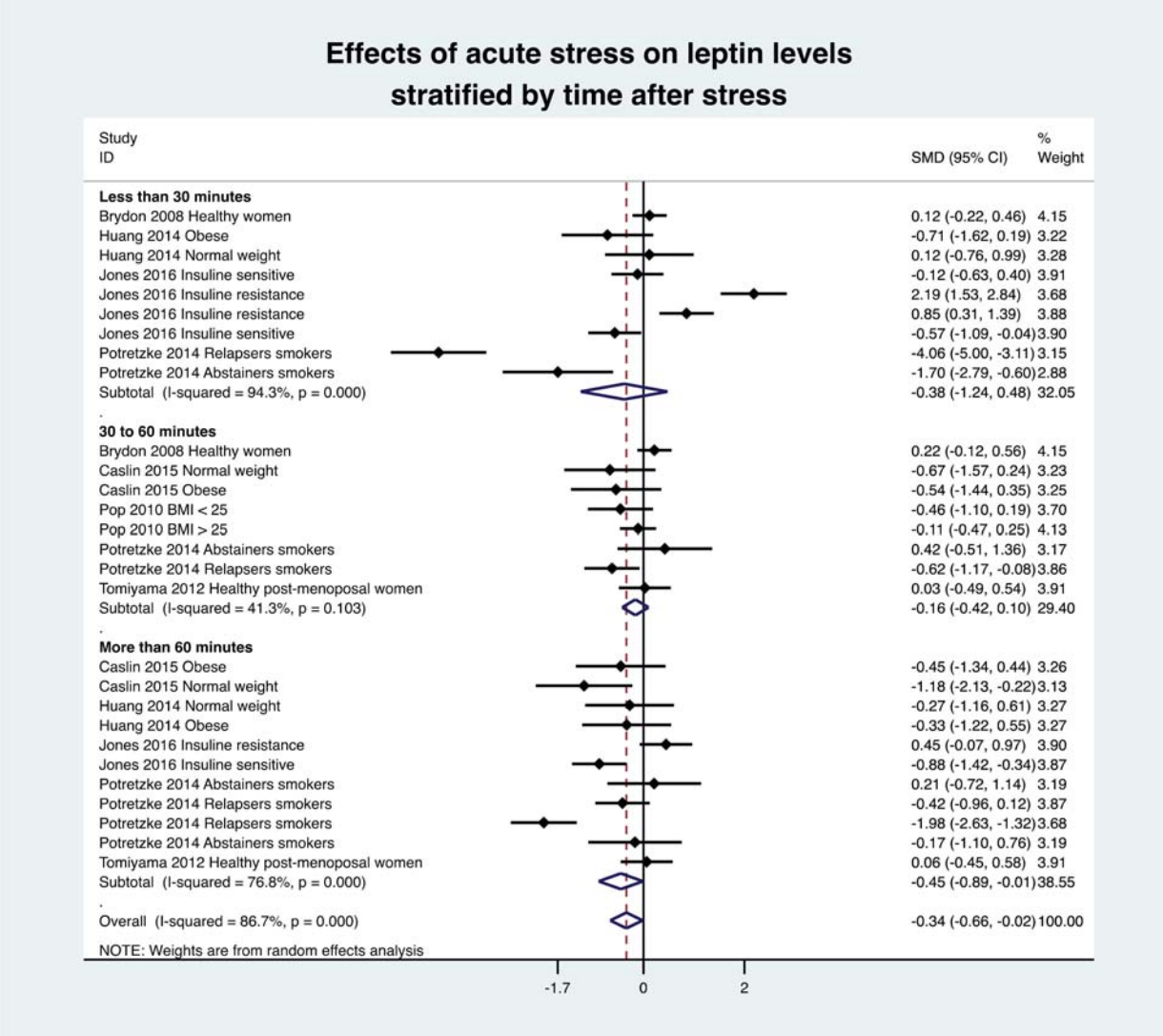

Figure 3. Meta-analysis of leptin levels following acute stress compared to baseline. SMD, standardized mean difference.

3.9. Metafunnel and Meta-Analysis after Exclusion of Studies Outside of the Metafunnel

We produced a metafunnel of the seven studies (28 groups) that showed eight groups outside. Meta-analysis after the exclusion of those groups showed similar results, i.e., an overall decrease in leptin levels (ES = −0.18, 95CI −0.32 to −0.04; $p = 0.010$). After exclusion from metafunnel, stratification by time showed a significant decrease between 30 and 60 min (−0.25, −0.50 to −0.00; $p = 0.049$) but a non-significant decrease in the first 30 min (−0.18, −0.50 to 0.15; $p = 0.29$) and after 60 min (−0.19, −0.32 to 0.09; $p = 0.18$) (Figure 5), and there were a tendency for a decrease in leptin levels following an acute stress in 12 groups of normal-weight individuals (−0.27, −0.54 to 0.01; $p = 0.056$) and in seven overweight individuals groups (−0.16, −0.34 to 0.02; $p = 0.078$) (Appendix B).

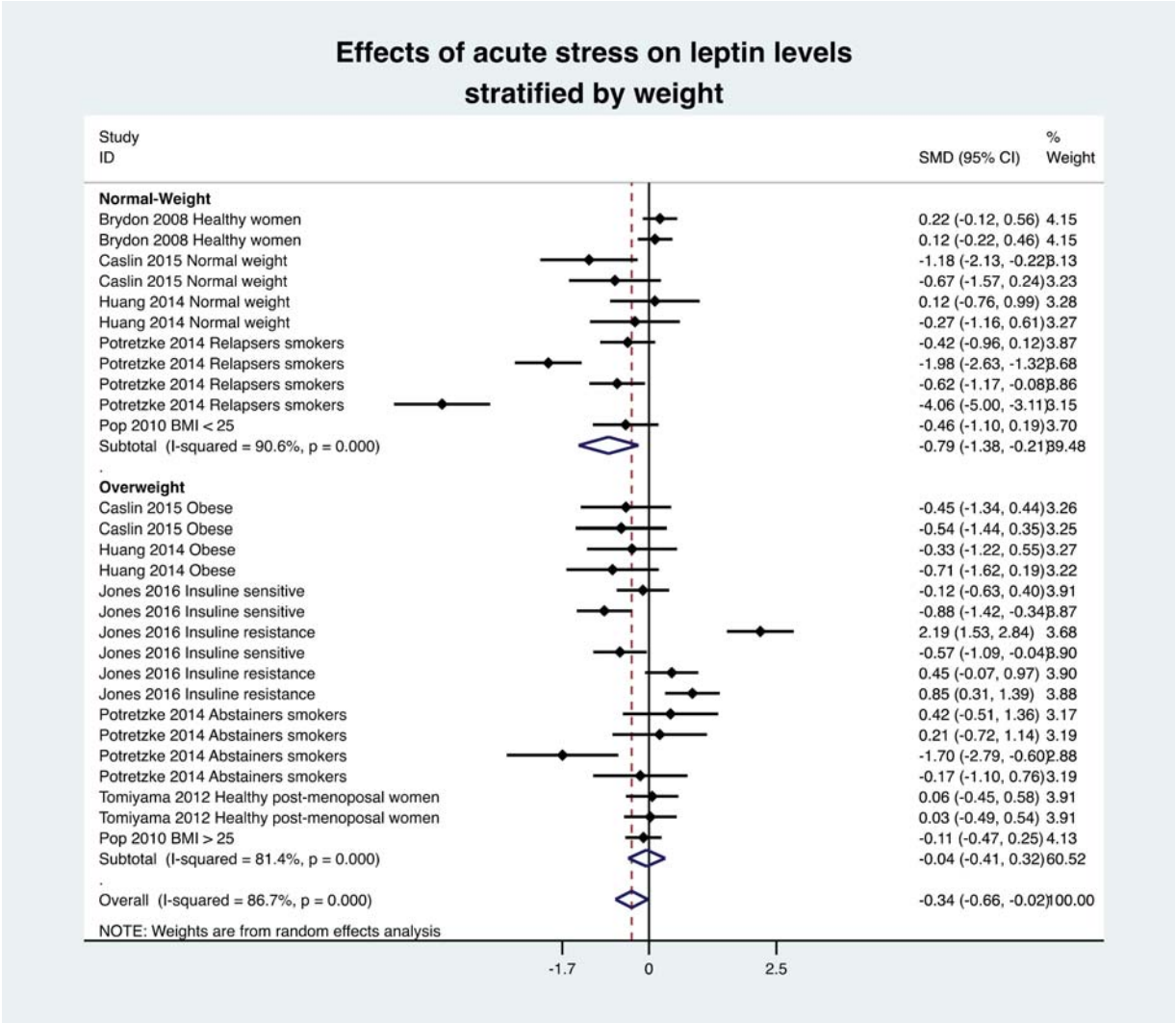

Figure 4. Meta-analysis of leptin levels following acute stress compared to baseline levels, stratified by weight of individuals. SMD, standardized mean difference.

3.10. Metaregressions

Levels of leptin after stress decreased with sex ratio—ratio of males to females (ES = −0.924, 95CI −1.58 to −0.27, p = 0.008)—and increased with the baseline levels of leptin (0.039, 0.01 to 0.07, p = 0.026). Other clinical characteristics did not significantly influence leptin's level (age, BMI, percentage of men) and neither did the duration of stress nor the time after the beginning or end of the stress (Figure 6). We also performed a meta-regression on the impact of percentage of women on leptin level: leptin levels increase with percentage of women (ES = 0.01, 95CI 0.004 to 0.016, p = 0.008).

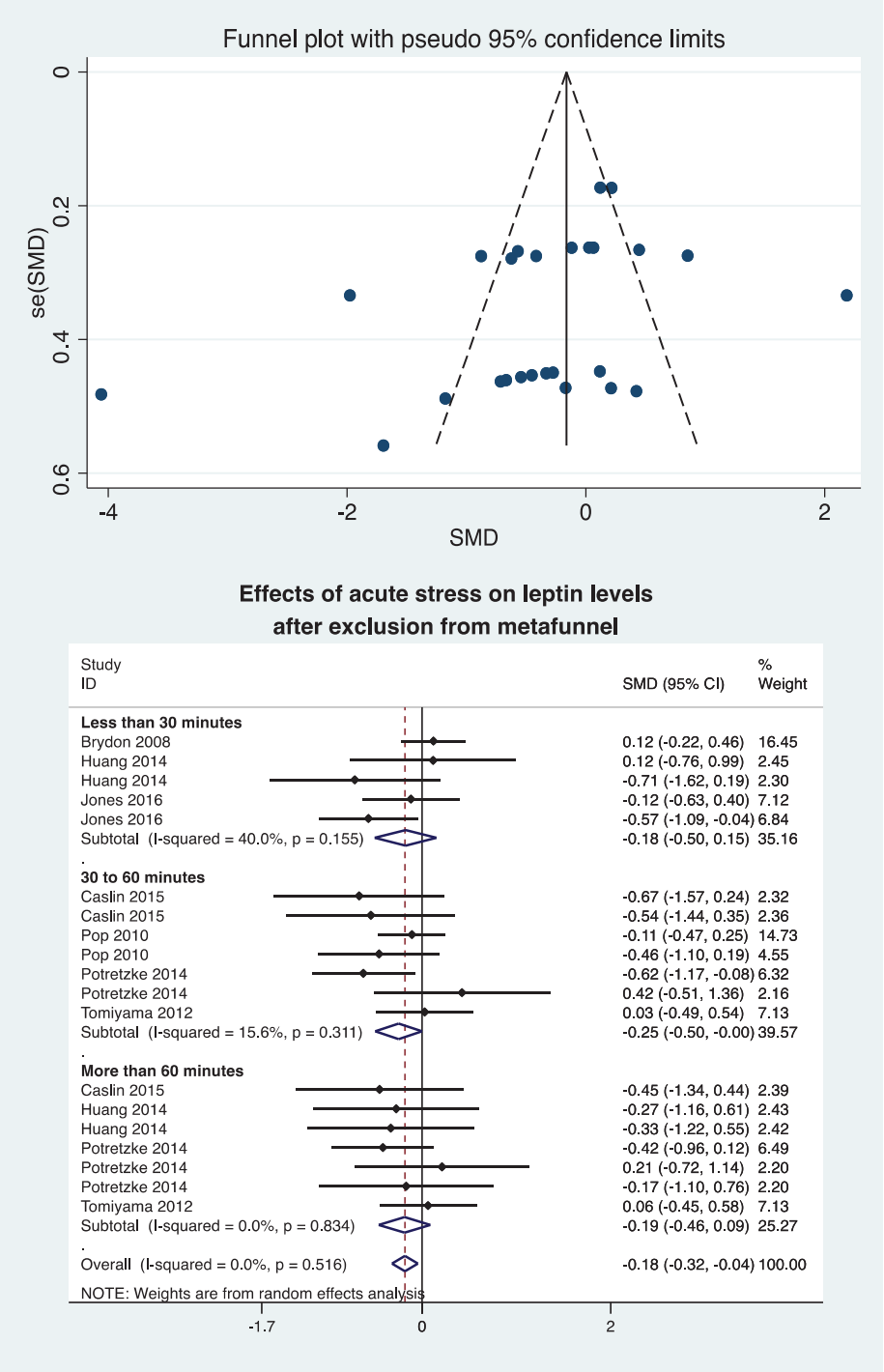

Figure 5. Meta-analysis of leptin levels after acute stress compared to baseline levels after exclusion of studies outside of the metafunnel. SMD, standardized mean difference.

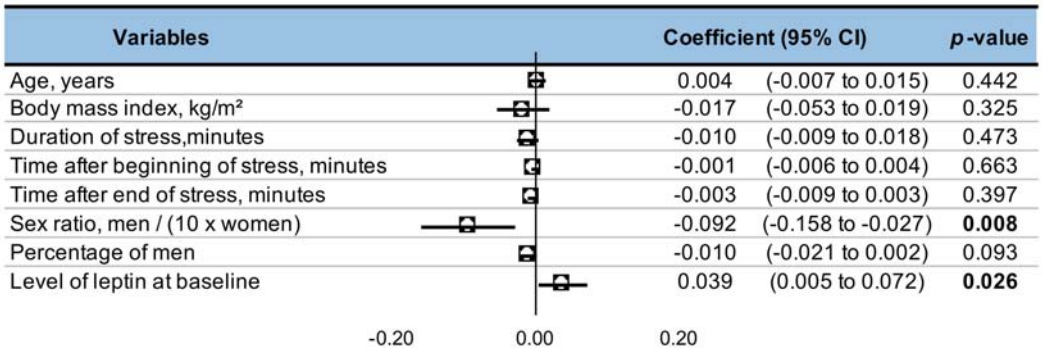

Figure 6. Meta-regression.

4. Discussion

Our main findings were that leptin is a biomarker of stress, with a decrease following an acute stress intervention. Moreover, normal-weight individuals and women seem to have a higher response than overweight individuals and men, demonstrating the link between obesity and stress. If other biomarkers of stress are routinely used, leptin should be more studied because of its impact on appetite, obesity genesis, and reproductive function.

4.1. Leptin as a Biomarker of Stress

Leptin is a 167-amino-acid peptide discovered in 1994 [37], with the majority produced by the white adipose tissue and the minority produced in other tissues, such as ovary, mammal glands, pituitary gland, skeletal muscle, lymphoid tissue, and stomach, with a prominent effect on the central nervous system [22]. Its receptors are primarily expressed in the hypothalamus and in other brain locations that regulate energy homeostasis and neuroendocrine function [38]. Very interestingly, we demonstrated that leptin is also a biomarker of stress, decreasing after exposure to a stressful environment. Leptin, also named satiety hormone, has two main effects. The first is to stop the food intake with a negative feedback loop [39]. Leptin receptors are mainly located in the arcuate, a part of the hypothalamus that produces pro-opiomelanocortin (POMC) [40]. POMC is a precursor of three main pathways: the melanocyte-stimulating-hormone axis, whose role is to regulate appetite [41] and sexual behaviour [42]; the adrenocorticotropic hormone (ACTH) axis regulating the glucocorticoids secretion mainly implicated in the stress reaction [43]; and the beta-endorphin axis producing endogenous opioids peptides [43]. The decrease of leptin levels after acute stress can be an adaptative mechanism that may help people respond to stress. Indeed, stressful events make it difficult to stay focused on a possibly intense task that could need a great deal of energy. The decrease in leptin levels could induce the signal to increase the food intake in the case that the situation will occur again. Secondly, leptin has a positive effect on energy expenditure [44], with a paracrine pathway in WAT that could be part of the fat-reducing activity of leptin and thermogenesis via the leptin receptor skeletal activation muscle [45]. The sensitivity analysis performed by the exclusion of studies outside of the funnel plot confirm this result. Indeed, funnel plots were first described in 1984 to assess the quality of articles [46]. It is primarily used as a visual aid for detecting bias or systematic heterogeneity [46]. Studies outside of the funnel plot seem to have non-comparable population with the majority of those included in the meta-analysis [46].

4.2. Acute Response to an Acute Stress Intervention

We demonstrated that leptin levels decreased in response to acute stress, mainly due to its impact on HPA axis. Therefore, leptin can be considered a biomarker of stress, such as catecholamines [47], heart rate variability [48], cytokines [49], ghrelin [50], or DHEA [51]. Moreover, leptin's main action is on the hypothalamic-pituitary-axis by increasing POMC,

the precursor of glucocorticoids. The strong relationship between leptin and corticoids has been proven with the delayed (6 h) but long-lasting increase in serum leptin (over 16 h) after a single bolus of dexamethasone given before a single large meal [52]. Furthermore, leptin has circadian variations, with the lowest concentration during the day and a higher concentration during the night. More specifically, it has been shown that zenith at midnight and nadir between 9 a.m. and 12 p.m. helps maintain sleep by inhibiting food intake behaviour [53]. Circadian rhythm can be modified by age and BMI [54]. Interestingly, leptin levels need time to decrease, with the lowest levels more than 1 h after the acute stress. It could be explained by its half-life of around 30 min, whereas other biomarkers with a shorter half-life decrease sooner [50]. As no studies assessed leptin levels more than two hours after the acute stress, the duration of the effects of the acute stress on leptin are still unknown. The relationship between obesity and stress is so strong that proposals for international recommendations suggest the implementation of stress management programs in obesity for sustainable weight loss [55,56]. Our study's benefit is the proof that acute stress decreases leptin levels and thus promotes food intake and may be a pathway towards obesity.

4.3. Impact of the Body Mass Index on Leptin

We demonstrated a higher effect on leptin levels in the normal-weight population compared to the overweight people. A possible explanation is the leptin resistance in overweight individuals [57]. This hypothesis is strengthened by our meta-regressions. Indeed, we found a significant impact of a high baseline level of leptin, which is found in overweight and obese individuals [58]. Even if genetic predispositions to diet-induced obesity exist, it is the 24/7 availability of a highly palatable diet that drives overeating [59]. High food intake increases triglyceride production and therefore the WAT production and the leptin levels (leptin being produced by WAT). The vicious circle continues with the apparition of cellular leptin resistance [57]. To achieve this, circulating leptin will rise to create a new equilibrium after expanding the fat mass. The increase of leptin levels in overweight people is associated with diminished leptin transport across the brain–blood barrier. An inhibitory negative feedback appears leading to diminished leptin receptor signal. The increase of free fatty acids and chronic overnutrition seem to induce lipotoxicity and endoplasmic reticulum stress. This inflammatory response might contribute to a blunted physiological response to leptin in obesity [60] even if overweight individuals have a higher circulating leptin level [61] throughout the circadian rhythm [62]. However, the daily variations in overweight individuals are smaller than those in normal-weight individuals. The amplitude as well as the average 24-h leptin concentration were increased by 280% and 420%, respectively, in obese compared to normal-weight women [17]. Furthermore, many genetic models have proven that the leptin gene's absence induces obesity in animals [60] and in humans [63]. For more than five decades, the energy balance equation had a significant impact on the obesity pandemic. Physical activity decreased drastically, whereas food quantity and availability of high caloric food increased [57]. Initiation of food intake is mediated via ghrelin, insulin, and cannabinoid (36). The main action of leptin arrives after the meal initiation and is responsible of satiety [22].

Unfortunately, the number of studies limited comparisons to two groups (BMI > 25 vs. BMI < 25 kg/m^2)—insufficient data precluded to further divide the BMI > 25 group into overweight and obese individuals. Moreover, most consequences of fat accumulation begin with a BMI > 25, such as an increased risk of type II diabetes, all cancers except oesophageal (female), pancreatic and prostate cancer, all cardiovascular diseases (except congestive heart failure), asthma, gallbladder disease, osteoarthritis, and chronic back pain [64]. If we did not find any impact of BMI on meta-regression, stratification by weight, i.e., overweight versus normal-weight individuals, showed a significant decrease in normal-weight individuals compared to overweight individuals. The influence of BMI on the relationship between stress and leptin may not be linear. Exploring this relationship would

require more data to find some possible threshold. Our study also lacked underweight participants to demonstrate possible U curve.

4.4. Impact of Sex on Leptin Levels

Very interestingly, we demonstrated a higher variation of leptin levels in women compared to men after acute stress. Men and women do not have the same WAT repartition. Women had a significantly lower visceral adipose tissue volume than men but a more significant subcutaneous adipose tissue [65]. Studies showed that subcutaneous fat tissue produced more leptin than visceral fat tissue [57]. Secondly, the study of circadian misalignment in shift workers showed that females had lower 24-h leptin levels, while males had higher 24-h leptin levels when misaligned [66]. Those results could promote the implication of leptin in the development of obesity in female shift workers. Furthermore, leptin has also an impact on reproduction, mainly because of the energy state of the body. Sufficient levels of leptin are a pre-requisite for the reproductive capacity in all aspects (regulation of gonadotrophs secretion, ovary function, preimplantation embryo, implantation, placentation, pregnancy, and foetal development). Furthermore, at the ovary level, leptin antagonizes the effect of growth factors on gonadotropin-stimulated steroidogenesis to augment the reproductive function of females [67]. Leptin also seems to be involved on pathogenesis of endometriosis. Indeed, even if there is no difference in serum and plasma, a higher leptin concentration level in peritoneal fluid has been showed in women with endometriosis compared to control. This should induce a local impact of leptin on endometriosis [68]. The link between sex steroids hormones and leptin is strong. Indeed, they are involved in the regulation of leptin transcription, protein secretion in adipocytes, and sexual dimorphism. Amenorrhea can result from a too-low leptin level due to a severe loss of weight. It is a possible adaptive response to low subcutaneous fat to support pregnancy and lactation [69]. Additionally, oestradiol treatment resulted in increased leptin levels, suggesting a role for this steroid in sexual dimorphism. It suggests the higher ratio of oestrogen/androgen is in part responsible for higher leptin levels observed in females compared to males [70]. Lastly, higher circulating leptin concentrations and/or elevated expression of leptin receptors in tumours may be poor prognostic factors [71]. Because of its impact on inflammation, oxidative stress, cell proliferation, inhibition of apoptosis, angiogenesis and immune modulation, leptin seems to impact the development of cancer [71] and specially of breast cancer in obese premenopausal women [72].

4.5. Limitations

Our study has some limitations. Meta-analyses inherit the limitations of the individual studies of which they are composed and therefore are subjected to the bias of included studies. Another limitation is related to the publication bias. Indeed, studies with positive effects are more likely published than those with negative effects. However, the use of broader keywords in the search strategy limits the number of missing studies. Only seven monocentric studies were available for meta-analysis, and the total number of subjects included was not as extensive as one would prefer. No included studies had a randomized controlled design. Moreover, blinding of the stress interventions were deemed not feasible. Though there were similarities between the inclusion criteria, they were not identical. Limiting our meta-analysis to studies sharing precisely the same inclusion and exclusion criteria was impossible due to limited data. All studies were monocentric, limiting the generalizability of our results. However, our selection of articles was rigorous, and few studies were outliers when considering metafunnels. The high I^2 attested heterogeneity between studies. Nevertheless, after the exclusion of studies outside the metafunnel, our results stayed statistically significant. Even if leptin levels follow a circadian rhythm, and time of procedure differs between studies, our meta-analysis is still valid, as each participant is his own control (comparison of leptin levels after the stress to before the stress) within a limited period of time (90 maximum after the stress). Due to the lack of information, we failed to perform meta regressions on the impact of smoking, physical

activity, insulin resistance, or levels of cholesterol (LDL, HDL, triglycerides). Unfortunately, the low number of studies (one) precluded analysis on physical stress. After exclusion of studies outside of the metafunnel, we failed to find a significant decrease of leptin levels stratified by weight, mainly because of the weak number of groups (19 versus 28 before exclusion of metafunnel) and only seven in the group "overweight" versus eleven. However, tendency is strong in overweight group, with a $p = 0.056$.

5. Conclusions

Leptin is a biomarker of stress, with a decrease following an acute stress intervention. Normal-weight individuals have a higher response, emphasizing the link between stress, obesity, and leptin resistance. Women also have a higher variation of leptin levels after an acute stress. Our findings suggests that leptin may have implications in obesity development in response to stress in a sex-dependent manner. The link between appetite regulation and stress warrants further investigation, and better understanding may be used as a component of weight management strategies. The responses to acute stressful events may provide a novel therapeutic strategy to modify risk factors of obesity development in the hope of improving stress vulnerability, especially in the female population. Furthermore, it could be relevant to study longer or repeated stress to be more related to real-life events.

Author Contributions: J.-B.B.-M. conceived and designed the analysis. J.-B.B.-M., M.T., and F.D. conducted the systematic literature search. D.T., J.S., and F.M. corrected the manuscript. J.-B.B.-M., D.B., A.C.B., and F.D. wrote the manuscript. All authors gave final approval for the eligibility of all articles included in the analysis and provided critical revision of the article. J.-B.B.-M. and F.D. analysed the data. J.-B.B.-M. and F.D. wrote the first draft of the manuscript and were responsible for the integrity of the data analysis. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

Details for the search strategy used within each database.

PUBMED

("leptin"[MH] OR "ob protein"[TW] OR "ob gene product"[TW] OR "obesity factor"[TW] OR "obese gene product"[TW] OR "obese protein"[TW] OR "leptin"[TW])

AND

("Stress, Psychological"[Mesh] OR "Anxiety"[Mesh:NoExp] OR anxie*[TIAB] OR anxious*[TIAB] OR stress*[TIAB] OR mood[TIAB] OR emotion[TIAB])

Filter Language = none Filter Dates = none

Web of science (WOS)

(leptin OR "ob protein" OR "ob gene product" OR "obesity factor" OR "obese gene product" OR "obese protein")

AND

(anxie* OR anxious* OR stress* OR mood OR emotion)

Filter Language = none Filter Dates = none

Cochrane Library

(leptin OR "ob protein" OR "ob gene product" OR "obesity factor" OR "obese gene product" OR "obese protein")

AND
(anxie* OR anxious* OR stress* OR mood OR emotion)
Filter Language = none
Filter Dates = none
Embase
(leptin OR "ob protein" OR "ob gene product" OR "obesity factor" OR "obese gene product" OR "obese protein")
AND
(anxie* OR anxious* OR stress* OR mood OR emotion)
Filter Language = none; Filter Dates = none

Appendix B

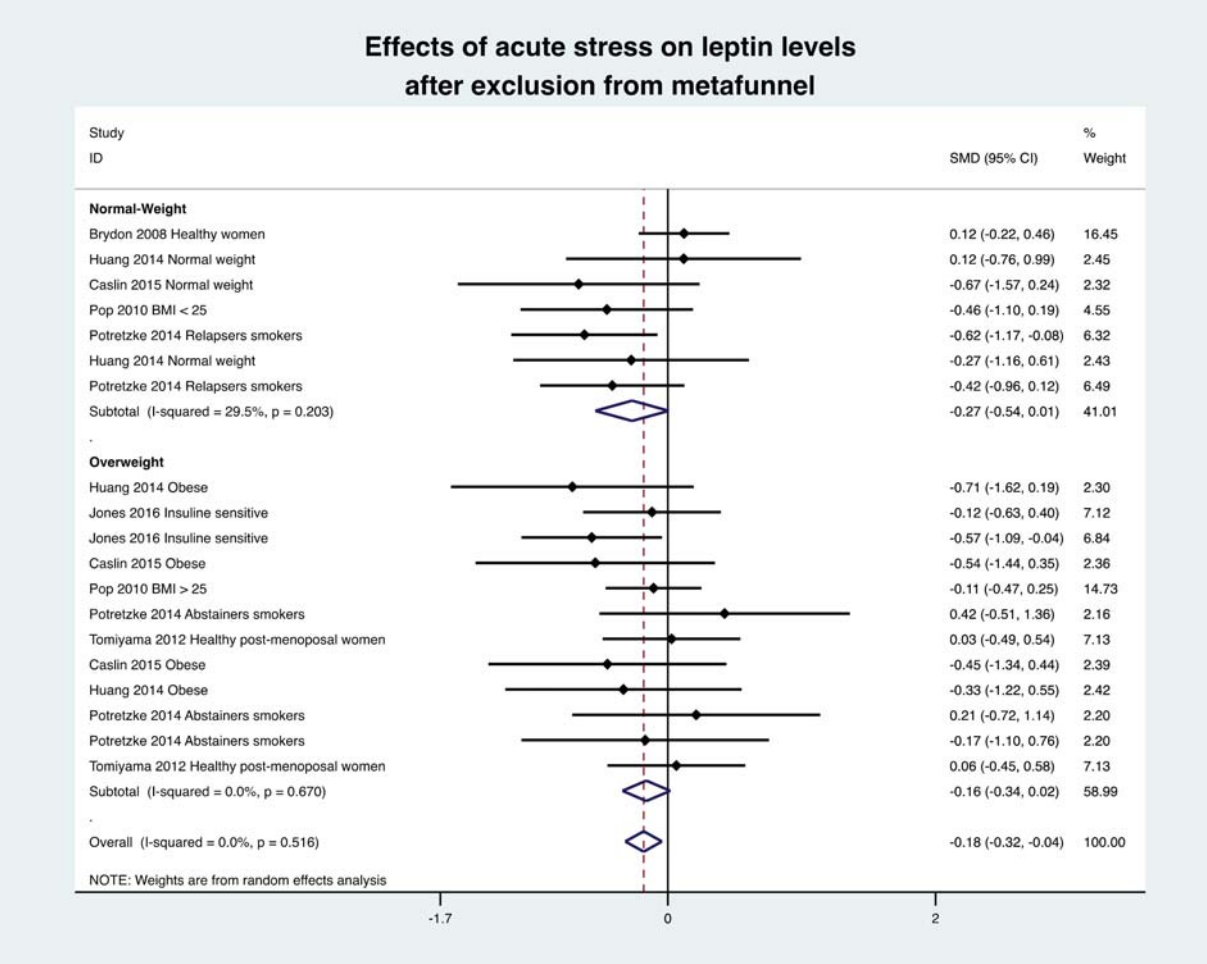

Figure A1. Meta-analysis of leptin levels after an acute stress compared to baseline levels after exclusion of studies outside of the metafunnel.

References

1. Graham, N.M. Psychological stress as a public health problem: How much do we know? *Community Health Stud.* **1988**, *12*, 151–160. [CrossRef]
2. Steen, P.B.; Poulsen, P.H.; Andersen, J.H.; Biering, K. Subjective social status is an important determinant of perceived stress among adolescents: A cross-sectional study. *BMC Public Health* **2020**, *20*, 396. [CrossRef]

3. Mathers, C.; Fat, D.M.; Boerma, J.T. *The Global Burden of Disease: 2004 Update*; World Health Organization, Ed.; World Health Organization: Geneva, Switzerland, 2008; ISBN 978-9241563710.
4. Wekenborg, M.K.; von Dawans, B.; Hill, L.K.; Thayer, J.F.; Penz, M.; Kirschbaum, C. Examining reactivity patterns in burnout and other indicators of chronic stress. *Psychoneuroendocrinology* **2019**, *106*, 195–205. [CrossRef] [PubMed]
5. Vinkers, C.H.; Kuzminskaite, E.; Lamers, F.; Giltay, E.J.; Penninx, B.W. An integrated approach to understand biological stress system dysregulation across depressive and anxiety disorders. *J. Affect. Disord.* **2021**, *283*, 139–146. [CrossRef] [PubMed]
6. Southwick, S.M.; Vythilingam, M.; Charney, D.S. The psychobiology of depression and resilience to stress: Implications for prevention and treatment. *Annu. Rev. Clin. Psychol.* **2005**, *1*, 255–291. [CrossRef] [PubMed]
7. Dutheil, F.; Aubert, C.; Pereira, B.; Dambrun, M.; Moustafa, F.; Mermillod, M.; Baker, J.S.; Trousselard, M.; Lesage, F.-X.; Navel, V. Suicide among physicians and health-care workers: A systematic review and meta-analysis. *PLoS ONE* **2019**, *14*, e0226361. [CrossRef]
8. Kivimaki, M.; Steptoe, A. Effects of stress on the development and progression of cardiovascular disease. *Nat. Rev. Cardiol.* **2018**, *15*, 215–229. [CrossRef] [PubMed]
9. Chami, R.; Monteleone, A.M.; Treasure, J.; Monteleone, P. Stress hormones and eating disorders. *Mol. Cell. Endocrinol.* **2019**, *497*, 110349. [CrossRef] [PubMed]
10. Tomiyama, A.J. Stress and obesity. *Annu. Rev. Psychol.* **2019**, *70*, 703–718. [CrossRef]
11. Zamkah, A.; Hui, T.; Andrews, S.; Dey, N.; Shi, F.; Sherratt, R.S. Identification of suitable biomarkers for stress and emotion detection for future personal affective wearable sensors. *Biosensors* **2020**, *10*, 40. [CrossRef] [PubMed]
12. Condon, E.M. Chronic stress in children and adolescents: A review of biomarkers for use in pediatric research. *Biol. Res. Nurs.* **2018**, *20*, 473–496. [CrossRef]
13. Chojnowska, S.; Ptaszyńska-Sarosiek, I.; Kępka, A.; Knaś, M.; Waszkiewicz, N. Salivary biomarkers of stress, anxiety and depression. *J. Clin. Med.* **2021**, *10*, 517. [CrossRef]
14. García-León, M.Á.; Pérez-Mármol, J.M.; Gonzalez-Pérez, R.; García-Ríos, M.D.C.; Peralta-Ramírez, M.I. Relationship between resilience and stress: Perceived stress, stressful life events, hpa axis response during a stressful task and hair cortisol. *Physiol. Behav.* **2019**, *202*, 87–93. [CrossRef] [PubMed]
15. Münzberg, H.; Morrison, C. Structure, production and signaling of leptin. *Metabolism* **2015**, *64*, 13–23. [CrossRef]
16. Scheja, L.; Heeren, J. The endocrine function of adipose tissues in health and cardiometabolic disease. *Nat. Rev. Endocrinol.* **2019**, *15*, 507–524. [CrossRef]
17. Langendonk, J.G.; Pijl, H.; Toornvliet, A.C.; Burggraaf, J.; Frölich, M.; Schoemaker, R.C.; Doornbos, J.; Cohen, A.F.; Meinders, A.E. Circadian rhythm of plasma leptin levels in upper and lower body obese women: Influence of body fat distribution and weight loss. *J. Clin. Endocrinol. Metab.* **1998**, *83*, 1706–1712. [CrossRef] [PubMed]
18. Gijón-Conde, T.; Graciani, A.; Guallar-Castillón, P.; Aguilera, M.T.; Rodríguez-Artalejo, F.; Banegas, J.R. Leptin reference values and cutoffs for identifying cardiometabolic abnormalities in the spanish population. *Rev. Esp. Cardiol. Engl. Ed.* **2015**, *68*, 672–679. [CrossRef]
19. Triantafyllou, G.A.; Paschou, S.A.; Mantzoros, C.S. Leptin and hormones: Energy homeostasis. *Endocrinol. Metab. Clin. N. Am.* **2016**, *45*, 633–645. [CrossRef] [PubMed]
20. Park, H.-K.; Ahima, R.S. Physiology of leptin: Energy homeostasis, neuroendocrine function and metabolism. *Metabolism* **2015**, *64*, 24–34. [CrossRef] [PubMed]
21. Bird, L. Exercise lowers leptin and leukocytosis. *Nat. Rev. Immunol.* **2020**, *20*, 2–3. [CrossRef]
22. Zhang, Y.; Chua, S. Leptin function and regulation. *Compr. Physiol.* **2017**, *8*, 351–369. [CrossRef] [PubMed]
23. Simon, C.; Gronfier, C.; Schlienger, J.L.; Brandenberger, G. Circadian and ultradian variations of leptin in normal man under continuous enteral nutrition: Relationship to sleep and body temperature. *J. Clin. Endocrinol. Metab.* **1998**, *83*, 1893–1899. [CrossRef]
24. Torres, S.J.; Nowson, C.A. Relationship between stress, eating behavior, and obesity. *Nutr. Burbank Los Angel. City Calif.* **2007**, *23*, 887–894. [CrossRef] [PubMed]
25. Wells, G.A.; Shea, B.; O'Connell, D.; Peterson, J.; Welch, V.; Losos, M.; Tugwell, P. *The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Non-Randomised Studies in Meta-Analyses*; Ottawa Hospital Research Institute: Ottawa, ON, Canada, 2011; pp. 1–12.
26. DerSimonian, R.; Laird, N. Meta-analysis in clinical trials. *Control. Clin. Trials* **1986**, *7*, 177–188. [CrossRef]
27. Brydon, L.; Wright, C.; O'Donnell, K.; Zachary, I.; Wardle, J.; Steptoe, A. Stress-induced cytokine responses and central adiposity in young women. *Int. J. Obes.* **2008**, *32*, 443–450. [CrossRef]
28. Caslin, H.L.; Franco, R.L.; Crabb, E.B.; Huang, C.J.; Bowen, M.K.; Acevedo, E.O. The effect of obesity on inflammatory cytokine and leptin production following acute mental stress. *Psychophysiology* **2016**, *53*, 151–158. [CrossRef]
29. Huang, C.-J.; Stewart, J.K.; Shibata, Y.; Slusher, A.L.; Acevedo, E.O. Lipopolysaccharide-binding protein and leptin are associated with stress-induced interleukin-6 cytokine expression ex vivo in obesity. *Psychophysiology* **2015**, *52*, 687–694. [CrossRef]
30. Tomiyama, A.J.; Schamarek, I.; Lustig, R.H.; Kirschbaum, C.; Puterman, E.; Havel, P.J.; Epel, E.S. Leptin concentrations in response to acute stress predict subsequent intake of comfort foods. *Physiol. Behav.* **2012**, *107*, 34–39. [CrossRef] [PubMed]
31. Jones, K.T.; Shelton, R.C.; Wan, J.; Li, L. Impact of acute psychological stress on cardiovascular risk factors in face of insulin resistance. *Stress Amst. Neth.* **2016**, *19*, 585–592. [CrossRef] [PubMed]

32. Pop, D.; Bodisz, G.; Petrovai, D.; Borz, B.; Zdrenghea, V.; Zdrenghea, D. The effect of very short duration acute physical exercise upon adiponectin and leptin in overweight subjects. *Rom. J. Intern. Med. Rev. Roum. Med. Interne* **2010**, *48*, 39–45.
33. Potretzke, S.; Nakajima, M.; Cragin, T.; Al'Absi, M. Changes in circulating leptin levels during acute stress and associations with craving in abstinent smokers: A preliminary investigation. *Psychoneuroendocrinology* **2014**, *47*, 232–240. [CrossRef]
34. Katz, A.; Nambi, S.S.; Mather, K.; Baron, A.D.; Follmann, D.A.; Sullivan, G.; Quon, M.J. Quantitative insulin sensitivity check index: A simple, accurate method for assessing insulin sensitivity in humans. *J. Clin. Endocrinol. Metab.* **2000**, *85*, 2402–2410. [CrossRef] [PubMed]
35. Acevedo, E.O.; Webb, H.E.; Weldy, M.L.; Fabianke, E.C.; Orndorff, G.R.; Starks, M.A. Cardiorespiratory responses of hi fit and low fit subjects to mental challenge during exercise. *Int. J. Sports Med.* **2006**, *27*, 1013–1022. [CrossRef]
36. Pop, L.C.; Sukumar, D.; Tomaino, K.; Schlussel, Y.; Schneider, S.H.; Gordon, C.L.; Wang, X.; Shapses, S.A. Moderate weight loss in obese and overweight men preserves bone quality. *Am. J. Clin. Nutr.* **2015**, *101*, 659–667. [CrossRef] [PubMed]
37. Zhang, Y.; Proenca, R.; Maffei, M.; Barone, M.; Leopold, L.; Friedman, J.M. Positional cloning of the mouse obese gene and its human homologue. *Nature* **1994**, *372*, 425–432. [CrossRef]
38. Seoane-Collazo, P.; Martínez-Sánchez, N.; Milbank, E.; Contreras, C. Incendiary leptin. *Nutrients* **2020**, *12*, 472. [CrossRef] [PubMed]
39. Zanchi, D.; Depoorter, A.; Egloff, L.; Haller, S.; Mählmann, L.; Lang, U.E.; Drewe, J.; Beglinger, C.; Schmidt, A.; Borgwardt, S. The impact of gut hormones on the neural circuit of appetite and satiety: A systematic review. *Neurosci. Biobehav. Rev.* **2017**, *80*, 457–475. [CrossRef] [PubMed]
40. Dodd, G.T.; Decherf, S.; Loh, K.; Simonds, S.E.; Wiede, F.; Balland, E.; Merry, T.L.; Münzberg, H.; Zhang, Z.-Y.; Kahn, B.B.; et al. Leptin and insulin act on POMC neurons to promote the browning of white Fat. *Cell* **2015**, *160*, 88–104. [CrossRef] [PubMed]
41. Baldini, G.; Phelan, K.D. The melanocortin pathway and control of appetite-progress and therapeutic implications. *J. Endocrinol.* **2019**, *241*, R1–R33. [CrossRef]
42. Argiolas, A.; Melis, M.R. Neuropeptides and central control of sexual behaviour from the past to the present: A review. *Prog. Neurobiol.* **2013**, *108*, 80–107. [CrossRef] [PubMed]
43. Rousseau, K.; Kauser, S.; Pritchard, L.E.; Warhurst, A.; Oliver, R.L.; Slominski, A.; Wei, E.T.; Thody, A.J.; Tobin, D.J.; White, A. Proopiomelanocortin (POMC), the ACTH/Melanocortin precursor, is secreted by human epidermal keratinocytes and melanocytes and stimulates melanogenesis. *FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol.* **2007**, *21*, 1844–1856. [CrossRef] [PubMed]
44. Pandit, R.; Beerens, S.; Adan, R.A.H. Role of leptin in energy expenditure: The hypothalamic perspective. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2017**, *312*, R938–R947. [CrossRef] [PubMed]
45. Nwadozi, E.; Ng, A.; Strömberg, A.; Liu, H.-Y.; Olsson, K.; Gustafsson, T.; Haas, T.L. Leptin is a physiological regulator of skeletal muscle angiogenesis and is locally produced by PDGFRα and PDGFRβ expressing perivascular cells. *Angiogenesis* **2018**, *22*, 103–115. [CrossRef] [PubMed]
46. Copas, J. Meta-analysis, funnel plots and sensitivity analysis. *Biostatistics* **2000**, *1*, 247–262. [CrossRef]
47. Tank, A.W.; Wong, D.L. Peripheral and central effects of circulating catecholamines. *Compr. Physiol.* **2014**, *5*, 1–15. [CrossRef]
48. Goessl, V.C.; Curtiss, J.E.; Hofmann, S.G. The effect of heart rate variability biofeedback training on stress and anxiety: A meta-analysis. *Psychol. Med.* **2017**, *47*, 2578–2586. [CrossRef]
49. Jung, Y.-H.; Shin, N.Y.; Jang, J.H.; Lee, W.J.; Lee, D.; Choi, Y.; Choi, S.-H.; Kang, D.-H. Relationships among stress, emotional intelligence, cognitive intelligence, and cytokines. *Medicine* **2019**, *98*, e15345. [CrossRef]
50. Bouillon-Minois, J.-B.; Trousselard, M.; Thivel, D.; Gordon, B.; Schmidt, J.; Moustafa, F.; Oris, C.; Dutheil, F. Ghrelin as a Biomarker of stress: A systematic review and meta-analysis. *Nutrients* **2021**, *13*, 784. [CrossRef] [PubMed]
51. Dutheil, F.; de Saint Vincent, S.; Pereira, B.; Schmidt, J.; Moustafa, F.; Charkhabi, M.; Bouillon-Minois, J.-B.; Clinchamps, M. DHEA as a biomarker of stress: A systematic review and meta-analysis. *Front. Psychiatry* **2021**, *12*, 688367. [CrossRef]
52. Laferrère, B.; Fried, S.K.; Osborne, T.; Pi-Sunyer, F.X. Effect of one morning meal and a bolus of dexamethasone on 24-hour variation of serum leptin levels in humans. *Obes. Res.* **2000**, *8*, 481–486. [CrossRef]
53. Jha, K.P.; Challet, E.; Kalsbeek, A. circadian rhythms in glucose and lipid metabolism in nocturnal and diurnal mammals. *Mol. Cell. Endocrinol.* **2015**, *418 Pt 1*, 74–88. [CrossRef]
54. Zhao, Z.-Y.; Fu, Y.-R.; Li, X.-H.; Li, Y.-Y.; Bogdan, A.; Touitou, Y. Age-related modifications of circadian rhythm of serum leptin in healthy men. *Gerontology* **2002**, *48*, 309–314. [CrossRef] [PubMed]
55. Isasi, C.R.; Parrinello, C.M.; Jung, M.M.; Carnethon, M.R.; Birnbaum-Weitzman, O.; Espinoza, R.A.; Penedo, F.J.; Perreira, K.M.; Schneiderman, N.; Sotres-Alvarez, D.; et al. Psychosocial stress is associated with obesity and diet quality in Hispanic/Latino adults. *Ann. Epidemiol.* **2015**, *25*, 84–89. [CrossRef]
56. Czeglédi, E. Options for stress management in obesity treatment. *Orv. Hetil.* **2016**, *157*, 260–267. [CrossRef]
57. Myers, M.G.; Leibel, R.L.; Seeley, R.J.; Schwartz, M.W. Obesity and leptin resistance: Distinguishing cause from effect. *Trends Endocrinol. Metab. TEM* **2010**, *21*, 643–651. [CrossRef]
58. Friedman, J.M. Leptin and the endocrine control of energy balance. *Nat. Metab.* **2019**, *1*, 754–764. [CrossRef]
59. Levin, B.E.; Dunn-Meynell, A.A.; McMinn, J.E.; Alperovich, M.; Cunningham-Bussel, A.; Chua, S.C. A New obesity-prone, glucose-intolerant rat strain (F.DIO). *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2003**, *285*, R1184–R1191. [CrossRef]
60. Cui, H.; López, M.; Rahmouni, K. The cellular and molecular bases of leptin and ghrelin resistance in obesity. *Nat. Rev. Endocrinol.* **2017**, *13*, 338–351. [CrossRef] [PubMed]

61. Perakakis, N.; Farr, O.M.; Mantzoros, C.S. Leptin in leanness and obesity: JACC state-of-the-art review. *J. Am. Coll. Cardiol.* **2021**, *77*, 745–760. [CrossRef]
62. Majeed, M.; Majeed, S.; Nagabhushanam, K.; Gnanamani, M.; Mundkur, L. Lesser investigated natural ingredients for the management of obesity. *Nutrients* **2021**, *13*, 510. [CrossRef]
63. Montague, C.T.; Farooqi, I.S.; Whitehead, J.P.; Soos, M.A.; Rau, H.; Wareham, N.J.; Sewter, C.P.; Digby, J.E.; Mohammed, S.N.; Hurst, J.A.; et al. Congenital leptin deficiency is associated with severe early-onset obesity in humans. *Nature* **1997**, *387*, 903–908. [CrossRef] [PubMed]
64. Guh, D.P.; Zhang, W.; Bansback, N.; Amarsi, Z.; Birmingham, C.L.; Anis, A.H. The incidence of co-morbidities related to obesity and overweight: A systematic review and meta-analysis. *BMC Public Health* **2009**, *9*, 88. [CrossRef]
65. Demerath, E.W.; Sun, S.S.; Rogers, N.; Lee, M.; Reed, D.; Choh, A.C.; Couch, W.; Czerwinski, S.A.; Chumlea, W.C.; Siervogel, R.M.; et al. Anatomical patterning of visceral adipose tissue: Race, sex, and age variation. *Obes. Silver Spring Md.* **2007**, *15*, 2984–2993. [CrossRef] [PubMed]
66. Qian, J.; Morris, C.J.; Caputo, R.; Wang, W.; Garaulet, M.; Scheer, F.A.J.L. Sex differences in the circadian misalignment effects on energy regulation. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 23806–23812. [CrossRef] [PubMed]
67. Pérez-Pérez, A.; Sánchez-Jiménez, F.; Maymó, J.; Dueñas, J.L.; Varone, C.; Sánchez-Margalet, V. Role of leptin in female reproduction. *Clin. Chem. Lab. Med. CCLM* **2015**, *53*, 15–28. [CrossRef]
68. Kalaitzopoulos, D.R.; Lempesis, I.G.; Samartzis, N.; Kolovos, G.; Dedes, I.; Daniilidis, A.; Nirgianakis, K.; Leeners, B.; Goulis, D.G.; Samartzis, E.P. Leptin concentrations in endometriosis: A systematic review and meta-analysis. *J. Reprod. Immunol.* **2021**, *146*, 103338. [CrossRef]
69. Palmer, B.F.; Clegg, D.J. The sexual dimorphism of obesity. *Mol. Cell. Endocrinol.* **2015**, *402*, 113–119. [CrossRef]
70. Jenks, M.Z.; Fairfield, H.E.; Johnson, E.C.; Morrison, R.F.; Muday, G.K. Sex steroid hormones regulate leptin transcript accumulation and protein secretion in 3T3-L1 Cells. *Sci. Rep.* **2017**, *7*, 8232. [CrossRef] [PubMed]
71. Ray, A.; Cleary, M.P. The potential role of leptin in tumor invasion and metastasis. *Cytokine Growth Factor Rev.* **2017**, *38*, 80–97. [CrossRef]
72. Atoum, M.F.; Alzoughool, F.; Al-Hourani, H. Linkage between obesity leptin and breast cancer. *Breast Cancer Basic Clin. Res.* **2020**, *14*, 1178223419898458. [CrossRef] [PubMed]

4. Conclusion

Nous avons montré que la ghréline et la leptine, hormones de régulation de l'appétit, peuvent être toutes les deux considérées comme des biomarqueurs de stress puisque leur concentration varie après un stress aigu en laboratoire. De manière très intéressante, nous avons montré que la ghréline subit des variations très rapides (dans les cinq minutes suivant le stress) suivi d'un retour à l'état basal dans la demi-heure. La leptine, quant à elle, n'a pas de variation significative immédiatement après le stress. En revanche, sa diminution apparaît environ 30 minutes après le stress. Nous pouvons alors supposer qu'il existe un effet synergique entre les deux hormones et que l'une – la leptine – prend le relais de l'autre – la ghréline – pour maintenir le signal d'ingestion.

ETUDE 6

« The impact of job-demand-control-support on Leptin and Ghrelin as biomarkers of stress in Emergency Healthcare Workers»

1. Introduction

Il y a deux façons de voir cet article. Soit comme l'objectif principal, soit comme un article de synthèse du travail de thèse dont le cheminement a été complexe. Dans les deux cas, il représente l'aboutissement du travail. La littérature sur les conséquences du travail de nuit sur le stress et la prise alimentaire est présente mais faible. Son impact sur la leptine et la ghréline n'a jamais été étudié.

Cet article est actuellement « under review » dans la revue Nutrients (IF 6.706)

2. **Article**

nutrients

MDPI

Type of the Paper (Article)

The impact of job-demand-control-support on leptin and ghrelin as biomarkers of stress in emergency healthcare workers

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Abstract: Despite the available literature on the consequences of night shiftwork on stress and food intake, its impact on leptin and ghrelin has never been studied. We previously demonstrated that leptin and ghrelin were biomarkers related to stress, and acute stress induced a decrease in leptin levels and an increase in ghrelin levels. We performed a prospective observational study to assess the influence of night work, nutrition and stress on the levels of ghrelin and leptin among emergency healthcare workers (HCWs). We took salivary samples at the beginning of a day shift and/or at the end of a night shift. We also monitored stress using the job demand-control-support model of Karasek. We recorded 24-hour food intake during the day shift and the consecutive night shift, and during night work and the day before. We included 161 emergency HCWs. Emergency HCWs had a tendency for decreased levels of leptin following the night shift compared to before dayshift (p=0.067). Furthermore, the main factors explaining the decrease in leptin levels were an increase in job-demand (coefficient -54.1, 95CI -99.0 to -0.92) and a decrease in job control (-24.9, -49.5 to -0.29). Despite no significant changes in ghrelin levels between shifts, the main factor explaining the increase in ghrelin was social support (6.12, 0.74 to 11.5). Food intake (kcal) also had a negative impact on leptin levels, in addition to age. Ghrelin levels also decreased with body mass index while age had the opposite effect. In conclusion, we confirmed that ghrelin and leptin as biomarkers of stress

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were directly linked to the job demand-control-support model of Karasek, when the main cofounders were considered.

Keywords: nutrients, work, well-being, quality of life, leptin, ghrelin

1. Introduction

Stress at work is a major public health concern. This is especially true among healthcare workers (HCWs) and even more concerning in the Emergency Departments (ED) due to shift work, fatigue and lack of sleep [1], poor food intake [2], and life-threatening emergencies in the context of overcrowding and job demands [3,4]. Currently, the best scale to assess stress level at work is the job-demand-control-support model (JDCS), a self-reported psychological questionnaire, created and validated by Karasek in 1981 [5,6]. Night work, defined as "all work which is performed during a period of not less than seven consecutive hours, including the interval from midnight to 5 a.m." [7], has many health consequences. These include, disturbance of circadian rhythm [8], obesity and cardiometabolic disorders [9–11] which are putative consequences of eating disorders [12] and stress [13]. Eating behavior can be influenced by sociodemographic criteria such as age and gender [14] and by occupational characteristics such as experience [15] and workload [16,17]. Night work also induce a conflict between socially determined diurnal mealtimes, eating habits, the biological rhythm of hunger, satiety, and metabolism [18,19]. The main hormones that control the physiology of appetite are ghrelin and leptin. Ghrelin leads the orexigenic role [20]. Increased ghrelin levels influence meal initiation and food-seeking behavior [21]. In response to a meal, levels vary quickly and intensely, due to its short half-life [22,23]. Leptin, a peptide mainly produced in white adipose tissue is commonly known as a satiety hormone with low levels observed during meal initiation and high levels after the meal [24]. Its baseline blood levels are influenced by body mass index (BMI), mainly due to the white adipose tissue component [25]. Furthermore, both ghrelin and leptin are influenced by stress and can be considered as biomarkers of stress [26,27]. Emergency HCWs are a perfect example for studying the impact of night shift and stress on biomarkers of nutrition [28]. Indeed, HCWs work under stressful conditions such as overcrowding – lack of beds in hospitals [3], life-threatening emergencies [29], the wait for possible disasters [30] all having consequences on the biomarkers of stress [31,32]. Furthermore, the night shift has a bad influence on water consumption and food intake among emergency HCWs, in both quantity and quality [2]. To date, no studies have assessed the influence of night work and stress on the levels of nutrition biomarkers among emergency HCWs, nor in relation to their occupational characteristics.

Therefore, we performed this study to assess the influence of night work, stress and sociodemographic characteristics on ghrelin and leptin levels among emergency HCWs.

2. Materials and Methods

2.1 Study Design

We performed a prospective nationwide observational study in five French hospitals – two university hospitals and three non-university hospitals. The main inclusion criterion was to work as an emergency HCW. Exclusion criteria were refusal to participate and pregnancy. This study was part of the SEEK protocol [2,28,30]. We obtained ethical approval from the French Ethics Committee South-East I with reference DC-2014-2151, and the protocol was registered on ClinicalTrials.gov number NCT02401607. The study was performed during two shifts (day shift and night shift). During day shift, participants started to work between 7:30 and 8:30 am and finished between 6:30 and 7:30 pm. For

nightshift, they began between 6:30 and 7:30 pm and finished between 7:30 and 8:30 am the following day. All participants volunteered and signed consent forms before answering questionnaires and providing samples. They performed the study for one dayshift and/or one nightshift. Salivary sampling were collected at the beginning of a dayshift and at the end of a nightshift, i.e. between 7:00 am and 8:30 am for both conditions. Furthermore, food intake was monitored twice over 24 consecutive hours: 1) during a day shift (from 8:30 am to 6:30 pm) + the night after (no work, 6:30 pm to 8.30 am), and 2) during a rest day before (from 8:30 am to 6:30 pm) and a night shift (6:30 pm to 8:30 am) [2]. Participants had also to complete a questionnaire collecting their level of stress using the JDCS model of Karasek [6] and sociodemographic data (Figure 1).

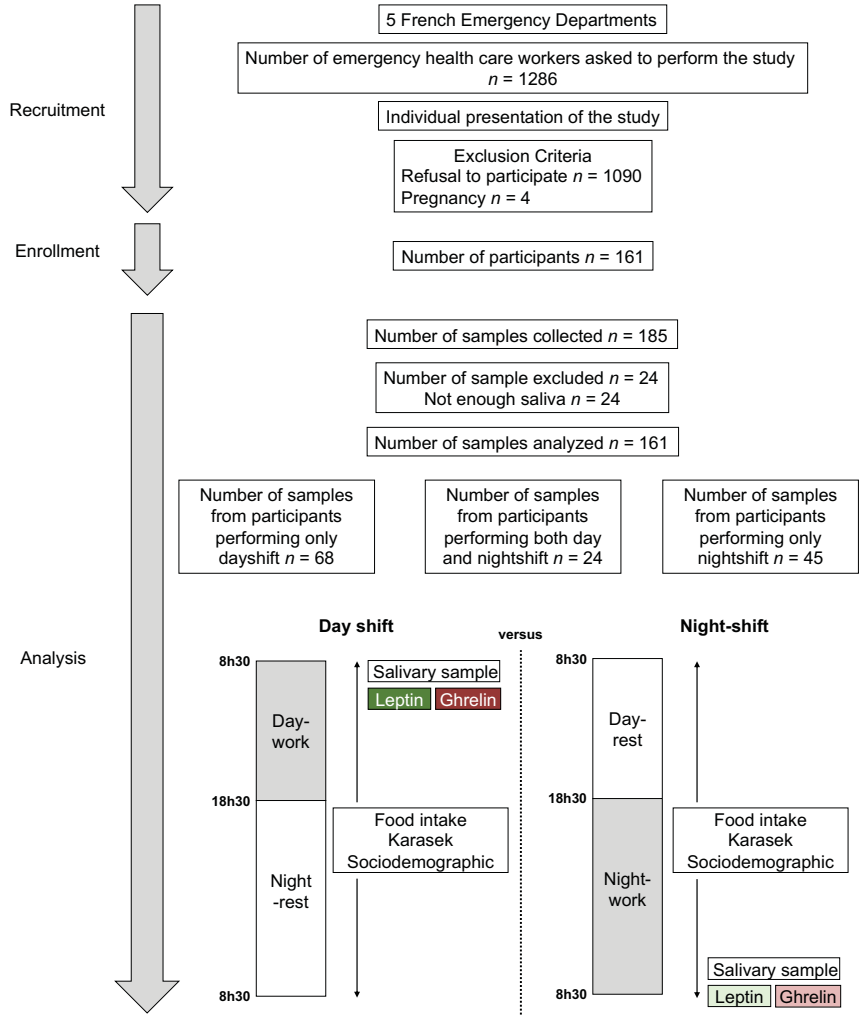

Figure 1. Study design. Among five French Emergency Departments we were able to recruit 161 emergency health care workers for a total of 185 salivary samples. Twenty-four were excluded because of a low quantity of saliva. Ghrelin and leptin levels were assessed from 161 samples.

2.2 Outcomes

Ghrelin and leptin levels were measured from saliva samples. Saliva samples were stored at -80°C at the Institute of Occupational Medicine of Clermont-Ferrand. Total ghrelin was assessed by ELISA using commercial kits (kit CEA991Hu de Clound Clone Corp (USA) with a detection range from 12.35 to 1000pg/mL, a sensitivity level at

<4.87pg/mL, an intra-assay coefficient <10% and an inter-assay coefficient <12%. Leptin was assessed using ALPCO, Salem, NH, USA / 22-LEPHUU-e01 / kit ultrasensitive with a range from 0.05 to 5 ng/mL, a sensitivity level at 0.01 ng/mL, an intra-assay coefficient at 7.2 % and an inter-assay coefficient at 4.35%. Karasek's job-content questionnaire (JCQ) is composed of three dimensions: psychological demands, decision latitude, and social support. Participants were assessed by the 26 items of the JCQ (nine for both decision latitude and psychological demand and eight for social support). Each participant was asked to answer using a 4-level Likert-type scale for each item, ranging from 1 (strongly disagree) to 4 (strongly agree). Decision latitude was calculated using the following formula: 4*Q4 + 4*(5-Q6) + 4* Q8 + 2*(5-Q2) + 2*Q5 + 2*Q7 +2*Q1 + 2*Q3 + 2*Q9. A score less than 71 reflects low decision latitude. Psychological demand was calculated with the following formula: Q10 + Q11 + Q12 + (5-Q13) + Q14 + Q15 + Q16 + Q17 + Q18. A score below 20 reflected a low psychological demand. Social support was calculated with the following formula: Q19 + Q20 + Q21 + Q22 + Q23 + Q24 + Q25 + Q26. A score below 24 reflected low social support [6]. Participants were also asked to complete a 24-hour dietary recall that was explained and detailed to them by a member of the investigation team. The participants were asked to indicate as precisely as possible all the details regarding the food ingested during each meal and in-between meals. The diaries were reviewed with the participants during a dedicated interview. We next used Nutrilog® (Nutrilog, version 3.2), a diet and nutrition software for health care professionals, to translate participants answers on nutrient intake using a nutrition table Ciqual® based on this software. We calculated total energy intake (kcal), carbohydrates, lipids, proteins (grams and % energy intake), and water consumption in milliliters (mL) [2]. Participants also had to complete a questionnaire about their sociodemographic (age, gender, marital status, kids at home, tobacco) and work situation (occupation, seniority).

2.3 Statistics

Continuous variables were expressed as mean and standard deviation (SD), or median [interquartile range] (IQR) and categorical variables were expressed as number (percentage - %). The assumption of Gaussian distribution was analyzed by Shapiro-Wilk test. As data could be repeated for a part of participants habits (measures for nightshift and dayshift), linear mixed method were performed (i) to compare values between nightshift and dayshift (i.e. to assess the influence of night work on ghrelin and leptin levels) and then (ii) to assess the influence on ghrelin and leptin levels on: stress (using job demand, job control and social support), nutrition (food intake in kcal, carbohydrates, lipids and proteins in grams), water consumption and sociodemographic data (job, age, BMI). Time (nightshift versus dayshift) was considered as fixed effect whereas participants were considered as random effects in order to model between and within subject variability. The normality of residuals was analyzed with Shapiro-Wilk test and a visual plot. Accordingly, ghrelin and leptin levels were log-transformed. The results were expressed as coefficient regressions and 95 confidence intervals (95CI). To increase readability, results were expressed using the following formulas: 1000xlog(leptin) or 100xlog(ghrelin). Statistical analyses were performed with Stata software (v17, College Station, Texas, US). Significance was set at the $p < 0.05$ level. Sensitivity analysis was conducted among emergency HCWs that engaged in the study on both the dayshift and nightshift. Both were compared for their main characteristics to evaluate the sample representativeness.

3. Results

3.1 Characteristics of the population

We enrolled 161 emergency HCWs from five hospitals and obtained a total of 185 samples of saliva. Twenty-four samples were excluded due to the insufficiency of saliva. In total, we analyzed 161 saliva samples. Twenty-four (14.9%) performed the study twice

(one during day shift and one during night shift) (Figure 1). The representativeness of the emergency HCWs was examined. We did not find any differences between the HCWs that performed the study twice versus those who performed only one shift. Fifty-seven HCWs were physicians, 79 were nurses and 24 had other occupations (administrative, maid). Participants were 37.4 ±10.4 years old, mainly female (57.5%, sex ratio = 1.37), with a mean BMI at 23.2 ± 4.4 kg/m^2. Fifty-three (32.9%) were single, and 77 (58.3%) had no children. Median seniority as a HCWs was 6 [IQR 13] years, 3 [9] years in the ED (Table 1).

	Total n=161	**Physician n=57**	**Paramedics n=79**	**Other n=24**
Age, years, mean ± SD	37.4 ± 10.4	35.7 ± 10.4	39.5 ± 10.2	34.9 ± 10.3
Sex, n (%) male	68 (42.5)	29 (50.9)	28 (35.4)	11 (45.8)
BMI, kg/m², mean ± SD	23.2 ± 4.4	22.9 ± 4.3	23.2 ± 3.6	23.7 ± 4.4
Underweight, n (%)	10 (6.2)	3 (5.3)	6 (7.6)	1 (4.2)
Normal weight, n (%)	107 (66.5)	39 (68.4)	53 (67.1)	15 (62.5)
Overweight, n (%)	36 (22.4)	14 (24.6)	17 (21.5)	5 (20.8)
Obesity class 1, n (%)	4 (2.5)	0	1 (1.3)	3 (12.5)
Obesity class 2, n (%)	1 (0.6)	0	1 (1.3)	0
Obesity class 3, n (%)	3 (1.9)	1 (1.8)	1 (1.3)	0
Seniority, years, median [IQR]				
In the job	6 [13]	4 [8.5]	11 [13]	4.5 [8.5]
In the department	3 [9]	2 [4.5]	5 [9]	1 [6]
Physical activity, h/week, median [IQR]	2 [4]	2 [5]	2 [4]	2 [3]
Tea/coffee, cup/day, median [IQR]	3 [3]	4 [2]	6 [12]	5 [3.5]
Smoker, n (%)	57 (35.6)	17 (29.8)	31 (39.7)	9 (37.5)
Cig/day for smokers, median [IQR]	6 [9]	8 [5]	6 [12]	5 [3.5]
Family situation				
Married-engaged, n (%)	108 (67.1)	35 (61.4)	63 (79.7)	9 (37.5)
Single-divorced, n (%)	53 (32.9)	22 (38.6)	16 (20.2)	15 (62.5)
Kids at home, n (%)	55 (41.7)	16 (33.3)	35 (53.0)	4 (22.2)

Table 1. Sociodemographic. SD = standard deviation, BMI = body mass index, kg=kilograms, kg/m^2=kilogram per square meter, IQR = interquartile range, n = number, % = percentage. Results are expressed as mean ± standard deviation or median [interquartile range] or number (percentage).

3.2 Assessment of ghrelin and leptin's levels

We found a lower level of both ghrelin and leptin levels after the end of the night shift compared to the level at the beginning of the day shift (Figure 2).

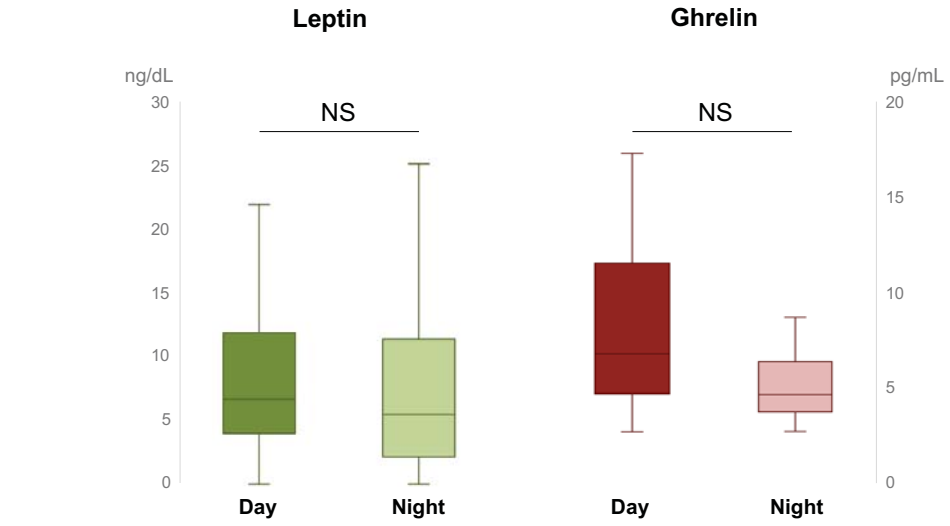

Figure 2: Median [interquartile range] salivary levels of leptin and ghrelin, before the beginning of a day shift and at the end of a night shift. Results of leptin are expressed in nanogram per deciliter. Results of ghrelin are expressed in picogram per milliliter. ng=nanogram, pg=picogram, dL=deciliter, mL=milliliter, NS=not significant, n=number of samples studied, SD=standard deviation, IQR=interquartile range.

3.3 Impact of stress, night shift, sociodemographic and nutrition on leptin and ghrelin levels

Regarding leptin levels (expressed as 1000*log leptin) – we found a negative impact of job demand on leptin levels (Coefficient -54.1 per 10-unit; 95CI -99.0 to -0.92) while job control increased leptin levels (24.9 per 10-unit; 0.29 to 49.5). Age increases parallelly with leptin level (1.93 per year; 0.26 to 3.61). We also found a negative tendency for night shift (-40.2; -83.2 to 2.82), BMI (-5.36 per kg/m^2; -10.8 to 0.09) and food intake (-2.39 per 100 kcal/24h; -4.83 to 0.58) while water consumption tended to increase leptin levels (2.94 per dL/24h; -2.58 to 6.13). Regarding ghrelin (expressed as 100*log ghrelin), we found a positive impact of social support (6.12 per unit; 0.74 to 11.5), and age (2.34 per year; 0.46 to 4.25), and a negative impact for BMI (-8.31 per kg/m^2; -14.0 to -2.60).

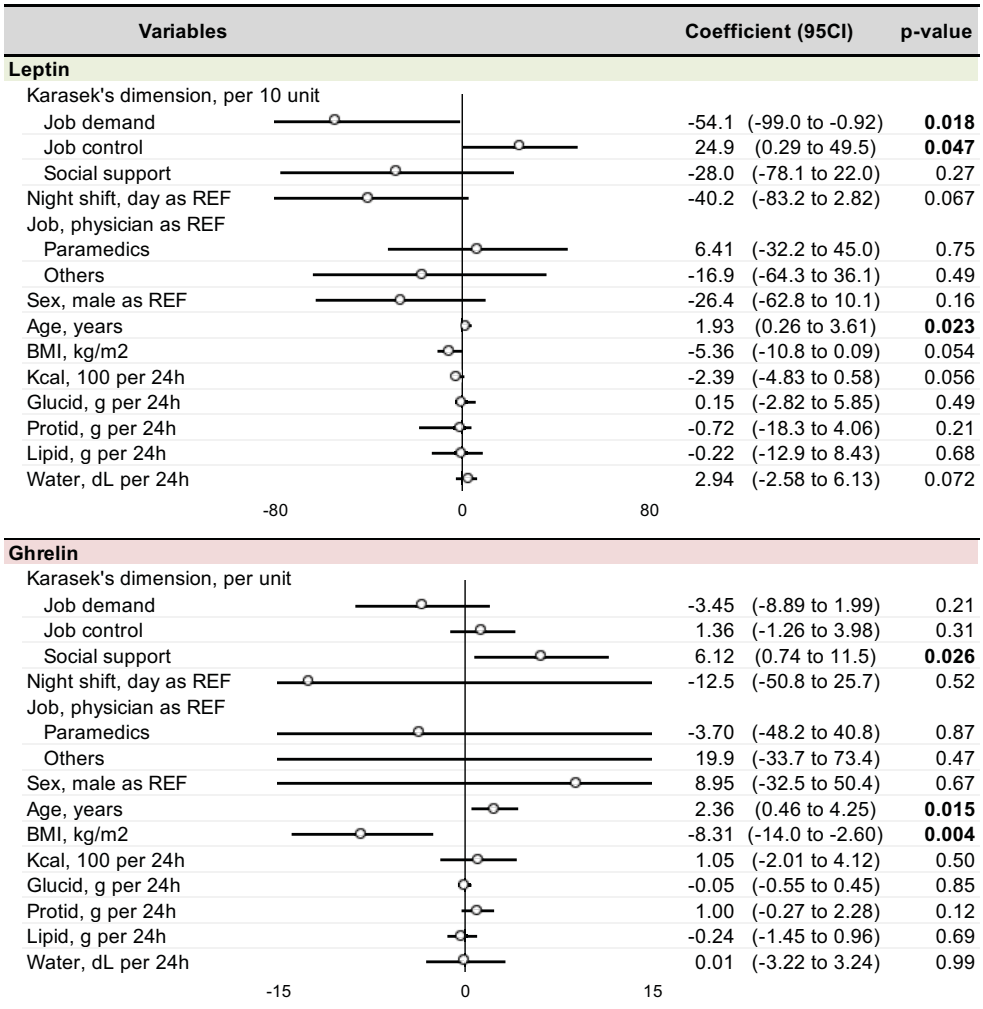

Figure 3. Impact of stress, night, sociodemographic status and nutrition on leptin and ghrelin salivary levels using a linear mixed model. Results were expressed using coefficient regression (95% confidence interval). Results were considered significant for p-value <0.05 and 95CI not containing 0. BMI=body mass index, kg=kilogram, m^2=square meter, g=gram, dL=deciliter.

4. Discussion

We demonstrated that both stress, nightshift and food intake have an impact on nutrition biomarkers represented by ghrelin and leptin.

4.1 The impact of night shift and stress

We found a lower level of both ghrelin and leptin after the night shift compared to before the beginning of the day shift. Considering that these hormones act inversely, this result needs to be discussed. Ghrelin is considered as the main orexigenic hormone. A high level of ghrelin promotes food intake while a low level is observed at the end of a meal. Literature on the impact of night work on ghrelin levels is not strong and is controversial. Indeed, one study did not find any difference in 24h ghrelin levels recorded between day and nightshifts [33] while another study found a lower ghrelin level among night shift workers compared to dayshift workers [34]. However, all studies observed that ghrelin levels are unstable (in a range of minutes) to be considered using mean levels. Conversely, leptin is the main satiety hormone with low levels observed during meal

initiation and high levels after the meal. However, the impact of night work on leptin levels seems to be negative. Indeed, it seems that average 24h leptin levels decreased up to 40% during the nightshift compared to baseline in two studies that experimentally created night and day shifts [33,35]. Furthermore, this impact seems to increase for participants that have a non-synchronized schedule [36]. However, a further study noted different results, i.e., an increase of leptin levels among hospital nurses, among night workers that worked exclusively during the night for at least one year [37]. Regarding the impact of stress on ghrelin, we did not find any significant impact of job demand and job control. However, it seems that social support increases ghrelin levels (coeff 6.12; 95CI 0.74 to 11.5). Regarding leptin, job demand decreased leptin levels while job control increased levels. This confirms the influence of stress on leptin levels and more widely the impact of stress on biomarker responses. We previously published that both ghrelin and leptin are influenced by stress. More precisely, ghrelin increases very quickly once stress is induced – within less than five minutes – and returns to baseline levels within 45 minutes. Leptin decreases more slowly with a significant decrease after 60 minutes [26,27].

4.2 Impact of food intake and sociodemographic status

We found a negative impact of kcal per day intake on leptin levels with no impact on ghrelin levels. This result is not logical when initially considered. Indeed, leptin is a satiety hormone, so we would expect that greater amounts of food would induce higher levels of leptin. Furthermore, we also found a negative impact of BMI (coef -0.005; 95CI -0.011 to 0.0001). Indeed, overweight individuals have a higher circulating leptin level and leptin resistance due to the availability of highly palatable food that increases triglyceride production and therefore white adipose tissue production of leptin [38,39]. A possible explanation for this could be the negative impact of sleep deprivation. Indeed, several studies found lower leptin levels among healthy volunteers with acute sleep deprivation or chronic partial sleep deprivation [40–42]. Very interestingly, we did not find any impact of qualitative nutrients, i.e., carbohydrates, lipids, or proteins, on biomarker levels. Furthermore, water consumption seems to increase leptin levels although we did not find an explanation why in the literature. A possible answer is that participants declared drinking with soft drink and not water, a high concentrated fructose drink, linked to obesity [43]. Lastly, we found a higher level of leptin among older participants, which is consistent with the literature [44]. Regarding ghrelin, we did not find significant covariates. This could be explained by fluctuations in homeostasis. We only found a negative correlation between BMI and ghrelin level, which is consistent with the literature [45]. However, we found a positive impact of age on ghrelin levels, which is controversial in the literature [46–48]. No other data was significant regarding food intake, water consumption, stress, or quality of food.

4.3 Limitations

Our study has some limitations, none of which affects our results. First, we performed only one measurement but both ghrelin and leptin have a circadian rhythm [49]. However, every sample was collected and studied under the same conditions. Second, total ghrelin was assayed rather than its active, acylated form. Nevertheless, most of the physiology of ghrelin has been defined based on the assay of total ghrelin. Thirdly, even if we tried to monitor the time of breakfast, data were too unprecise to be used. Indeed, HCWs eat their breakfast before work during dayshift but it is not consistent with those working on nightshift. Considering that ghrelin levels decrease quickly and intensely after the beginning of food intake, and increase slowly until lunch, the putative results could be more significant. Some devices are now able to continuously monitor certain biomarkers. Advances in technology should soon facilitate the circadian rhythm of leptin and ghrelin in emergency HCWs, making it feasible to study the underlying mechanisms of stress regulation.

5. Conclusions

In conclusion, we confirmed that ghrelin and leptin are biomarkers of stress directly linked to the job demand-control-support model of Karasek, in a study that considered the main cofounders. Understanding mechanisms of stress in a comprehensive study may help to build efficient health promotion and/or preventive strategies.

6. Patents

Author Contributions: The following statements should be used "Conceptualization, F.D. and J.S.; methodology, F.D. and B.P..; validation, All authors.; formal analysis, J-B.B-M, S.S-V and F.D.; investigation, F.D. and J.S.; writing—original draft preparation, J-B.B-M; writing—review and editing, J.O., O.J.A., V.S., D.B., D.T., U.C.U, J.S.B., R.B, and M.T.; supervision, F.D.; All authors have read and agreed to the published version of the manuscript."

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

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References

1. Dutheil, F.; Danini, B.; Bagheri, R.; Fantini, M.L.; Pereira, B.; Moustafa, F.; Trousselard, M.; Navel, V. Effects of a Short Daytime Nap on the Cognitive Performance: A Systematic Review and Meta-Analysis. *Int J Environ Res Public Health* **2021**, *18*, 10212, doi:10.3390/ijerph181910212.
2. Bouillon-Minois, J.-B.; Thivel, D.; Croizier, C.; Ajebo, É.; Cambier, S.; Boudet, G.; Adeyemi, O.J.; Ugbolue, U.C.; Bagheri, R.; Vallet, G.T.; et al. The Negative Impact of Night Shifts on Diet in Emergency Healthcare Workers. *Nutrients* **2022**, *14*, 829, doi:10.3390/nu14040829.
3. Bouillon-Minois, J.-B.; Raconnat, J.; Clinchamps, M.; Schmidt, J.; Dutheil, F. Emergency Department and Overcrowding During COVID-19 Outbreak; a Letter to Editor. *1* **2021**, *9*, e28–e28, doi:10.22037/aaem.v9i1.1167.
4. Bouillon-Minois, J.-B.; Schmidt, J.; Dutheil, F. SARS-CoV-2 Pandemic and Emergency Medicine: The Worst Is yet to Come. *Am J Emerg Med* **2020**, doi:10.1016/j.ajem.2020.06.014.
5. Karasek, R.A. Job Demands, Job Decision Latitude, and Mental Strain : Implications for Job Redesign. *Adm. Sci. Q.* **1979**, *24*, 285–308.
6. Karasek, R.A. *Job Decision Latitude, Job Design, and Coronary Heart Disease*; Machine pacing and occupational stress.; Taylor and Francis Ltd: London, 1981;
7. Convention C171 - Night Work Convention, 1990 (No. 171) Available online: https://www.ilo.org/dyn/normlex/en/f?p=NORMLEXPUB:12100:0::NO::P12100_INSTRUMENT_ID:312316 (accessed on 4 November 2021).
8. Boivin, D.B.; Boudreau, P. Impacts of Shift Work on Sleep and Circadian Rhythms. *Pathol Biol (Paris)* **2014**, *62*, 292–301, doi:10.1016/j.patbio.2014.08.001.
9. Ganesan, S.; Magee, M.; Stone, J.E.; Mulhall, M.D.; Collins, A.; Howard, M.E.; Lockley, S.W.; Rajaratnam, S.M.W.; Sletten, T.L. The Impact of Shift Work on Sleep, Alertness and Performance in Healthcare Workers. *Sci Rep* **2019**, *9*, 4635, doi:10.1038/s41598-019-40914-x.

10. Kosmadopoulos, A.; Kervezee, L.; Boudreau, P.; Gonzales-Aste, F.; Vujovic, N.; Scheer, F.A.J.L.; Boivin, D.B. Effects of Shift Work on the Eating Behavior of Police Officers on Patrol. *Nutrients* **2020**, *12*, E999, doi:10.3390/nu12040999.
11. Lim, Y.C.; Hoe, V.C.W.; Darus, A.; Bhoo-Pathy, N. Association between Night-Shift Work, Sleep Quality and Metabolic Syndrome. *Occup Environ Med* **2018**, *75*, 716–723, doi:10.1136/oemed-2018-105104.
12. Keski-Rahkonen, A.; Mustelin, L. Epidemiology of Eating Disorders in Europe: Prevalence, Incidence, Comorbidity, Course, Consequences, and Risk Factors. *Curr Opin Psychiatry* **2016**, *29*, 340–345, doi:10.1097/YCO.0000000000000278.
13. Dutheil, F.; Chaplais, E.; Vilmant, A.; Courteix, D.; Duche, P.; Abergel, A.; Pfabigan, D.M.; Han, S.; Mobdillon, L.; Vallet, G.T.; et al. Stress Management in Obesity during a Thermal Spa Residential Programme (ObesiStress): Protocol for a Randomised Controlled Trial Study. *BMJ Open* **2019**, *9*, e027058, doi:10.1136/bmjopen-2018-027058.
14. Abdella, H.M.; El Farssi, H.O.; Broom, D.R.; Hadden, D.A.; Dalton, C.F. Eating Behaviours and Food Cravings; Influence of Age, Sex, BMI and FTO Genotype. *Nutrients* **2019**, *11*, E377, doi:10.3390/nu11020377.
15. Gifkins, J.; Johnston, A.; Loudoun, R. The Impact of Shift Work on Eating Patterns and Self-Care Strategies Utilised by Experienced and Inexperienced Nurses. *Chronobiol Int* **2018**, *35*, 811–820, doi:10.1080/07420528.2018.1466790.
16. Padilla, H.M.; Wilson, M.; Vandenberg, R.J.; Davis, M.; Clark, M.A. Health Behavior among Working Adults: Workload and Exhaustion Are Associated with Nutrition and Physical Activity Behaviors That Lead to Weight Gain. *J Health Psychol* **2021**, *26*, 892–904, doi:10.1177/1359105319851205.
17. Nishitani, N.; Sakakibara, H.; Akiyama, I. Eating Behavior Related to Obesity and Job Stress in Male Japanese Workers. *Nutrition* **2009**, *25*, 45–50, doi:10.1016/j.nut.2008.07.008.
18. Palla, L.; Almoosawi, S. Diurnal Patterns of Energy Intake Derived via Principal Component Analysis and Their Relationship with Adiposity Measures in Adolescents: Results from the National Diet and Nutrition Survey RP (2008–2012). *Nutrients* **2019**, *11*, E422, doi:10.3390/nu11020422.
19. Bonham, M.P.; Kaias, E.; Zimberg, I.; Leung, G.K.W.; Davis, R.; Sletten, T.L.; Windsor-Aubrey, H.; Huggins, C.E. Effect of Night Time Eating on Postprandial Triglyceride Metabolism in Healthy Adults: A Systematic Literature Review. *J Biol Rhythms* **2019**, *34*, 119–130, doi:10.1177/0748730418824214.
20. Bali, A.; Jaggi, A.S. An Integrative Review on Role and Mechanisms of Ghrelin in Stress, Anxiety and Depression. *Curr Drug Targets* **2016**, *17*, 495–507, doi:10.2174/1389450116666150518095650.
21. Hansson, C.; Shirazi, R.H.; Näslund, J.; Vogel, H.; Neuber, C.; Holm, G.; Anckarsäter, H.; Dickson, S.L.; Eriksson, E.; Skibicka, K.P. Ghrelin Influences Novelty Seeking Behavior in Rodents and Men. *PLoS ONE* **2012**, *7*, e50409, doi:10.1371/journal.pone.0050409.
22. Cummings, D.E. Ghrelin and the Short- and Long-Term Regulation of Appetite and Body Weight. *Physiol Behav* **2006**, *89*, 71–84, doi:10.1016/j.physbeh.2006.05.022.
23. Nagaya, N.; Kojima, M.; Uematsu, M.; Yamagishi, M.; Hosoda, H.; Oya, H.; Hayashi, Y.; Kangawa, K. Hemodynamic and Hormonal Effects of Human Ghrelin in Healthy Volunteers. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2001**, *280*, R1483-1487, doi:10.1152/ajpregu.2001.280.5.R1483.
24. Münzberg, H.; Morrison, C.D. Structure, Production and Signaling of Leptin. *Metabolism* **2015**, *64*, 13–23, doi:10.1016/j.metabol.2014.09.010.
25. Gijón-Conde, T.; Graciani, A.; Guallar-Castillón, P.; Aguilera, M.T.; Rodríguez-Artalejo, F.; Banegas, J.R. Leptin Reference Values and Cutoffs for Identifying Cardiometabolic Abnormalities in the Spanish Population. *Rev Esp Cardiol (Engl Ed)* **2015**, *68*, 672–679, doi:10.1016/j.rec.2014.08.015.
26. Bouillon-Minois, J.-B.; Trousselard, M.; Thivel, D.; Benson, A.C.; Schmidt, J.; Moustafa, F.; Bouvier, D.; Dutheil, F. Leptin as a Biomarker of Stress: A Systematic Review and Meta-Analysis. *Nutrients* **2021**, *13*, 3350, doi:10.3390/nu13103350.

27. Bouillon-Minois, J.-B.; Trousselard, M.; Thivel, D.; Gordon, B.A.; Schmidt, J.; Moustafa, F.; Oris, C.; Dutheil, F. Ghrelin as a Biomarker of Stress: A Systematic Review and Meta-Analysis. *Nutrients* **2021**, *13*, doi:10.3390/nu13030784.
28. Bouillon-Minois, J.-B.; Trousselard, M.; Pereira, B.; Schmidt, J.; Clinchamps, M.; Thivel, D.; Ugbolue, U.C.; Moustafa, F.; Occelli, C.; Vallet, G.; et al. Protocol of the Study on Emergency Health Care Workers' Responses Evaluated by Karasek Questionnaire: The SEEK-Study Protocol. *Int J Environ Res Public Health* **2021**, *18*, 4068, doi:10.3390/ijerph18084068.
29. Durand, A.-C.; Bompard, C.; Sportiello, J.; Michelet, P.; Gentile, S. Stress and Burnout among Professionals Working in the Emergency Department in a French University Hospital: Prevalence and Associated Factors. *Work* **2019**, *63*, 57–67, doi:10.3233/WOR-192908.
30. Bouillon-Minois, J.-B.; Roux, V.; Pereira, B.; Flannery, M.; Pelissier, C.; Occelli, C.; Schmidt, J.; Navel, V.; Dutheil, F. Stress among Emergency Health Care Workers on Nuclear or Radiation Disaster: A Preliminary State Survey. *Int J Environ Res Public Health* **2021**, *18*, 8384, doi:10.3390/ijerph18168384.
31. Dutheil, F.; Trousselard, M.; Perrier, C.; Lac, G.; Chamoux, A.; Duclos, M.; Naughton, G.; Mnatzaganian, G.; Schmidt, J. Urinary Interleukin-8 Is a Biomarker of Stress in Emergency Physicians, Especially with Advancing Age - The JOBSTRESS* Randomized Trial. *PLoS One* **2013**, *8*, e71658, doi:10.1371/journal.pone.0071658.
32. Dutheil, F.; Boudet, G.; Perrier, C.; Lac, G.; Ouchchane, L.; Chamoux, A.; Duclos, M.; Schmidt, J. JOBSTRESS Study: Comparison of Heart Rate Variability in Emergency Physicians Working a 24-Hour Shift or a 14-Hour Night Shift - a Randomized Trial. *Int. J. Cardiol.* **2012**, *158*, 322–325, doi:10.1016/j.ijcard.2012.04.141.
33. McHill, A.W.; Melanson, E.L.; Higgins, J.; Connick, E.; Moehlman, T.M.; Stothard, E.R.; Wright, K.P. Impact of Circadian Misalignment on Energy Metabolism during Simulated Nightshift Work. *Proc Natl Acad Sci U S A* **2014**, *111*, 17302–17307, doi:10.1073/pnas.1412021111.
34. Crispim, C.A.; Waterhouse, J.; Dâmaso, A.R.; Zimberg, I.Z.; Padilha, H.G.; Oyama, L.M.; Tufik, S.; de Mello, M.T. Hormonal Appetite Control Is Altered by Shift Work: A Preliminary Study. *Metabolism* **2011**, *60*, 1726–1735, doi:10.1016/j.metabol.2011.04.014.
35. Scheer, F.A.J.L.; Hilton, M.F.; Mantzoros, C.S.; Shea, S.A. Adverse Metabolic and Cardiovascular Consequences of Circadian Misalignment. *Proc Natl Acad Sci U S A* **2009**, *106*, 4453–4458, doi:10.1073/pnas.0808180106.
36. Nguyen, J.; Wright, K.P. Influence of Weeks of Circadian Misalignment on Leptin Levels. *Nat Sci Sleep* **2010**, *2*, 9–18, doi:10.2147/nss.s7624.
37. Molzof, H.E.; Peterson, C.M.; Thomas, S.J.; Gloston, G.F.; Johnson, R.L.; Gamble, K.L. Nightshift Work and Nighttime Eating Are Associated With Higher Insulin and Leptin Levels in Hospital Nurses. *Front Endocrinol (Lausanne)* **2022**, *13*, 876752, doi:10.3389/fendo.2022.876752.
38. Izquierdo, A.G.; Crujeiras, A.B.; Casanueva, F.F.; Carreira, M.C. Leptin, Obesity, and Leptin Resistance: Where Are We 25 Years Later? *Nutrients* **2019**, *11*, doi:10.3390/nu11112704.
39. Myers, M.G.; Leibel, R.L.; Seeley, R.J.; Schwartz, M.W. Obesity and Leptin Resistance: Distinguishing Cause from Effect. *Trends Endocrinol Metab* **2010**, *21*, 643–651, doi:10.1016/j.tem.2010.08.002.
40. Taheri, S.; Lin, L.; Austin, D.; Young, T.; Mignot, E. Short Sleep Duration Is Associated with Reduced Leptin, Elevated Ghrelin, and Increased Body Mass Index. *PLoS Med* **2004**, *1*, e62, doi:10.1371/journal.pmed.0010062.
41. Mullington, J.M.; Chan, J.L.; Van Dongen, H.P.A.; Szuba, M.P.; Samaras, J.; Price, N.J.; Meier-Ewert, H.K.; Dinges, D.F.; Mantzoros, C.S. Sleep Loss Reduces Diurnal Rhythm Amplitude of Leptin in Healthy Men. *J Neuroendocrinol* **2003**, *15*, 851–854, doi:10.1046/j.1365-2826.2003.01069.x.
42. Spiegel, K.; Tasali, E.; Penev, P.; Van Cauter, E. Brief Communication: Sleep Curtailment in Healthy Young Men Is Associated with Decreased Leptin Levels, Elevated Ghrelin Levels, and Increased Hunger and Appetite. *Ann Intern Med* **2004**, *141*, 846–850, doi:10.7326/0003-4819-141-11-200412070-00008.

43. Bray, G.A. Soft Drink Consumption and Obesity: It Is All about Fructose. *Curr Opin Lipidol* **2010**, *21*, 51–57, doi:10.1097/MOL.0b013e3283346ca2.
44. Biercewicz, M.; Slusarz, R.; Kedziora-Kornatowska, K.; Filipska, K.; Bielawski, K.; Ruszkowska-Ciastek, B. Assessment of Leptin-to-Adiponectin Ratio in Prediction of Insulin Resistance and Nutrition Status in a Geriatric Female Population. *J Physiol Pharmacol* **2020**, *71*, doi:10.26402/jpp.2020.1.02.
45. Langenberg, C.; Bergstrom, J.; Laughlin, G.A.; Barrett-Connor, E. Ghrelin and the Metabolic Syndrome in Older Adults. *J Clin Endocrinol Metab* **2005**, *90*, 6448–6453, doi:10.1210/jc.2005-1358.
46. Rigamonti, A.E.; Pincelli, A.I.; Corrà, B.; Viarengo, R.; Bonomo, S.M.; Galimberti, D.; Scacchi, M.; Scarpini, E.; Cavagnini, F.; Müller, E.E. Plasma Ghrelin Concentrations in Elderly Subjects: Comparison with Anorexic and Obese Patients. *J Endocrinol* **2002**, *175*, R1-5, doi:10.1677/joe.0.175r001.
47. Marchesini, G.; Bianchi, G.; Lucidi, P.; Villanova, N.; Zoli, M.; De Feo, P. Plasma Ghrelin Concentrations, Food Intake, and Anorexia in Liver Failure. *J Clin Endocrinol Metab* **2004**, *89*, 2136–2141, doi:10.1210/jc.2003-031771.
48. Bauer, J.M.; Wirth, R.; Troegner, J.; Erdmann, J.; Eberl, T.; Heppner, H.J.; Schusdziarra, V.; Sieber, C.C. Ghrelin, Anthropometry and Nutritional Assessment in Geriatric Hospital Patients. *Z Gerontol Geriatr* **2007**, *40*, 31–36, doi:10.1007/s00391-007-0429-3.
49. Al-Rawi, N.; Madkour, M.; Jahrami, H.; Salahat, D.; Alhasan, F.; BaHammam, A.; Al-Islam Faris, M. Effect of Diurnal Intermittent Fasting during Ramadan on Ghrelin, Leptin, Melatonin, and Cortisol Levels among Overweight and Obese Subjects: A Prospective Observational Study. *PLoS One* **2020**, *15*, e0237922, doi:10.1371/journal.pone.0237922.

3. **Conclusion**

Nous avons confirmé que la ghréline et la leptine sont des biomarqueurs du stress directement liés au modèle demande-contrôle-soutien au travail de Karasek, dans une étude qui a pris en compte les principaux confondants que sont l'âge, l'indice de masse corporelle, le sexe, la nutrition et les gardes de nuit. Les soignants de l'urgence ont tendance à avoir des taux de leptine plus faibles après une garde de nuit par rapport à avant une garde de jour. Les facteurs explicatifs majeurs influençant ces taux de leptine sont l'augmentation de la demande psychologique, et la diminution de la latitude décisionnelle, et dans une moindre mesure les apports alimentaires et l'âge. Malgré l'absence de changements significatifs dans les niveaux de ghréline entre les gardes de nuit et de jour, le principal facteur expliquant l'augmentation de la ghréline semble être le soutien social. Les niveaux de ghréline ont également diminué avec l'indice de masse corporelle tandis que l'âge a un effet opposé.

CONCLUSION ET PERSPECTIVES

Les soignants de l'urgence représentent une population complexe, dont le travail semble avoir des conséquences sur leur santé physique et mentale. Les étudier n'est pas chose aisée. En effet, à cause de la surcharge de travail, de la faible quantité de temps pour faire des pauses, voire boire, manger ou aller aux toilettes, il est difficile de leur demander en plus de rajouter des prélèvements, des questionnaires longs et difficiles. Or, ces données apparaissent essentielles pour dresser un constat fiable sur les points forts et les points faibles des soignants de l'urgence. Sans cette étape, il est impossible d'envisager la mise en place de politiques d'amélioration des conditions de travail. Nous avons, grâce aux soignants étudiés, pu constater plusieurs choses. Premièrement un taux de stress catastrophique en utilisant le modèle de Karasek – job-demand-control-support. Deuxièmement un impact majeur du travail sur l'alimentation des soignants avec un effet encore plus important des gardes de nuit. Puis, nous avons montré que la ghréline et la leptine, les deux principales hormones de régulation de l'appétit sont également influencées par le stress et peuvent donc être considérées comme des biomarqueurs du stress. Enfin, nous avons combiné l'ensemble des données et montrer que le stress influence les taux de ghréline et de leptine chez les soignants de l'urgence. Ces données vous nous permettre directement d'agir pour les soignants de l'urgence, surtout au niveau de l'alimentation en revoyant avec les cuisines et les nutritionnistes l'approvisionnement des repas pour les soignants de l'urgence.

Bien que nous ayons montrer que les soignants sont stressés, nous n'avons pas identifié de facteurs de stress précis sur lesquels agir. C'est l'objet du projet de recherche en cours sur les interruptions de tâches, le projet JOBSTRESS-DSE (Biomarkes Of Job STRess In Emergency Senior physicians – Detection of stressful

events) au cours duquel nous souhaitons repérer de manière subjective et objective les évènements stressants chez les médecins. Pour cela nous monitorons en continue leur fréquence cardiaque et la variabilité sinusale de la fréquence cardiaque, connue pour être un biomarqueur de stress objectif. Un observateur suit également le médecin pour détecter l'ensemble des tâches et interruptions de tâches réalisées sur une journée et une nuit.

REFERENCES

1. Riou B. 2017 : création du CNU de médecine d'urgence. Ann Fr Med Urgence. 1 juin 2017;7(3):149-50.
2. Riou B. 2017 : l'an 1 du diplôme d'études spécialisées de médecine d'urgence. Ann Fr Med Urgence. 1 févr 2017;7(1):1-4.
3. Bouillon-Minois JB, Vromant A, Baicry F, Chevalier A, Cluzol L, Coisy F, et al. Phase de consolidation du DES de médecine d'urgence. Enquête nationale sur la première année de Docteur Junior. Ann Fr Med Urgence. 1 sept 2022;12(5):278-84.
4. Menthonnex P, Menthonnex E. Histoire de la médecine d'urgence de Napoléon à nos jours. 2010;30.
5. Loi n°70-1318 du 31 décembre 1970 portant réforme hospitalière. 70-1318 déc 31, 1970.
6. Dans un rapport remis au gouvernement Le professeur Steg propose une restructuration complète de l'organisation des urgences. Le Monde.fr [Internet]. 18 sept 1993 [cité 14 oct 2022]; Disponible sur: https://www.lemonde.fr/archives/article/1993/09/18/dans-un-rapport-remis-au-gouvernement-le-professeur-steg-propose-une-restructuration-complete-de-l-organisation-des-urgences_3936780_1819218.html
7. 62_soulat.pdf [Internet]. [cité 14 oct 2022]. Disponible sur: https://www.sfmu.org/upload/70_formation/02_eformation/02_congres/Urgences/urgences2007/donnees/pdf/62_soulat.pdf
8. Bouzat P. Construire une filière de soins pour les traumatismes graves à l'échelle nationale : un groupe d'experts se positionne. Ann Fr Med Urgence. 1 janv 2019;9(1):7-9.
9. Bouillon-Minois JB, Schmidt J, Dutheil F. SARS-CoV-2 pandemic and emergency medicine: The worst is yet to come. Am J Emerg Med. 10 juin 2020;
10. Bouillon-Minois JB, Raconnat J, Clinchamps M, Schmidt J, Dutheil F. Emergency Department and Overcrowding During COVID-19 Outbreak; a Letter to Editor. 1. 25 mars 2021;9(1):e28-e28.
11. Chiffres Clés Urgences - 2021 [Internet]. [cité 14 oct 2022]. Disponible sur: https://fedoru.fr/chiffres-cles-urgences-2021/
12. Shanafelt TD, West CP, Sinsky C, Trockel M, Tutty M, Satele DV, et al. Changes in Burnout and Satisfaction With Work-Life Integration in Physicians and the General US Working Population Between 2011 and 2017. Mayo Clinic Proceedings. 1 sept 2019;94(9):1681-94.
13. West CP, Dyrbye LN, Sinsky C, Trockel M, Tutty M, Nedelec L, et al. Resilience and Burnout Among Physicians and the General US Working Population. JAMA Network Open. 2 juill 2020;3(7):e209385.
14. Dutheil F, Boudet G, Perrier C, Lac G, Ouchchane L, Chamoux A, et al. JOBSTRESS study: comparison of heart rate variability in emergency physicians working a 24-hour shift or a 14-hour night shift - a randomized trial. Int J Cardiol. 12 juill 2012;158(2):322-5.
15. Bouillon-Minois JB, Trousselard M, Pereira B, Schmidt J, Clinchamps M, Thivel D, et al. Protocol of the Study on Emergency Health Care Workers' Responses Evaluated by Karasek Questionnaire: The SEEK-Study Protocol. Int J Environ Res Public Health. 12 avr 2021;18(8):4068.
16. Dutheil F, Aubert C, Pereira B, Dambrun M, Moustafa F, Mermillod M, et al. Suicide among physicians and health-care workers: A systematic review and meta-analysis. PLoS ONE. 2019;14(12):e0226361.
17. Torquati L, Mielke GI, Brown WJ, Burton NW, Kolbe-Alexander TL. Shift Work and Poor Mental Health: A Meta-Analysis of Longitudinal Studies. Am J Public Health. nov 2019;109(11):e13-20.

18. Wang N, Sun Y, Zhang H, Wang B, Chen C, Wang Y, et al. Long-term night shift work is associated with the risk of atrial fibrillation and coronary heart disease. Eur Heart J. 21 oct 2021;42(40):4180-8.
19. Sun M, Feng W, Wang F, Li P, Li Z, Li M, et al. Meta-analysis on shift work and risks of specific obesity types. Obes Rev. janv 2018;19(1):28-40.
20. Shan Z, Li Y, Zong G, Guo Y, Li J, Manson JE, et al. Rotating night shift work and adherence to unhealthy lifestyle in predicting risk of type 2 diabetes: results from two large US cohorts of female nurses. BMJ. 21 nov 2018;363:k4641.
21. Gamboa Madeira S, Fernandes C, Paiva T, Santos Moreira C, Caldeira D. The Impact of Different Types of Shift Work on Blood Pressure and Hypertension: A Systematic Review and Meta-Analysis. Int J Environ Res Public Health. 23 juin 2021;18(13):6738.
22. Kang E. Differences in Clinical Indicators of Diabetes, Hypertension, and Dyslipidemia Among Workers Who Worked Long Hours and Shift Work. Workplace Health Saf. juin 2021;69(6):268-76.
23. Khan WAA, Conduit R, Kennedy GA, Jackson ML. The relationship between shift-work, sleep, and mental health among paramedics in Australia. Sleep Health. juin 2020;6(3):330-7.
24. Pepłońska B, Nowak P, Trafalska E. The association between night shift work and nutrition patterns among nurses: a literature review. Med Pr. 14 juin 2019;70(3):363-76.
25. Freimann T, Merisalu E. Work-related psychosocial risk factors and mental health problems amongst nurses at a university hospital in Estonia: a cross-sectional study. Scand J Public Health. juill 2015;43(5):447-52.
26. Ilić IM, Arandjelović MŽ, Jovanović JM, Nešić MM. Relationships of work-related psychosocial risks, stress, individual factors and burnout - Questionnaire survey among emergency physicians and nurses. Med Pr. 24 mars 2017;68(2):167-78.
27. House S, Havens D. Nurses' and Physicians' Perceptions of Nurse-Physician Collaboration: A Systematic Review. J Nurs Adm. mars 2017;47(3):165-71.
28. Sabroe I, Mather S, Wilson A, Hall-Flavin DK, Fricker M, Barron LA, et al. Error, injustice, and physician wellbeing. Lancet. 6 mars 2021;397(10277):872-3.
29. Shanafelt TD, Noseworthy JH. Executive Leadership and Physician Well-being: Nine Organizational Strategies to Promote Engagement and Reduce Burnout. Mayo Clin Proc. janv 2017;92(1):129-46.
30. Cantaert GR, Van Hecke A, Smolderen K. Perceptions of physicians, medical and nursing students concerning shared decision-making: a cross-sectional study. Acta Clin Belg. févr 2021;76(1):1-9.
31. Riou B. Protocole de coopération infirmier et infirmier de pratiques avancées : quelles pistes pour la médecine d'urgence ? Ann Fr Med Urgence. 1 sept 2019;9(5):281-3.
32. Mangory KY, Ali LY, Rø KI, Tyssen R. Effect of burnout among physicians on observed adverse patient outcomes: a literature review. BMC Health Serv Res. 21 avr 2021;21(1):369.
33. Hartling O. [Collegiality, brotherhood and confidentiality]. Ugeskr Laeger. 6 mai 2013;175(19):1363.
34. Macrae A. The brotherhood of medicine. Br Med J. 30 janv 1954;1(Suppl 2558):25-7.
35. Song X, Li H, Jiang N, Song W, Ding N, Wen D. The mediating role of social support in the relationship between physician burnout and professionalism behaviors. Patient Educ Couns. déc 2021;104(12):3059-65.
36. Linos E, Lasky-Fink J, Halley M, Sarkar U, Mangurian C, Sabry H, et al. Impact of Sexual Harassment and Social Support on Burnout in Physician Mothers. J Womens Health (Larchmt). juill 2022;31(7):932-40.
37. Velando-Soriano A, Ortega-Campos E, Gómez-Urquiza JL, Ramírez-Baena L, De La

Fuente EI, Cañadas-De La Fuente GA. Impact of social support in preventing burnout syndrome in nurses: A systematic review. Jpn J Nurs Sci. janv 2020;17(1):e12269.
38. Karasek RA. Job demands, job decision latitude, and mental strain : implications for job redesign. Adm Sci Q. 1979;24:285-308.
39. Karasek RA. Job decision latitude, job design, and coronary heart disease. London: Taylor and Francis Ltd; 1981. 45-55 p. (Salvendy G SM. Machine pacing and occupational stress.).
40. Bland JM, Altman DG. Statistics notes: Cronbach's alpha. BMJ. 22 févr 1997;314(7080):572.
41. Guttman L. A Basis for Scaling Qualitative Data. American Sociological Review. 1944;9(2):139-50.
42. Kessel N. Society, Stress and Disease, Volume I. The Psychosocial Environment and Psychosomatic Diseases. Br J Ind Med. juill 1972;29(3):346.
43. Kohn ML, Schooler C. Occupational Experience and Psychological Functioning: An Assessment of Reciprocal Effects. American Sociological Review. 1973;38(1):97-118.
44. Hackman JR, Oldham GR. Development of the Job Diagnostic Survey. Journal of Applied Psychology. 1975;60:159-70.
45. Vaughan E, Gardner G. Technology as an Explanatory Variable in the Study of Workers' Attitudes. 1976;
46. Gardell B. Department of Psychology University of Stockholm Technology, Alienation and Mental Health. Summary of a Social Psychological Study of Technology and the Worker. Acta Sociologica. 1 janv 1976;19(1):83-93.
47. Parker SK, Sprigg CA. Minimizing strain and maximizing learning: the role of job demands, job control, and proactive personality. J Appl Psychol. déc 1999;84(6):925-39.
48. Fan W, Moen P, Kelly EL, Hammer LB, Berkman LF. Job Strain, Time Strain, and Well-Being: A Longitudinal, Person-Centered Approach in Two Industries. J Vocat Behav. févr 2019;110(Pt A):102-16.
49. Durand AC, Bompard C, Sportiello J, Michelet P, Gentile S. Stress and burnout among professionals working in the emergency department in a French university hospital: Prevalence and associated factors. Work. 2019;63(1):57-67.
50. Stansfeld S, Candy B. Psychosocial work environment and mental health--a meta-analytic review. Scand J Work Environ Health. déc 2006;32(6):443-62.
51. Framke E, Sørensen JK, Andersen PK, Svane-Petersen AC, Alexanderson K, Bonde JP, et al. Contribution of income and job strain to the association between education and cardiovascular disease in 1.6 million Danish employees. Eur Heart J. 14 mars 2020;41(11):1164-78.
52. Sara JD, Prasad M, Eleid MF, Zhang M, Widmer RJ, Lerman A. Association Between Work-Related Stress and Coronary Heart Disease: A Review of Prospective Studies Through the Job Strain, Effort-Reward Balance, and Organizational Justice Models. J Am Heart Assoc. 27 avr 2018;7(9).
53. Aboa-Eboulé C, Brisson C, Maunsell E, Mâsse B, Bourbonnais R, Vézina M, et al. Job strain and risk of acute recurrent coronary heart disease events. JAMA. 10 oct 2007;298(14):1652-60.
54. AbuAlRub RF. Job stress, job performance, and social support among hospital nurses. J Nurs Scholarsh. 2004;36(1):73-8.
55. Clinchamps M, Auclair C, Prunet D, Pfabigan D, Lesage FX, Baker JS, et al. Burnout Among Hospital Non-Healthcare Staff: Influence of Job Demand-Control-Support, and Effort-Reward Imbalance. J Occup Environ Med. 1 janv 2021;63(1):e13-20.
56. Niedhammer I, Milner A, Geoffroy-Perez B, Coutrot T, LaMontagne AD, Chastang JF. Psychosocial factors at work from the job strain model and preventable mortality in

France: The STRESSJEM prospective study. Prev Med. déc 2021;153:106178.
57. Casini A, Clays E, Godin I, De Backer G, Kornitzer M, Kittel F. The differential impact of job isostrain and home-work interference on indicators of physical and mental health in women and men. J Occup Environ Med. déc 2010;52(12):1236-44.
58. Hoang TG, Corbière M, Negrini A, Pham MK, Reinharz D, Hoang TG, et al. Validation of the Karasek-Job Content Questionnaire to measure job strain in Vietnam. Psychol Rep. oct 2013;113(2):363-79.
59. Zołnierczyk-Zreda D, Bedyńska S. Psychometric properties of the Polish version of Karasek's Job Content Questionnaire. Int J Occup Saf Ergon. 2014;20(4):583-93.
60. Phakthongsuk P, Apakupakul N. Psychometric properties of the Thai version of the 22-item and 45-item Karasek job content questionnaire. Int J Occup Med Environ Health. 2008;21(4):331-44.
61. Duchaine CS, Brisson C, Talbot D, Gilbert-Ouimet M, Trudel X, Vézina M, et al. Psychosocial stressors at work and inflammatory biomarkers: PROspective Quebec Study on Work and Health. Psychoneuroendocrinology. nov 2021;133:105400.
62. Larocque B, Brisson C, Blanchette C. [Internal consistency, factorial validity and discriminant validity of the French version of the psychological demands and decision latitude scales of the Karasek « Job Content Questionnaire »]. Rev Epidemiol Sante Publique. nov 1998;46(5):371-81.
63. Nana B, Sawadogo A, Kaboré A, Tanimomo L. [Causes of stress in the workplace: survey of 223 formal private sector employees in the city of Ouagadougou]. Pan Afr Med J. 2021;40:50.
64. Boada-Grau J, Prizmic-Kuzmica AJ, González-Fernández MD, Vigil-Colet A. Spanish version of Bus Drivers' Job Demands Scale (BDJD-24). Psicothema. 2013;25(2):258-65.
65. Na A, Kf Q, Ja O, Rm N, R N. Validity and Reliability of Malay Version of the Job Content Questionnaire among Public Hospital Female Nurses in Malaysia. The international journal of occupational and environmental medicine [Internet]. oct 2015 [cité 16 oct 2022];6(4). Disponible sur: https://pubmed.ncbi.nlm.nih.gov/26498051/
66. Eum KD, Li J, Jhun HJ, Park JT, Tak SW, Karasek R, et al. Psychometric properties of the Korean version of the job content questionnaire: data from health care workers. Int Arch Occup Environ Health. mai 2007;80(6):497-504.
67. Barrientos-Gutiérrez T, Martínez-Alcántara S, Méndez-Ramírez I. [Construct validity, reliability, and cutoff point of the Subjective Symptoms of Fatigue Test in Mexican workers]. Salud Publica Mex. déc 2004;46(6):516-23.
68. Sundin L, Hochwalder J, Bildt C, Lisspers J. The relationship between different work-related sources of social support and burnout among registered and assistant nurses in Sweden: a questionnaire survey. Int J Nurs Stud. juill 2007;44(5):758-69.
69. Kawakami N, Fujigaki Y. Reliability and validity of the Japanese version of Job Content Questionnaire: replication and extension in computer company employees. Ind Health. 1996;34(4):295-306.
70. Niedhammer I, Chastang JF, Gendrey L, David S, Degioanni S. [Psychometric properties of the French version of Karasek's « Job Content Questionnaire » and its scales measuring psychological pressures, decisional latitude and social support: the results of the SUMER]. Sante Publique (Bucur). sept 2006;18(3):413-27.
71. Niedhammer I, Chastang JF, Levy D, David S, Degioanni S, Theorell T. Study of the validity of a job-exposure matrix for psychosocial work factors: results from the national French SUMER survey. Int Arch Occup Environ Health. oct 2008;82(1):87-97.
72. Matthews TA, Robbins W, Preisig M, von Känel R, Li J. Associations of job strain and family strain with risk of major depressive episode: A prospective cohort study in U.S. working men and women. J Psychosom Res. août 2021;147:110541.

73. Cocker F, Joss N. Compassion Fatigue among Healthcare, Emergency and Community Service Workers: A Systematic Review. Int J Environ Res Public Health. 22 juin 2016;13(6).
74. Hall LH, Johnson J, Watt I, Tsipa A, O'Connor DB. Healthcare Staff Wellbeing, Burnout, and Patient Safety: A Systematic Review. PLoS One. 2016;11(7):e0159015.
75. Awa WL, Plaumann M, Walter U. Burnout prevention: a review of intervention programs. Patient Educ Couns. févr 2010;78(2):184-90.
76. Dutheil F, Pereira B, Bouillon-Minois JB, Clinchamps M, Brousses G, Dewavrin S, et al. Validation of Visual Analogue Scales of job demand and job control at the workplace: a cross-sectional study. BMJ Open. 17 mars 2022;12(3):e046403.
77. Lin LI. A concordance correlation coefficient to evaluate reproducibility. Biometrics. mars 1989;45(1):255-68.
78. Job Content Questionnaire (JCQ). (Questionnaire dit de Karasek) - Article de revue - INRS [Internet]. [cité 16 oct 2022]. Disponible sur: https://www.inrs.fr/media.html?refINRS=FRPS%202
79. Peen NF, Duque-Wilckens N, Trainor BC. Convergent neuroendocrine mechanisms of social buffering and stress contagion. Horm Behav. mars 2021;129:104933.
80. Faessler L, Brodbeck J, Schuetz P, Haubitz S, Mueller B, Perrig-Chiello P. Medical patients' affective well-being after emergency department admission: The role of personal and social resources and health-related variables. PLoS One. 2019;14(3):e0212900.
81. Convention C171 - Night Work Convention, 1990 (No. 171) [Internet]. [cité 4 nov 2021]. Disponible sur: https://www.ilo.org/dyn/normlex/en/f?p=NORMLEXPUB:12100:0::NO::P12100_INSTRUMENT_ID:312316
82. Rajaratnam SM, Arendt J. Health in a 24-h society. Lancet. 22 sept 2001;358(9286):999-1005.
83. Boivin DB, Boudreau P. Impacts of shift work on sleep and circadian rhythms. Pathol Biol (Paris). oct 2014;62(5):292-301.
84. Ganesan S, Magee M, Stone JE, Mulhall MD, Collins A, Howard ME, et al. The Impact of Shift Work on Sleep, Alertness and Performance in Healthcare Workers. Sci Rep. 15 mars 2019;9(1):4635.
85. Kosmadopoulos A, Kervezee L, Boudreau P, Gonzales-Aste F, Vujovic N, Scheer FAJL, et al. Effects of Shift Work on the Eating Behavior of Police Officers on Patrol. Nutrients. 4 avr 2020;12(4):E999.
86. Lim YC, Hoe VCW, Darus A, Bhoo-Pathy N. Association between night-shift work, sleep quality and metabolic syndrome. Occup Environ Med. oct 2018;75(10):716-23.
87. Vetter C, Devore EE, Wegrzyn LR, Massa J, Speizer FE, Kawachi I, et al. Association Between Rotating Night Shift Work and Risk of Coronary Heart Disease Among Women. JAMA. 26 avr 2016;315(16):1726-34.
88. Dutheil F, Baker JS, Mermillod M, De Cesare M, Vidal A, Moustafa F, et al. Shift work, and particularly permanent night shifts, promote dyslipidaemia: A systematic review and meta-analysis. Atherosclerosis. nov 2020;313:156-69.
89. Keski-Rahkonen A, Mustelin L. Epidemiology of eating disorders in Europe: prevalence, incidence, comorbidity, course, consequences, and risk factors. Curr Opin Psychiatry. 2016;29(6):340-5.
90. Samhat Z, Attieh R, Sacre Y. Relationship between night shift work, eating habits and BMI among nurses in Lebanon. BMC Nurs. 2020;19:25.
91. Ramin C, Devore EE, Wang W, Pierre-Paul J, Wegrzyn LR, Schernhammer ES. Night shift work at specific age ranges and chronic disease risk factors. Occup Environ Med. 1 févr 2015;72(2):100-7.

92. Reeves SL, Newling-Ward E, Gissane C. The effect of shift-work on food intake and eating habits. Nutrition & Food Science. 1 janv 2004;34(5):216-21.
93. Sahu S, Dey M. Changes in Food Intake Pattern of Nurses Working in Rapidly Rotating Shift. 2011;4:9.
94. Palla L, Almoosawi S. Diurnal Patterns of Energy Intake Derived via Principal Component Analysis and Their Relationship with Adiposity Measures in Adolescents: Results from the National Diet and Nutrition Survey RP (2008–2012). Nutrients. 17 févr 2019;11(2):E422.
95. Bonham MP, Kaias E, Zimberg I, Leung GKW, Davis R, Sletten TL, et al. Effect of Night Time Eating on Postprandial Triglyceride Metabolism in Healthy Adults: A Systematic Literature Review. J Biol Rhythms. avr 2019;34(2):119-30.
96. Gupta CC, Centofanti S, Dorrian J, Coates A, Stepien JM, Kennaway D, et al. Altering meal timing to improve cognitive performance during simulated nightshifts. Chronobiol Int. déc 2019;36(12):1691-713.
97. Gupta CC, Centofanti S, Dorrian J, Coates AM, Stepien JM, Kennaway D, et al. The impact of a meal, snack, or not eating during the night shift on simulated driving performance post-shift. Scand J Work Environ Health. 1 janv 2021;47(1):78-84.
98. Geliebter A, Gluck ME, Tanowitz M, Aronoff NJ, Zammit GK. Work-shift period and weight change. Nutrition. janv 2000;16(1):27-9.
99. Roskoden FC, Krüger J, Vogt LJ, Gärtner S, Hannich HJ, Steveling A, et al. Physical Activity, Energy Expenditure, Nutritional Habits, Quality of Sleep and Stress Levels in Shift-Working Health Care Personnel. PLOS ONE. 12 janv 2017;12(1):e0169983.
100. Han K, Choi-Kwon S, Kim KS. Poor dietary behaviors among hospital nurses in Seoul, South Korea. Appl Nurs Res. mai 2016;30:38-44.
101. Almajwal AM. Stress, shift duty, and eating behavior among nurses in Central Saudi Arabia. Saudi Medical Journal. 1 févr 2016;37(2):191-8.
102. Beebe D, Chang JJ, Kress K, Mattfeldt-Beman M. Diet quality and sleep quality among day and night shift nurses. Journal of Nursing Management. 2017;25(7):549-57.
103. Elizabeth L, Machado P, Zinöcker M, Baker P, Lawrence M. Ultra-Processed Foods and Health Outcomes: A Narrative Review. Nutrients. 30 juin 2020;12(7):E1955.
104. Jia P, Luo M, Li Y, Zheng JS, Xiao Q, Luo J. Fast-food restaurant, unhealthy eating, and childhood obesity: A systematic review and meta-analysis. Obes Rev. févr 2021;22 Suppl 1:e12944.
105. Bilski B. [Influence of shift work on the diet and gastrointestinal complains among nurses. A pilot study]. Med Pr. 2006;57(1):15-9.
106. Abdella HM, El Farssi HO, Broom DR, Hadden DA, Dalton CF. Eating Behaviours and Food Cravings; Influence of Age, Sex, BMI and FTO Genotype. Nutrients. 12 févr 2019;11(2):E377.
107. Padilla HM, Wilson M, Vandenberg RJ, Davis M, Clark MA. Health behavior among working adults: Workload and exhaustion are associated with nutrition and physical activity behaviors that lead to weight gain. J Health Psychol. mai 2021;26(6):892-904.
108. Nishitani N, Sakakibara H, Akiyama I. Eating behavior related to obesity and job stress in male Japanese workers. Nutrition. janv 2009;25(1):45-50.
109. Morikawa Y, Miura K, Sasaki S, Yoshita K, Yoneyama S, Sakurai M, et al. Evaluation of the effects of shift work on nutrient intake: a cross-sectional study. J Occup Health. 2008;50(3):270-8.
110. Dietary behavior and its relation with lifestyle, rotating work shifts and job satisfaction among nurses of Ain Shams university hospitals. The Egyptian Journal of Community Medicine. 1 avr 2016;34(2):75-86.
111. Grzymisławska M, Puch EA, Zawada A, Grzymisławski M. Do nutritional behaviors

depend on biological sex and cultural gender? Adv Clin Exp Med. janv 2020;29(1):165-72.
112. Dutheil F, Chaplais E, Vilmant A, Courteix D, Duche P, Abergel A, et al. Stress management in obesity during a thermal spa residential programme (ObesiStress): protocol for a randomised controlled trial study. BMJ Open. 23 déc 2019;9(12):e027058.
113. Santa Cecília Silva AA, Lopes T do VC, Teixeira KR, Mendes JA, de Souza Borba ME, Mota MC, et al. The association between anxiety, hunger, the enjoyment of eating foods and the satiety after food intake in individuals working a night shift compared with after taking a nocturnal sleep: A prospective and observational study. Appetite. 1 janv 2017;108:255-62.
114. Bremner JD, Moazzami K, Wittbrodt MT, Nye JA, Lima BB, Gillespie CF, et al. Diet, Stress and Mental Health. Nutrients. 13 août 2020;12(8).
115. St-Onge MP, Pizinger T, Kovtun K, RoyChoudhury A. Sleep and meal timing influence food intake and its hormonal regulation in healthy adults with overweight/obesity. Eur J Clin Nutr. juill 2019;72(Suppl 1):76-82.
116. Bouillon-Minois JB, Roux V, Pereira B, Flannery M, Pelissier C, Occelli C, et al. Stress among Emergency Health Care Workers on Nuclear or Radiation Disaster: A Preliminary State Survey. Int J Environ Res Public Health. 8 août 2021;18(16):8384.
117. Dutheil F, Trousselard M, Perrier C, Lac G, Chamoux A, Duclos M, et al. Urinary Interleukin-8 Is a Biomarker of Stress in Emergency Physicians, Especially with Advancing Age - The JOBSTRESS* Randomized Trial. PLoS One. 2013;8(8):e71658.
118. O'Neill M, Mujahid M, Hutson M, Fukutome A, Robichaud R, Lopez J. Investing in Public School Kitchens and Equipment as a Pathway to Healthy Eating and Equitable Access to Healthy Food. J Sch Health. juin 2020;90(6):492-503.
119. Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature. 9 déc 1999;402(6762):656-60.
120. Yanagi S, Sato T, Kangawa K, Nakazato M. The Homeostatic Force of Ghrelin. Cell Metab. 3 avr 2018;27(4):786-804.
121. Ueberberg B, Unger N, Saeger W, Mann K, Petersenn S. Expression of ghrelin and its receptor in human tissues. Horm Metab Res. nov 2009;41(11):814-21.
122. Poher AL, Tschöp MH, Müller TD. Ghrelin regulation of glucose metabolism. Peptides. févr 2018;100:236-42.
123. Hansson C, Shirazi RH, Näslund J, Vogel H, Neuber C, Holm G, et al. Ghrelin influences novelty seeking behavior in rodents and men. PLoS ONE. 2012;7(12):e50409.
124. Cummings DE. Ghrelin and the short- and long-term regulation of appetite and body weight. Physiol Behav. 30 août 2006;89(1):71-84.
125. Akamizu T, Takaya K, Irako T, Hosoda H, Teramukai S, Matsuyama A, et al. Pharmacokinetics, safety, and endocrine and appetite effects of ghrelin administration in young healthy subjects. Eur J Endocrinol. avr 2004;150(4):447-55.
126. Nagaya N, Kojima M, Uematsu M, Yamagishi M, Hosoda H, Oya H, et al. Hemodynamic and hormonal effects of human ghrelin in healthy volunteers. Am J Physiol Regul Integr Comp Physiol. mai 2001;280(5):R1483-1487.
127. Bellone S, Rapa A, Vivenza D, Castellino N, Petri A, Bellone J, et al. Circulating ghrelin levels as function of gender, pubertal status and adiposity in childhood. J Endocrinol Invest. mai 2002;25(5):RC13-15.
128. Sakata I, Yang J, Lee CE, Osborne-Lawrence S, Rovinsky SA, Elmquist JK, et al. Colocalization of ghrelin O-acyltransferase and ghrelin in gastric mucosal cells. Am J Physiol Endocrinol Metab. juill 2009;297(1):E134-141.
129. Spencer SJ, Xu L, Clarke MA, Lemus M, Reichenbach A, Geenen B, et al. Ghrelin regulates the hypothalamic-pituitary-adrenal axis and restricts anxiety after acute stress. Biol

Psychiatry. 15 sept 2012;72(6):457-65.
130. Bali A, Jaggi AS. An Integrative Review on Role and Mechanisms of Ghrelin in Stress, Anxiety and Depression. Curr Drug Targets. 2016;17(5):495-507.
131. Broom DR, Stensel DJ, Bishop NC, Burns SF, Miyashita M. Exercise-induced suppression of acylated ghrelin in humans. J Appl Physiol. juin 2007;102(6):2165-71.
132. Geliebter A, Carnell S, Gluck ME. Cortisol and ghrelin concentrations following a cold pressor stress test in overweight individuals with and without Night Eating. Int J Obes (Lond). août 2013;37(8):1104-8.
133. Allen AP, Kennedy PJ, Dockray S, Cryan JF, Dinan TG, Clarke G. The Trier Social Stress Test: Principles and practice. Neurobiol Stress. févr 2017;6:113-26.
134. Sinha R, Jastreboff AM. Stress as a Common Risk Factor for Obesity and Addiction. Biol Psychiatry. 26 mars 2013;73(9):827-35.
135. Cui H, López M, Rahmouni K. The cellular and molecular bases of leptin and ghrelin resistance in obesity. Nat Rev Endocrinol. 2017;13(6):338-51.
136. Quine L. Workplace bullying in NHS community trust: staff questionnaire survey. BMJ. 23 janv 1999;318(7178):228-32.
137. Dutheil F, Lac G, Lesourd B, Chapier R, Walther G, Vinet A, et al. Different modalities of exercise to reduce visceral fat mass and cardiovascular risk in metabolic syndrome: the RESOLVE randomized trial. Int J Cardiol. 25 mai 2013;168(4):3634-42.
138. Foss B, Dyrstad SM. Stress in obesity: cause or consequence? Med Hypotheses. juill 2011;77(1):7-10.
139. Robinson E, Hunger JM, Daly M. Perceived weight status and risk of weight gain across life in US and UK adults. Int J Obes (Lond). 7 août 2015;39(12):1721-6.
140. Schellekens H, Finger BC, Dinan TG, Cryan JF. Ghrelin signalling and obesity: at the interface of stress, mood and food reward. Pharmacol Ther. sept 2012;135(3):316-26.
141. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature. 1 déc 1994;372(6505):425-32.
142. Zhang Y, Chua S. Leptin Function and Regulation. Compr Physiol. 12 déc 2017;8(1):351-69.
143. Dodd GT, Decherf S, Loh K, Simonds SE, Wiede F, Balland E, et al. Leptin and insulin act on POMC neurons to promote the browning of white fat. Cell. 15 janv 2015;160(1-2):88-104.
144. Baldini G, Phelan KD. The melanocortin pathway and control of appetite-progress and therapeutic implications. J Endocrinol. 1 avr 2019;241(1):R1-33.
145. Argiolas A, Melis MR. Neuropeptides and central control of sexual behaviour from the past to the present: a review. Prog Neurobiol. sept 2013;108:80-107.
146. Rousseau K, Kauser S, Pritchard LE, Warhurst A, Oliver RL, Slominski A, et al. Proopiomelanocortin (POMC), the ACTH/melanocortin precursor, is secreted by human epidermal keratinocytes and melanocytes and stimulates melanogenesis. FASEB J. juin 2007;21(8):1844-56.
147. Scheja L, Heeren J. The endocrine function of adipose tissues in health and cardiometabolic disease. Nat Rev Endocrinol. sept 2019;15(9):507-24.
148. Simon C, Gronfier C, Schlienger JL, Brandenberger G. Circadian and ultradian variations of leptin in normal man under continuous enteral nutrition: relationship to sleep and body temperature. J Clin Endocrinol Metab. juin 1998;83(6):1893-9.
149. Münzberg H, Morrison CD. Structure, production and signaling of leptin. Metabolism. janv 2015;64(1):13-23.
150. Langendonk JG, Pijl H, Toornvliet AC, Burggraaf J, Frölich M, Schoemaker RC, et al. Circadian rhythm of plasma leptin levels in upper and lower body obese women: influence of

body fat distribution and weight loss. J Clin Endocrinol Metab. mai 1998;83(5):1706-12.
151. Gijón-Conde T, Graciani A, Guallar-Castillón P, Aguilera MT, Rodríguez-Artalejo F, Banegas JR. Leptin Reference Values and Cutoffs for Identifying Cardiometabolic Abnormalities in the Spanish Population. Rev Esp Cardiol (Engl Ed). août 2015;68(8):672-9.
152. Triantafyllou GA, Paschou SA, Mantzoros CS. Leptin and Hormones: Energy Homeostasis. Endocrinol Metab Clin North Am. sept 2016;45(3):633-45.
153. Park HK, Ahima RS. Physiology of leptin: energy homeostasis, neuroendocrine function and metabolism. Metabolism. janv 2015;64(1):24-34.
154. Bird L. Exercise lowers leptin and leukocytosis. Nat Rev Immunol. janv 2020;20(1):2-3.
155. Zanchi D, Depoorter A, Egloff L, Haller S, Mählmann L, Lang UE, et al. The impact of gut hormones on the neural circuit of appetite and satiety: A systematic review. Neurosci Biobehav Rev. sept 2017;80:457-75.
156. Kumar Jha P, Challet E, Kalsbeek A. Circadian rhythms in glucose and lipid metabolism in nocturnal and diurnal mammals. Mol Cell Endocrinol. 15 déc 2015;418 Pt 1:74-88.
157. Zhao ZY, Fu YR, Li XH, Li YY, Bogdan A, Touitou Y. Age-related modifications of circadian rhythm of serum leptin in healthy men. Gerontology. oct 2002;48(5):309-14.
158. Dutheil F, de Saint Vincent S, Pereira B, Schmidt J, Moustafa F, Charkhabi M, et al. DHEA as a Biomarker of Stress: A Systematic Review and Meta-Analysis. Front Psychiatry. 2021;12:688367.
159. Laferrère B, Fried SK, Osborne T, Pi-Sunyer FX. Effect of one morning meal and a bolus of dexamethasone on 24-hour variation of serum leptin levels in humans. Obes Res. oct 2000;8(7):481-6.
160. Isasi CR, Parrinello CM, Jung MM, Carnethon MR, Birnbaum-Weitzman O, Espinoza RA, et al. Psychosocial stress is associated with obesity and diet quality in Hispanic/Latino adults. Ann Epidemiol. févr 2015;25(2):84-9.
161. Czeglédi E. [Options for stress management in obesity treatment]. Orv Hetil. 14 févr 2016;157(7):260-7.
162. Myers MG, Leibel RL, Seeley RJ, Schwartz MW. Obesity and leptin resistance: distinguishing cause from effect. Trends Endocrinol Metab. nov 2010;21(11):643-51.
163. Levin BE, Dunn-Meynell AA, McMinn JE, Alperovich M, Cunningham-Bussel A, Chua SC. A new obesity-prone, glucose-intolerant rat strain (F.DIO). Am J Physiol Regul Integr Comp Physiol. nov 2003;285(5):R1184-1191.
164. Perakakis N, Farr OM, Mantzoros CS. Leptin in Leanness and Obesity: JACC State-of-the-Art Review. J Am Coll Cardiol. 16 févr 2021;77(6):745-60.
165. Montague CT, Farooqi IS, Whitehead JP, Soos MA, Rau H, Wareham NJ, et al. Congenital leptin deficiency is associated with severe early-onset obesity in humans. Nature. 26 juin 1997;387(6636):903-8.
166. Demerath EW, Sun SS, Rogers N, Lee M, Reed D, Choh AC, et al. Anatomical patterning of visceral adipose tissue: race, sex, and age variation. Obesity (Silver Spring). déc 2007;15(12):2984-93.
167. Qian J, Morris CJ, Caputo R, Wang W, Garaulet M, Scheer FAJL. Sex differences in the circadian misalignment effects on energy regulation. Proc Natl Acad Sci U S A. 19 nov 2019;116(47):23806-12.
168. Atoum MF, Alzoughool F, Al-Hourani H. Linkage Between Obesity Leptin and Breast Cancer. Breast Cancer (Auckl). 2020;14:1178223419898458.

Jean-Baptiste BOUILLON-MINOIS: « Médecine d'Urgence, Nutrition et Biomarqueurs du Stress »
Thèse d'Université – Clermont-Ferrand - 2022

Résumé

Contexte : La médecine d'urgence est une spécialité stressante, mais l'évaluation du stress par le gold standard modèle de Karasek n'avait été faite, ni l'impact du travail sur les apports alimentaires. Nous avons démontré que la leptine et la ghréline, des hormones de régulation de l'appétit, sont également des biomarqueurs du stress. Toutefois aucune étude holistique intégrant tous ces paramètres n'avait jamais été faite, et encore moins dans le contexte de la médecine d'urgence. **Objectif** : Evaluer l'influence du travail de nuit, de la nutrition et du stress évalué par le modèle de Karasek sur les concentrations de ghréline et de leptine chez les soignants de l'urgence. **Méthode** : Etude observationnelle prospective avec recueils salivaires en début de poste de jour et/ou en fin de poste de nuit, associés à des évaluations du stress via le modèle job-demand-control-support de Karasek, et recueil des ingestas sur 24 heures pendant une garde de jour et la nuit consécutive, et pendant une garde de nuit et la journée précédente. **Résultats** : 161 soignants ont été inclus. Les taux de leptine étaient plus faibles après une garde de nuit par rapport à avant une garde de jour (p=0,067). Les principaux facteurs expliquant la diminution des taux de leptine étaient une augmentation de la demande psychologique (coefficient -54.1, IC95 -99.0 à -0.92) et une diminution de la latitude décisionnelle (-24.9, -49.5 à -0.29). Malgré l'absence de changements significatifs dans les niveaux de ghréline entre les gardes de nuit et de jour, le principal facteur expliquant l'augmentation de la ghréline était le soutien social (6.12, 0.74 à 11.5). L'apport alimentaire (kcal) et l'âge ont également un impact négatif sur les niveaux de leptine. Les niveaux de ghréline ont également diminué avec l'indice de masse corporelle tandis que l'âge a un effet opposé. **Conclusion** : Nous avons confirmé que la ghréline et la leptine sont des biomarqueurs de stress directement liés au modèle demande-contrôle-soutien au travail de Karasek, dans une étude qui a pris en compte les principaux confondants.

Abstract

Background: Emergency medicine is a stressful job, but stress assessment using the Karasek job demand-control-support model has not been done, nor the impact of work on food intake. We have demonstrated that leptin and ghrelin, hormones that regulate appetite, are also biomarkers of stress. However, no holistic study integrating all these parameters had ever been done, and even less among emergency healthcare workers. **Objective**: To assess the influence of night work, nutrition and stress assessed by Karasek's model on ghrelin and leptin concentrations among emergency healthcare worker. **Method**: Prospective observational study with saliva collections at the beginning of the day shift and/or at the end of the night shift, associated with stress assessments via Karasek's model, and collection of food intake over 24 hours during a day shift and the consecutive night, and during a night shift and the previous day. **Results**: 161 caregivers were included. Leptin levels were lower after night shift compared to before day shift (p=0.067). The main factors explaining the decrease in leptin levels were an increase in job demand (coefficient -54.1, 95CI -99.0 to -0.92) and a decrease in job control (-24.9, -49.5 to -0.29). Despite the lack of significant changes in ghrelin levels between night and day shifts, the main factor explaining the increase in ghrelin was social support (6.12, 0.74 to 11.5). Food intake (kcal) and age also have a negative impact on leptin levels. Ghrelin levels also decreased with body mass index while age had the opposite effect. **Conclusion**: We confirmed that ghrelin and leptin are biomarkers of stress directly related to Karasek's job demand-control-support model, in a study controlled for major confounders**.**

Mots-clés: nutrition, stress, médecine d'urgence, ghréline, leptine, Karasek
Keywords: nutrition, stress, emergency medicine, ghrelin, leptin, Karasek

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