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COGNITIVE IMPAIRMENT IN ADULTS SUFFERING FROM OBESITY:

A SYSTEMATIC LITERATURE REVIEW - PROTOCOL

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ABSTRACT

The prevalence of obesity among adults more than doubled worldwide between 1990 and 2022, affecting around 890 million people. Obesity is a chronic disease characterized by excessive body fat, which increases the risk of numerous comorbidities, such as type 2 diabetes, cardiovascular diseases and certain cancers. Emerging evidence suggests that obesity may also contribute to chronic low-grade neuro-inflammation, systemic inflammation and microbiome dysbiosis, potentially leading to neuropsychiatric disorders and cognitive impairment.

This systematic review aims to determine if obesity is an independent risk factor for cognitive impairment. Our review will focus on prospective cohort studies in order to establish a causal relationship, taking into account the limitations of previous reviews that relied mainly on cross-sectional studies. We will include studies of adult participants (aged between 20-50 years) suffering from obesity, using the body mass index as a measure of obesity, and who were compared with normal-weight control groups. Impaired cognitive function must have been established by means of valid cognitive tasks or psychological tests.

By updating and summarizing the latest evidence, this review attempts to clarify the independent effect of obesity on cognitive functioning. This understanding is crucial for the development of targeted prevention and intervention strategies to mitigate the adverse effects of obesity, ultimately contributing to improved public health outcomes.

This protocol was submitted to the "International prospective register of systematic reviews" PROSPERO on July 26, 2024.

Keywords: Obesity, Cognitive function, Executive functions, Adults, Cohort studies

INTRODUCTION

The prevalence of obesity among adults more than doubled worldwide between 1990 and 2022, affecting around 890 million people (World Health Organization, 2024). The causes of obesity are multifactorial, including genetic, environmental, behavioral and social factors. Obesity, which is a chronic and complex disease, is characterized by excessive fat deposits that can be health-threatening. Excess fat has indeed been linked to a significantly increased risk of developing various comorbidities, including type 2 diabetes, certain cancers, cardiovascular disease and respiratory problems, all of which increase the risk of a reduced life expectancy (Bray, 2004).

Obesity is associated with several pathophysiological mechanisms that may contribute to the development of cognitive impairment. For example, chronic low-grade neuro-inflammation and alterations in gut microbiota are significant biological mechanisms of obesity that can affect brain health and function (Amabebe et al., 2020; Chen & Devaraj, 2018; Kacířová et al., 2020; Ly et al., 2023; Miller & Raison, 2016, 2016; Monteiro & Azevedo, 2010).

Studies also show that obesity is associated with the impairment of certain cognitive functions, notably certain executive functions such as inhibition, mental flexibility and updating (Bartholdy et al., 2016; Smith et al., 2011). Cognitive functions include all processes that enable us to integrate, store and use information, and are mainly divided into attention, memory and executive functions. It is thought that executive functions and attention are the cognitive function groups that are most frequently impaired in people suffering from obesity (Smith et al., 2011). This impairment of cognitive functions, particularly executive functions, could have an impact on the establishment and maintenance of a healthy eating behavior, which could prevent individuals from correctly regulating their energy balance (Smith et al., 2011).

Some reviews examine the relationship between certain cognitive functions and obesity. However, these reviews mainly focus on cross-sectional studies, which do not allow for a causal relationship to be established. The originality of our review is that we include only cohort studies and meta-analyses of cohort studies, that can be used to determine whether there is a "dose-response" relationship between two variables. In addition, to diagnose obesity, some studies use the body mass index (BMI), but also other anthropometric measures such as waist circumference, which can make comparisons between populations difficult and do not allow for an informal diagnosis of obesity. Furthermore, reviews generally include studies on populations of broad age ranges, neglecting the fact that age may affect cognitive functions. Our main objectives are (1) to determine whether obesity is an independent risk factor for the impairment of certain cognitive functions, and (2) to identify whether there are any knowledge gaps in the scientific literature. An update of the relationship between cognitive function

in adults suffering from obesity is necessary to enable better management and prevention, thus helping to curb this major global public health problem.

METHODS

Protocol and registration

The protocol of this systematic literature review follows the checklist of “Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 : elaboration and explanation” (Shamseer et al., 2015). This protocol was submitted to the "International prospective register of systematic reviews" PROSPERO on July 26, 2024.

Research question

The aim of this systematic literature review is to investigate the following question: Is obesity an independent risk factor for cognitive impairment in adults? This research question was established using the PECOS technique, which is organized into four main categories: population, exposure, comparison, outcome and study.

Eligibility criteria

Population

The studies included in this systematic literature review only investigated participants who were between 20 and 50 years of age at baseline, with no restrictions on gender. At the start of the studies, participants must not have a history of, or current, cognitive impairment, mental health disorders, chronic diseases or bariatric surgery; they must not take certain medications that could impair cognitive function on a regular basis; they must not suffer from addictions (such as tobacco or alcohol); they must not be pregnant; and they must not be following a specific diet with the aim of weight loss. All studies using animal models as subjects are excluded.

Exposure

Since 1997, the World Health Organization has recommended the use of the BMI to diagnose obesity (WHO et al., 1997) (Supplementary table). This index is calculated by dividing a person's weight (in kilograms) by the square of their height (meters) and is used to classify individuals according to their

corpulence. Participants in the studies included must be suffering from obesity, determined either by a healthcare professional or self-reported using the body mass index (BMI ≥ 30).

Comparison

The participants in the control group must be in the same age range as the target population, i.e. between 20 and 50 years inclusive (at the start of the study). Participants in the control group must be exclusively of normal-weight (see supplementary table). In fact, many studies use a control group composed of both overweight and normal-weight people, although there are many differences in terms of physiology, quality of life and treatment. Participants in the control group must also be in the same state of health as the study population at the start of the study.

Outcomes

We will include all studies examining cognitive impairment. The outcomes included must be the most prevalent, and there must be a possibility of prevention, treatment and/or delay in disease progression. Outcomes with a genetic origin will not be included. The cognitive domains (e.g. executive functions and attention) must be assessed using valid cognitive tasks or psychological tests.

Study design

The studies included in our review are prospective cohort studies and meta-analyses of prospective cohort studies. The follow-up period of the cohort must be at least 2 years and the articles must be written in English or French and published after 1996. Indeed, it was in 1997 that the World Health Organization recognized the body mass index as the official system for classifying overweight and obesity.

Search strategy

The following electronic databases are used to carry out an exhaustive literature search: MEDLINE (via PubMed), American Psychological Association PsycINFO and Web of Science. In addition, we will carry out a manual search in the references of the included articles, and we will also use Elicit an artificial intelligence system. Search terms are based on the PECOS classification, using free keywords and controlled vocabulary such as Medical Subject Heading (MeSH) when available for each database (table 1 to 3). This step will be led by one author (C. S.).

Table 1 Search equation for PubMed

Population	"adult"[MeSH Terms] OR "humans"[MeSH Terms] OR "adult*"[Text Word] OR "human*"[Text Word] OR "women"[Text Word] OR "woman"[Text Word] OR "men"[Text Word] OR "man"[Text Word]
AND	
Exposure	"obesity"[MeSH Terms] OR "obesity, morbid"[MeSH Terms] OR "obesity, abdominal"[MeSH Terms] OR "obes*"[Text Word] OR "body mass index"[MeSH Terms] OR "bmi" [Text Word] OR "adiposity"[MeSH Terms]
AND	
Outcomes	"cognition"[MeSH Terms] OR "cogniti*"[Text Word] OR "cognitive function*"[Text Word] OR "executive function"[MeSH Terms] OR "executive function*"[Text Word] OR "executive control"[Text Word] OR "memory disorders"[MeSH Terms] OR "memory"[MeSH Terms] OR "memory impair*"[Text Word] OR "memor*"[Text Word] OR "cognition disorders"[MeSH Terms] OR "cognitive dysfunction"[MeSH Terms] OR "cognitive impairment*"[Text Word] OR "mild cognitive impairment"[Text Word] OR "inhibition, psychological"[MeSH Terms] OR "impulsive behavior"[MeSH Terms] OR "disruptive, impulse control, and conduct disorders"[MeSH Terms] OR "impuls*"[Text Word] OR "inhibition*"[Text Word] OR "inhibitory control"[Text Word] OR "mental competency"[MeSH Terms] OR "attention"[MeSH Terms] OR "attentional bias"[MeSH Terms] OR "attention deficit*"[Text Word] OR "attention*"[Text Word] OR "neuropsychological tests"[MeSH Terms] OR "cognitive test*"[Text Word] OR "neuropsychological* test*"[Text Word] OR "executive task*"[Text Word] OR "cognitive task*"[Text Word] OR "shifting"[Text Word] OR "updating"[Text Word] OR "working memory"[Text Word] OR "flexibility"[Text Word] OR "cognitive flexibility"[Text Word] OR "planning"[Text Word] OR "problem-solving"[Text Word] OR "reasoning"[Text Word]
AND	
Study design	"prevalence"[MeSH Terms] OR "prevalence"[Text Word] OR "cohort studies"[MeSH Terms] OR cohort*[Text Word] OR "longitudinal studies"[MeSH Terms] OR "longitudinal stud*"[Text Word] OR "prospective studies"[MeSH Terms] OR "prospective stud*"[Text Word] OR "meta analysis"[Text Word] OR "risk factors"[MeSH Terms] OR "odds ratio"[MeSH Terms] OR "odds ratio"[Text Word]

Table 2 Search equation for APA PsycINFO

Population	adult* OR human* OR women OR woman OR men OR man
AND	
Exposure	DE "Obesity" OR DE "Body Mass Index" OR obes* OR adiposity OR bmi
AND	
Outcomes	DE "Cognition" OR DE "Cognitions" OR cogniti* OR "cognitive function*" OR DE "Cognitive Ability" OR DE "Cognitive Assessment" OR DE "Cognitive Bias" OR DE "Cognitive Control" OR DE "Executive Function" OR "executive function*" OR "executive control" OR DE "Executive Functioning Measures"

	OR "executive task*" OR "cognitive task*" OR "cognitive impairment*" OR "mild cognitive impairment" OR DE "Memory Disorders" OR memor* OR "working memory" OR DE "Cognitive Impairment" OR impuls* OR "inhibition*" OR "inhibitory control" OR DE "Attention" OR DE "Attentional Bias" OR "attention deficit*" OR attention* OR "cognitive test*" OR "neuropsychological* test*" OR shifting OR updating OR flexibility OR "cognitive flexibility" OR planning OR "problem-solving" OR "reasoning"
AND	
Study design	prevalence OR cohort* OR DE "Longitudinal Studies" OR "longitudinal stud*" OR DE "Prospective Studies" OR "prospective stud*" OR "meta analysis" OR DE "Risk Factors" OR "odds ratio"

Table 3 Search equation for Web of Science

Population	ALL(adult*) OR ALL(human*) OR ALL(women) OR ALL(woman) OR ALL(men) OR ALL(man)
AND	
Exposure	TITLE-ABS-KEY(obes*) OR TITLE-ABS-KEY("body mass index") OR TITLE-ABS-KEY(bmi) OR TITLE-ABS-KEY(adiposity)
AND	
Outcomes	ALL=("cognition" OR "cognitions" OR "cognitive ability" OR "cognitive assessment*" OR "cognitive test*" OR "cognitive bias" OR "cognitive control" OR "executive function*" OR "executive functioning measures" OR "executive task*" OR "cognitive task*" OR "memory disorder*" OR "cognitive impairment*" OR "mild cognitive impairment" OR "inhibition*" OR "inhibitory control" OR "attention" OR "attentional bias" OR shifting OR updating OR flexibility OR "working memory" OR "cognitive flexibility" OR planning OR "problem-solving" OR reasoning)
AND	
Study design	ALL=(cohort* OR "longitudinal stud*" OR "prospective stud*" OR "meta analysis" OR "risk factor*")

Article selection process

In this step, we will use Rayyan, an artificial intelligence system, to screen articles according to previously established eligibility criteria. To do so, we will first delete all duplicates and then upload the references into the software. The selection will be carried out in two stages, in a “blind” situation, by the three authors C.S., S.C., and M.-C.B.: the first step, based on the titles and abstracts, and the second step, based on a complete reading of the article. In the event of a disagreement between two authors, the decision will be made based on the majority after a discussion.

Data extraction

The relevant data will be grouped in an Excel file according to the following categories: publication details (authors, year, country, years of data collection), study type, study population (body mass index, age range, gender), sample size, control group size, cognitive domains measured, tests used for this measurement, measurement dates, results (either prevalence or odds or relative risk and results adjusted for third factors). The results of the included studies are then analyzed in a qualitative synthesis.

Risk of bias

The risk of bias of the studies included in our review will be assessed using the "Quality assessment tool for observational cohort and cross-sectional studies" from the National Heart, Lung and Blood Institute (National Institutes of Health, 2014). This tool is based on a checklist of 14 criteria to determine whether the quality of a study is good, fair or poor. Each article will be evaluated by C.S. and checked by at least one author (S.C. or M.-C.B.).

LIMITATION

This systematic literature review has some limitations, particularly with regard to the eligibility criteria. Indeed, in order to carry out an exhaustive literature search, we chose a fairly wide age range of the adult population, i.e. from 20 to 50 years inclusive. However, brain development and maturation, particularly in the prefrontal cortex responsible for executive function, is not complete until around the age of 25 (Arain et al., 2013) and studies show that cognitive decline begins as early as the age of 45 years (Singh-Manoux et al., 2012). Although this review is based on updates to "Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)" made in 2020 (Page et al., 2021), reporting and methodological biases are always possible. This systematic literature review will only consider articles written in English and French, and will not include unpublished literature. In addition, we decided to include only studies published after 1996, thus excluding those published earlier. However, by setting 1997 as the starting date, we increase the likelihood of obtaining more homogeneous studies. Indeed, it was in 1997 that the WHO recognized the BMI as a classification system for obesity, making it more likely that BMI would be used in studies from this date onwards.

Abbreviations

ANR: Agence Nationale de la Recherche (French National Research Agency)

APA: American Psychological Association

BMI: Body Mass Index

MeSH: Medical Subject Headings

PECOS: Population, Exposure, Comparison, Outcomes, Study

PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses

Author's contributions

Camille S. led the development and writing of the protocol. Stéphanie C. and Marie-Claude B. supervised the entire process and critically reviewed all versions of the manuscript. Valentina A.A. managed the French National Research Agency funding and supervised the project management. Léopold K.F. and Cécilia S. contributed their expertise throughout the project.

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Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

This protocol is published in an open archive HAL. The systematic literature review will be published in a peer-reviewed scientific journal and in open access under HAL.

Competing interests

None

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SUPPLEMENTARY FILE

Classification	BMI (kilograms/meters ²)
Underweight	<18,5
Normal-weight	[18,5-24,9]
Overweight	[25-29,9]
Obesity	≥30

Supplementary table: Worldwide obesity classification