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Body mass index in midlife and dementia: Systematic review and meta-regression analysis of 589,649 men and women followed in longitudinal studies

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Abstract

Introduction: We conducted a meta-analysis of the conflicting epidemiologic evidence on the association between midlife body mass index (BMI) and dementia.

Methods: We searched standard databases to identify prospective, population-based studies of dementia risk by midlife underweight, overweight, and obesity. We performed random-effects meta-analyses and meta-regressions of adjusted relative risk (RR) estimates and formally explored between-study heterogeneity.

Results: We included 19 studies on 589,649 participants (2040 incident dementia cases) followed up for up to 42 years. Midlife (age 35 to 65 years) obesity (BMI $\geq$ 30) (RR, 1.33; 95% confidence interval [CI], 1.08–1.63), but not overweight (25 $<$ BMI $<$ 30) (RR, 1.07; 95% CI, 0.96–1.20), was associated with dementia in late life. The association with midlife underweight (RR, 1.39; 95% CI, 1.13–1.70) was potentially driven by residual confounding (P from meta-regression = .004), selection (P = .046), and information bias (P = .007).

Discussion: Obesity in midlife increases the risk of dementia. The association between underweight and dementia remains controversial.

Keywords: Dementia; Body mass index; BMI; Obesity; Meta-analysis

1. Introduction

Underweight, overweight, and obesity have been related to all-cause mortality risk [1] and to various poorer health outcomes [2], but their impact on the risk of dementia remains debated [3]. Although global epidemic of overweight and obesity accrues, underweight endures in poorer countries [4]. Therefore, the association of both obesity and underweight with dementia has enormous public health implications [5,6].

Excess body weight may increase dementia risk in late life by contributing to the accumulation of brain lesions, through vascular and dysmetabolic pathways [7,8]. However, because body weight tends to decline after midlife, and neuropathology subtly progresses during the long preclinical phase of dementia [9], issues of directionality may arise with age and high body mass index (BMI)

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in late life may appear to be protective [10,11]. Any excess risk is plausibly related to adiposity in midlife, when weight gain is more pronounced [12], and associations with dementia are least likely disease- and age-confounded. However, whether midlife underweight relates to dementia risk remains to be established.

Several systematic reviews and meta-analyses have been published of epidemiologic studies that explored the relationship of standard BMI (body weight in kilograms divided by height in meter square) definitions of underweight (BMI $<$ 18.5), overweight (25 $<$ BMI $<$ 30), and obesity (BMI $\geq$ 30) in midlife with risk of dementia at old age [13–17]. However, the evidence is rapidly expanding and has become highly conflicting. Positive [18,19], null [10,20,21], and inverse [22], associations between midlife BMI and dementia risk have been reported, but whether the study design and methods of primary studies introduced bias and errors, which may explain the marked heterogeneity of results across studies, is not known. A comprehensive and updated systematic review and meta-analysis, coupled with a formal exploration of sources of biases, is warranted. We undertook a systematic review of epidemiologic studies assessing the association of late-life dementia risk to midlife underweight, overweight, and obesity, and we quantified and formally explored the anticipated heterogeneity of results across studies.

2. Materials and methods

2.1. Search strategy and selection criteria

We used the Population, Intervention, Comparison, and Outcome (PICO) framework [23] to search PubMed, Embase, Google Scholar, and the Cochrane library. We searched for prospective, population-based studies published in English between January 1966 and October 2016 reporting risk of dementia in old age (65 years or more) as a function of exposure to underweight, overweight, or obesity in midlife, defined as the period between early adulthood and old age (35–65 years). To complement the electronic searches, we hand-searched the bibliographies of relevant publications and contacted experts in the field. Two independent reviewers (E.A. and K.E.) examined titles and abstracts using the following inclusion criteria: (1) cohort studies or studies conducted using observational routinely collected health data [24], with a 10 years or longer midlife to late-life follow-ups; (2) measures of midlife underweight, overweight, and obesity modeled as independent variables in the analysis, and (3) dementia diagnosis in late life (i.e., 65 years or more). We excluded clinical, cross-sectional and experimental studies, studies on trajectories of body weight by dementia status [25], and duplicated publications. Final decisions on inclusion were made by consensus. In the meta-analysis, we included studies that reported risk estimates for the association of midlife underweight, overweight, and obesity with a dementia diagnosis in late life.

2.2. Definitions

All included studies used BMI as a measure of total adiposity, with the standard World Health Organization BMI groups for underweight (BMI $\leq$ 18.5), normal weight (18.5 $<$ BMI $<$ 25), overweight (25 $\leq$ BMI $<$ 30), and obesity (BMI $\geq$ 30 kg/m^2); slightly different BMI cutoffs of underweight (i.e., BMI $<$ 20 kg/m^2) were deemed appropriate for our analysis (Launer LJ, personal communication, 2015) [22]. We considered dementia diagnosis according to standard diagnostic criteria, established using validated multiphase diagnostic procedures, or based on death certificates, medical records, and hospital records. We contacted the authors of primary studies to obtain further data and information when needed.

2.3. Data extraction

Two reviewers (E.A. and K.E.) used purposely designed forms to independently abstract the following information: study design, place, participants, outcome (e.g., dementia diagnosis), and exposure's ascertainment methods; covariates and confounders (including lifestyle, sociodemographic, health characteristics, and *APOE* polymorphisms); and the statistical methods used. The main results of the most adjusted models were abstracted and retained for the meta-analysis.

2.4. Assessment of risk of bias

We assessed the susceptibility to bias of the included studies combining the approaches recommended by the Methods in Longitudinal Research on Dementia (MELODEM) Initiative for dementia research [26] and by Sanderson et al. for cohort studies [27]. Two independent researchers (E.A. and K.E.) appraised the methodological quality (0 = low, 1 = adequate, and 2 = optimal) across seven criteria: (1) study design; (2) participants' mean (or median) age when body mass was measured; (3) underweight, overweight, and obesity ascertainment methods; (4) dementia diagnostic criteria and ascertainment procedures; (5) adjustment for potential confounders and relevant covariates [28]; (6) follow-up length between exposure assessment in midlife and dementia diagnosis at older ages; and (7) study sample attrition and proportion of participants at follow-up.

2.5. Statistical analysis

We combined the dementia risk estimates separately by midlife underweight, overweight, and obesity compared with normal BMI in random-effects models, pooling the log-transformed relative risks (RRs), hazard ratios, and odds ratios under the equivalence assumption for noncommon events. If multiple results were reported for the same cohort we used the later (i.e., with more years of follow-up) [29,30] or the most comprehensive findings [31], we combined risk estimates of men and women (except when