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Featured Article

Body mass index and risk of dementia: Analysis of individual-level data from 1.3 million individuals

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Abstract

Introduction: Higher midlife body mass index (BMI) is suggested to increase the risk of dementia, but weight loss during the preclinical dementia phase may mask such effects.

Methods: We examined this hypothesis in 1,349,857 dementia-free participants from 39 cohort studies. BMI was assessed at baseline. Dementia was ascertained at follow-up using linkage to electronic health records (N = 6894). We assumed BMI is little affected by preclinical dementia when assessed decades before dementia onset and much affected when assessed nearer diagnosis.

Results: Hazard ratios per 5-kg/m^2 increase in BMI for dementia were 0.71 (95% confidence interval = 0.66–0.77), 0.94 (0.89–0.99), and 1.16 (1.05–1.27) when BMI was assessed 10 years, 10-20 years, and >20 years before dementia diagnosis.

The authors have declared that no conflict of interest exists.
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Conclusions: The association between BMI and dementia is likely to be attributable to two different processes: a harmful effect of higher BMI, which is observable in long follow-up, and a reverse-causation effect that makes a higher BMI to appear protective when the follow-up is short.

Keywords: Body mass index; Dementia; Cohort study; Bias; Obesity

1. Introduction

The costs of dementia are enormous and increasing globally [1]. Current clinical guidelines for dementia prevention view obesity as one of the modifiable risk factors [2,3], but the evidence is based on a relatively limited number of observational studies and the findings are mixed [4–12]. The most recent meta-analysis, including 4 studies and 16,282 participants, suggested a 1.4-fold increased risk of dementia in the obese [9]. The largest study in the field, published after the inclusion date for the meta-analysis, found no increase in dementia incidence among the obese [13]. On the contrary, higher body mass index (BMI) was linked to lower dementia risk.

The reasons for this discordance in findings are unclear. One possibility is that the observed association between BMI and dementia is attributable to two processes: one is a direct association between higher BMI and increased dementia risk, and the other is an association confounded by weight loss during the preclinical dementia phase, which leads a harmful exposure to appear protective via reverse causation (Fig. 1). This hypothesis is supported by the fact that clinical diagnosis of dementia is often preceded by a long (20–30 years) preclinical phase [14–17] during which cardiometabolic changes, including weight loss, are common [5,6,18,19]. Thus, lower BMI close to dementia onset might be a consequence of preclinical disease rather than a cause of dementia. The investigations [4–7] supporting this two-process hypothesis are based on small numbers (N < 3000) and thus vulnerable to random errors. A further limitation is that these studies did not directly seek to determine the etiological phase at exposure measurement by stratifying the analyses by the length of follow-up between the assessment of BMI and dementia onset.

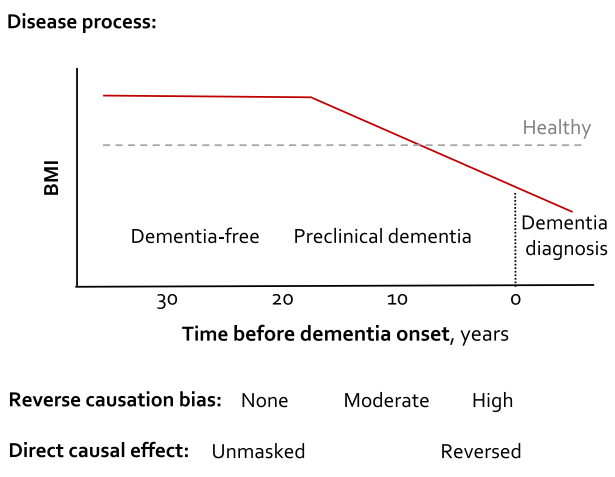

Fig. 1. Conceptual model: Effect of reverse causation (preclinical disease reduces weight) on BMI at different etiological periods before dementia diagnosis. Abbreviation: BMI, body mass index.

The purpose of the present analyses was to investigate the BMI-dementia association using raw unpublished data from over 1.3 million adults from Europe, the United States, and Asia. To separate direct and biased associations, we stratified the analysis by duration of follow-up. We assumed that BMI is little affected by preclinical dementia when the BMI assessment is long before dementia onset and is considerably affected when BMI is assessed nearer the diagnosis.

2. Methods

2.1. Study population

We searched the Individual-Participant Data Meta-analysis in Working Populations (IPD-Work) consortium [20,21], the Inter-University Consortium for Political and Social Research (www.icpsr.umich.edu/icpsrweb/ICPSR), and the UK Data Service (http://ukdataservice.ac.uk) to identify eligible large-scale prospective cohort studies for which data on BMI and dementia were available. We included 39 prospective cohort studies from Europe, the United States, and Asia (Appendix 1), which comprised a total of 1,349,857 participants with no history of dementia; were population based with BMI assessed from all participants before the ascertainment of dementia; recorded hospital-treated dementia or dementia deaths; and had accrued a minimum of 3 years of follow-up.

2.2. Measurements

Height and weight at baseline were measured in 11 studies and self-reported in 28 (Appendix 1, avaliable in the online Supplementary Materials). BMI was calculated as weight in kilograms divided by height in meters squared. We assessed the following baseline covariates because they are known to be associated with BMI and dementia risk: education/socioeconomic position (harmonized into high, intermediate, and low), smoking (current smoker vs. other), and prevalent cardiometabolic disease (coronary heart disease, stroke, and diabetes; one or more vs. none) [2,3].

We obtained information about dementia status at follow-up from national death and hospital admission registries, reimbursements for medical treatment of dementia, and