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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

the sex × BMI interaction terms in the primary study were statistically significant [19]), and we conducted sensitivity analyses stratified by sex. Because proneness to errors and bias in population-based cohort studies and in studies conducted using routinely collected health data differ substantially [24], we stratified the main meta-analyses by study design and compared the pooled dementia risk estimates and heterogeneities accordingly.

We quantified heterogeneity using the standard low (25%), moderate (50%), and high (75%) Higgins I^2 values cutoffs [32], and we investigated whether, and the extent to which, any difference between studies in dementia risk estimates could be explained by their study design characteristics in a set of meta-regression analyses.

In sensitivity analyses, we reran the meta-analyses for underweight, overweight, and obesity by length of follow-up time (the interval between ascertainment of midlife BMI and dementia diagnosis at old age, equal, or more than vs. less than 20 years), sex (studies conducted in men or women only, or both), method of dementia diagnosis, and statistical adjustment, and we formally explored the variation in between-study variance (tau squared) across models [33].

Finally we investigated any suggestion of publication bias and small-study effects by visual inspection of Funnel plots, and we calculated asymmetry with modified Egger regression using the Stata metabias routine [34,35]. For illustrative purposes, we presented graphically a meta-regression "bubble plot" by proneness to bias in the primary studies. Further details about our methods are reported in Appendix A. We used Stata 14 for all analyses (Stata Corp LP, College Station, TX, USA).

3. Results

3.1. Included and excluded studies

Of the 512 records identified 426 were excluded after title and abstract review. We examined the 86 potentially eligible publications and two more retrieved from other sources as full texts, 30 reports met the inclusion criteria. Of these, 11 were excluded because midlife BMI was predicted rather than measured in midlife [14], was modeled as a continuous variable [36], as a covariate in multivariate models [37,38], or data were previously published [21,39–43]. We retained

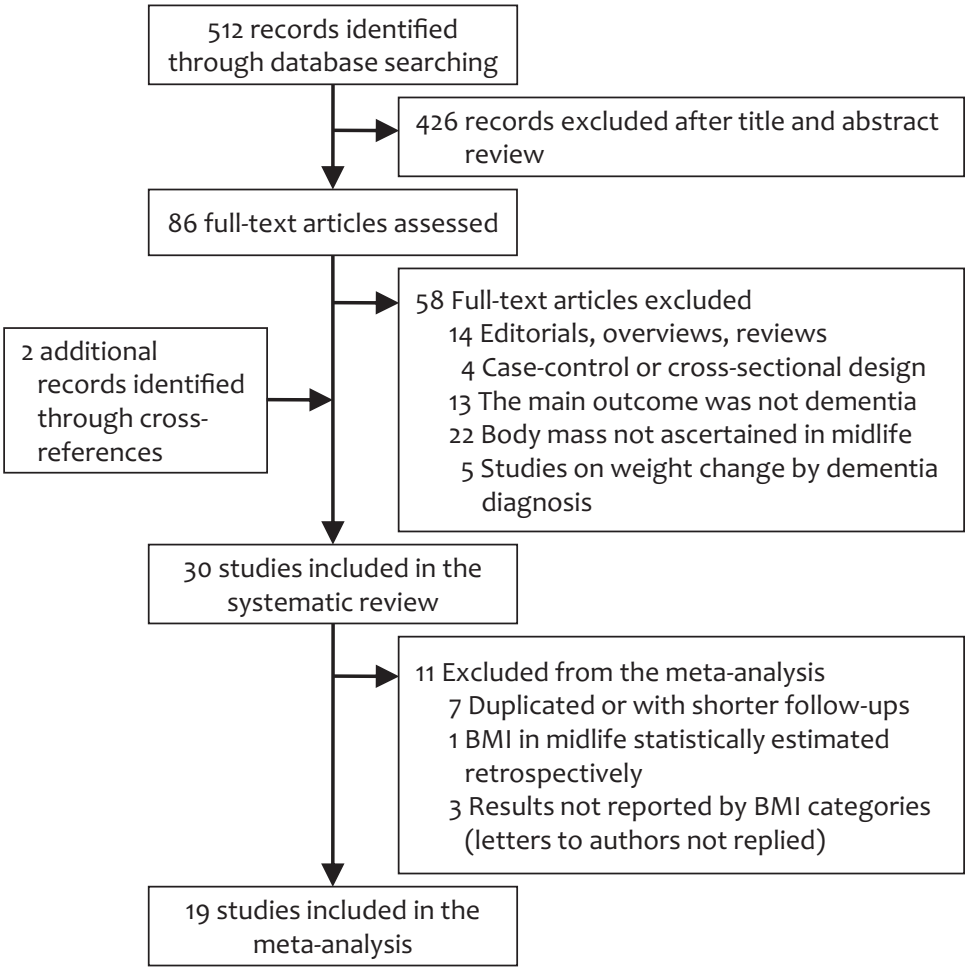

Fig. 1. Identification and selection of eligible studies.

Table 1
Characteristics of included studies

Study acronym or name (location)	Analytic sample (% of female)	Mean follow-up, years (SD)	Body mass ascertainment procedures	Mean age, y (SD or range) when BMI was ascertained	Dementia ascertainment (diagnostic criteria), number of cases	Confounders included in the adjusted model
Cohort studies						
CHS (USA) [48]	2616 (59)	20.0 (N/A)	Retrospectively self-reported estimates, obtained in late life	50 (N/A)	Multiphase consensus diagnosis (clinical consensus), 461	Age, race, sex, education, *APOE* ε4 allele, late life: CRP, IL-6, hypertension, cholesterol, diabetes, CHD, ankle-arm index, smoking, total kilocalories intake
PPSW (Sweden) [10]	651 (100)	32.0 (4.0)	Standard, direct measures of body height and weight (results on overweight only)	47 (N/A)	Clinical consensus (DSM-III-R), 161	Age, triglycerides, cholesterol, SBP, age at menopause, education, diabetes
Twin Registry (Sweden) [30]	8534 (60)	30.0 (N/A)	Self-reported estimates, obtained in midlife	43 (15)	Multiphase consensus diagnosis (DSM-IV), 464	Age, sex, education, diabetes, hypertension, stroke, and heart disease
IIHD (Israel) [51]	1620 (0)	37.0 (6.0)	Standardized direct measure of weight and self-reported height	44 (N/A)	Multiphase consensus diagnosis (DSM-IV), 307	Age, diabetes, body height, SES
Twin Registry (Finland) [52]	1601 (49)	22.6 (2.3)	Self-reported estimates, obtained in midlife (no results on underweight)	51 (6.1)	Automated algorithm (TELE; 16 cutoff), 650	Age, sex, education, *APOE* ε4 allele, follow-up years
CAIDE (Finland) [29]	1304 (61)	26.0 (5.1)	Standardized direct measures	50 (N/A)	Multiphase consensus diagnosis (DSM-IV), 169	Age, sex, *APOE*, residence, smoking, education, income, diabetes, CVD, cerebrovascular diseases, SBP, cholesterol
AGES (Island) [20]	3864 (57)	26.2 (4.9)	Standard, direct measures of body height and weight	50 (4.7)	Multiphase consensus diagnosis (DSM-IV), 190	Age, sex, follow-up years, *APOE* ε4 allele; midlife: education, exercise, SBP, DBP, cholesterol; late life: coronary artery calcium, coronary artery disease, hypertension, diabetes, depression, alcohol and smoking habits, and MRI brain measures (white matter lesions and intracranial volumes)
HAAS (USA) (Launer LJ, personal communication, 2015)	3733 (0)	23.0 (4.0)	Standard, direct measures of body height and weight	59 (51–74)	Multiphase consensus diagnosis (DSM-III-R) 112	Age, education, stroke, hypertension, diabetes, smoking, *APOE* ε4, impaired physical function, CES-D

Rotterdam study (the Netherlands) [47]	2085 (58)	15.0 (5.7)	Standard, direct measures of body height and weight	58 (1.4)	Multiphase consensus diagnosis, integrated with medical records (DSM-III-R) 81	Age, sex, study cohort, systolic and diastolic blood pressure, serum cholesterol and HDL, use of antihypertensive medication, use of lipid-lowering medication, diabetes mellitus, smoking (never, former, current), level of education, *APOE* genotype, history of stroke
Studies that used, in part or entirely, observational routinely collected health data						
MPPS (Sweden) [18]	7402 (0)	25.0 (7.0)	Standard, direct measures of body height and weight	52 (2)	Hospital discharge or death certificates (ICD-9; ICD-10) 254	Age, smoke, exercise, occupation; midlife: diabetes, SBP, cholesterol
Kaiser Permanent (USA) [19]	10,276 (55)	26.0 (9.0)	Standard, direct measures of body height and weight	43 (N/A)	Outpatient medical records (ICD-9; ICD-10) 713	Age, sex; midlife: education, race, marital status, hypertension, diabetes, cholesterol; and late-life hypertension, stroke, diabetes, IHD, cholesterol
MRMD and CSP (Taiwan) [46]	785 (45)	15.0 (4.0)	Standard, direct measures of body height and weight	58 (N/A)	Hospital records (DSM-IV, Chinese version) 157	Self-reported cardiovascular diseases and hypertension
ARIC (USA) [45]	11,151 (57)	12.8 (N/A)	Standard, direct measures of body height and weight	55 (N/A)	Medical records (ICD-9) 203	Age, sex, race, study site, education, occupational level, cognitive tests at baseline, CVRFs, *APOE* ε4 allele
7 Countries (Finland, Greece, Italy, the Netherlands, ex-Yugoslavia; Japan, USA) [44]	10,211 (0)	25.3 (6.0)	Standard, direct measures of body height and weight	49 (40–59)	Death certificates (ICD-8, code 290) 160	Age, study cohort, occupation, body height, smoking; midlife cholesterol, hypertension, FVC, CVD
LSUHCSD (USA) [49]	44,660 (N/A)	12.9 (N/A)	Midlife body height and weight direct measures (no results on underweight)	N/A (30–96)	Revised medical records (DSM-IV or ICD-9) 388	Age, sex, smoking, BP, cholesterol, triglycerides; diabetes, medications
HES (UK) [53]	241,146 (57)	15.0 (N/A)	Admission for clinically diagnosed obesity	50 (N/A)	Hospital records or death certificates (ICD-10) 321	Sex, place of residence
CPRD (UK) [22]	172,313 (55)	18.3 (2.2)	Standard, direct measures of body height and weight	55 (N/A)	Clinical records or death certificates (dementia subtypes diagnoses) 620	Age, sex, smoking, alcohol, statins, antihypertensive use, diabetes, myocardial infarction
Whitehall (UK) [50]	18,823 (0)	42.0 (N/A)	Standard, direct measures of body height and weight	55 (40–69)	Death certificates (not specified) 283	Smoking habit and birth cohort
NCS and CONOR (Norway) [31]	46,874 (51)	33.0 (N/A)	Standard, direct measures of body height and weight	43 (N/A)	Death certificates (ICD-9; ICD-10) 711	Age, sex, study site (county); midlife diabetes, physical inactivity, smoking, SBP, DBP, cholesterol, and education

Abbreviations: AGES, Age, Gene/Environment Susceptibility—Reykjavik Study (Reykjavik, Iceland); ARIC, atherosclerosis risk in communities; BMI, body mass index; CAIDE, cardiovascular risk factors aging and dementia; CES-D, centers for epidemiologic studies depression scale; CHD, coronary heart disease; CHS, Cardiovascular Health Study (four US centers in MD, CA, PA, NC); CONOR, the cohort of Norway; CPRD, Clinical Practice Research Datalink; CRP, C-reactive protein; CVD, cardiovascular disease; CVRF, cardiovascular risk factors; DBP, diastolic blood pressure; DSM, Diagnostic and Statistical Manual of Mental Disorders; FVC, forced vital capacity; HAAS, Honolulu-Asia Aging Study; HDL, high-density lipoproteins; HES, English National Hospital Episodes Statistics; ICD, International Statistical Classification of Diseases and Related Health Problems; IHD, ischemic heart disease; IIHD, Israel Ischemic Heart Disease Project; IL-6, interleukin 6; LSUHCSD, Louisiana State University Hospital-Based Longitudinal Study; MPPS, Multifactor Primary Prevention Study (Goteborg, Sweden); MRI, magnetic resonance imaging scan; MRMD and CSP, Multiple Risk Factors for Major Diseases and Cancer Screening Program; NCS, The Norwegian Counties Study; PPSW, Prospective Population Study of Women in Sweden; SD, standard deviation; SBP, systolic blood pressure; SES, socioeconomic status; TELE, validated telephone interview to detect cognitive impairment.

19 studies for further analysis (Launer LJ, personal communication, 2015) [10,18–20,22,29–31,44–53]. The selection process is shown in Fig. 1 and reported in detail in Appendix B and C.

Except for one multicenter study [44], one in Israel [51], and one in Taiwan [46], studies were conducted in Northern European countries including the UK [10,18,20,22, 29–31,49,50,52,53], or the USA (Launer LJ, personal communication, 2015) [19,45,48,49]. Nine were purposely designed population-based prospective cohort studies (Launer LJ, personal communication, 2015) [10,20,29,30,47,48,51,52], the other 10 were cohort studies that used, to different extents, routinely collected health data of exposure status (i.e., height and weight measured during routine health checks or visits in midlife) or outcome (i.e., dementia diagnosis from hospital records or death certificates). The sample sizes ranged from 651 [10] to 241,146 [53] for a total of 589,649 participants who were followed up for up to 42 years from midlife to late life [50]. There were 2040 incident dementia cases. Most studies included men and women, one study included only women [10], and five studies included only men (Launer LJ, personal communication, 2015) [18,44,50,51]. In one study, the first recorded clinical diagnosis of obesity was extracted from hospital admission records [53], in three studies body height and weight were self-reported in midlife [30,52], or retrospectively in late life by dementia-free participants [48]. Standard, direct measures of height and weight were collected at baseline and used to calculate BMI in the remaining studies. The participants' ages at baseline did not substantially differ, but the exact age ranges could be determined only for six studies [18,20,30,44,47,52]. All purposely designed cohort studies adjudicated dementia diagnosis through clinical consensus using validated, multiphase diagnostic procedures based on various screening instruments followed by in-depth clinical evaluation of screen positives. Dementia was ascertained from death certificates in three cohort studies [31,44,50], a combination of data extracted from medical and hospital records [18,19,22,45,46,49,53], or a validated algorithm of a telephone interview [52]. Dementia diagnostic criteria included the International Classification of Diseases [54], the Diagnostic and Statistical Manual of Mental Disorders (DSM, III-R and IV Edition) for all dementias and dementia subtypes including Alzheimer's disease (AD) and Vascular dementia (VaD) according to standard criteria (Table 1) [55–57].

3.2. Risk of bias assessment

In four studies, age ranges of participants were wide and a small proportion were likely older than 65 years at baseline when midlife exposure status was assessed (Launer LJ, personal communication, 2015) [49–51]. With two exceptions, recall bias [48] and measurement errors or inconsistencies [53] in exposure ascertainment were unlikely. Outcome ascertainment was considered unbiased in the eight studies that did not rely on death certificates or hospital records (Launer LJ, personal communication, 2015) [10,20,29,30,47,51]. Adjustment for confounders attenuated associations [29,48,52] and residual confounding was probable in the five studies that did not adjust for education [22,46,49,50,53]. The potential confounding effect of stroke or cerebrovascular damage was adjusted for in four studies only. Only few studies had relatively short midlife to late life follow-up periods (i.e., less than 20 years) [22,45–47,49,53]. Finally, relevant proportions of participants were lost at the follow-ups (i.e., up to 50%) in several studies, and potential bias because of attrition was addressed in only three studies (Table 2) [10,20,22].

3.3. Meta-analyses and meta-regressions

There were 12 studies contributing data on midlife underweight (with the Kaiser Permanente study contributing two data points, one for men and one for women). Compared with healthy weight being underweight in midlife was associated with 39% higher risk of dementia (RR, 1.39; 95% confidence interval [CI], 1.13–1.70). Results were heterogeneous across studies (Higgins' I^2 = 42.1%; Cochrane Q P = .055) and the increased risk for dementia was evident in studies that relied on routinely collected health data (RR, 1.73; 95% CI, 1.43–2.09), but not in the purposely designed cohort studies (RR, 1.03; 95% CI, 0.85–1.25; Fig. 2); P value for the interaction by study design in dementia risk from meta-regression = .007. The meta-regression results are presented in Appendix D.

Our random-effects meta-analysis indicated that being overweight in midlife does not increase dementia risk (RR, 1.07; 95% CI, 0.96–1.20) (Fig. 3). Results were heterogeneous across cohort studies (I^2 = 59.3%; P = .002), and the effect modification by study design in dementia risk was not significant (P = .434) (Appendix D).

The risk of dementia in those who were obese in midlife was 33% higher (RR, 1.33; 95% CI, 1.08–1.634), and the heterogeneity among studies was high (I^2 = 77.1%; $P < .001$). Among purposely designed cohort studies the combined RR indicated a significant 47% higher risk of dementia (RR, 1.47; 95% CI, 1.06–2.03). Results were markedly heterogeneous between studies that made use of routinely collected health data, including hospital records and death certificates (I^2 = 83.4%; $P < .001$), and the CIs for the meta-analyzed dementia risk of midlife obesity were wide and included one (RR, 1.23; 95% CI, 0.93–1.64) (Fig. 4). There was no interaction by study design in the association between midlife obesity and dementia (P = .826) (Appendix D). Fig. 5 displays the pooled adjusted RRs of dementia (with 95% CI) by midlife underweight, overweight, and obesity in all studies and by study design.

In the meta-regression, the association between midlife underweight and dementia was significantly more likely

Table 2
Critical appraisal of included studies

Study name or acronym (location)	Sampling procedure	Age at baseline	Exposure	Outcome	Adjustment	Follow-up length	Losses at follow-up
Cohort studies							
CHS (USA) [48]	1	2	0	1	2	2	0
PPSW (Sweden) [10]	2	2	2	2	1	2	0
Twin Registry (Sweden) [30]	1	2	1	1	1	2	0
IIHD (Israel) [51]	2	1	2	1	1	2	0
Twin Registry (Finland) [52]	1	2	1	0	2	2	1
CAIDE (Finland) [29]	2	2	2	1	2	2	0
AGES (Island) [20]	2	2	2	1	2	2	2
HAAS (USA) (Launer LJ, personal communication, 2015)	2	0	2	1	2	2	2
Rotterdam study (the Netherlands) [47]	2	2	2	1	2	1	2
Studies that used, in part or entirely, observational routinely collected health data							
MPPS (Sweden) [18]	1	2	2	0	1	2	2
Kaiser Permanente (USA) [19]	0	2	2	0	1	2	0
MRMD and CSP (Taiwan) [46]	0	2	2	0	0	0	0
ARIC (USA) [45]	0	2	2	0	2	0	2
7 Countries (Finland, Greece, Italy, the Netherlands, ex-Yugoslavia; Japan, USA) [44]	1	2	2	0	1	2	2
LSUHCSD (USA) [49]	0	0	1	0	0	0	1
HES (UK) [53]	0	1	0	0	0	0	0
CPRD (UK) [22]	0	2	2	0	0	1	0
Whitehall (UK) [50]	2	0	2	0	0	2	0
NCS and CONOR (Norway) [31]	1	2	2	0	1	2	2

Abbreviations: AGES, Age, Gene/Environment Susceptibility—Reykjavik Study (Reykjavik, Iceland); ARIC, atherosclerosis risk in communities; CAIDE, cardiovascular risk factors aging and dementia; CHS, Cardiovascular Health Study (four US centers in MD, CA, PA, NC); CONOR, The Cohort of Norway; CPRD, Clinical Practice Research Datalink; HAAS, Honolulu-Asia Aging Study; HES, English National Hospital Episodes Statistics; IIHD, Israel Ischemic Heart Disease Project; MPPS, Multifactor Primary Prevention Study (Goteborg, Sweden); MRMD and CSP, Multiple Risk Factors for Major Diseases and Cancer Screening Program; NCS, The Norwegian Counties Study; PPSW, Prospective Population Study of Women in Sweden.

NOTE. The critical appraisal criteria were defined as follows: *Sampling*: 0 = inadequate (sampling is neither random nor systematic or does not guarantee the representativeness of the target or frame population; twin studies are not considered representative of the general population); 1 = adequate (systematic samples drawn from community dwelling people); 2 = optimal (random, representative samples of the target population based on electoral or other registries). *Age at baseline* when BMI was measured: 0 = inadequate (wide age ranges that may exceed 60 years); 1 = adequate mean age for "midlife" (i.e., younger than 65 years) with wide ranges; 2 = optimal: mean age limited to midlife and narrow age ranges. *Exposure* ascertainment: 0 = inadequate (self-reported in late life; nonstandard measures); 1 = adequate (self-reported in midlife with validation of the procedure); 2 = optimal (direct, standard measures in midlife). *Outcome* ascertainment: 0 = record-linkage (based on hospital records and death certificates); 1 = clinical consensus diagnosis based on one or multiphase design with screening; 2 = one-phase designs or correctly applied multiphase designs (i.e., correct weighing back of those who screened negative in phase 1). *Adjustment*: 0 = inadequate (established potential confounders are missing, ex. education, sex, or age); 1 = adequate (includes sociodemographic and health characteristics); 2 = complete (includes established potential confounders spanning sociodemographic, health characteristics, and *APOE* ε4 polymorphism). *Follow-up* length (from midlife to late life): 0 = less than 15 years; 1 = more than 15 years for the all sample; 2 = 20 years or more than for the all sample. *Proportion of participants at follow-up*: 0 = less than 50%; 1 = 50.1% to 75%; 2 = 75.1% or more (for registry-based study we considered the size of the study sample relative to the database population). *Overall quality score*: this is obtained by summing up the scores of the eight quality criteria (range 0–14).

found in studies more prone to selection bias ($P = .046$) and outcome ascertainment bias ($P = .007$), with shorter follow-up periods ($P = .024$) and greater participants' attrition ($P = .007$), and in which potential confounders were less adequately controlled for ($P = .004$) (Appendix D). Overall, the RR of dementia by midlife underweight decreased by 9% (95% CI, 0.15–0.03; $P = .009$) per unit increase in the overall score obtained combining the individual elements of our critical appraisal tool. No such differences were found for the associations of dementia with midlife overweight and obesity when we accounted for the study design features of the included studies (Appendix D and e-Fig. 2).

In the sensitivity analysis, there was no association between obesity and dementia in the six studies with shorter follow-ups (i.e., less than 20 years) (RR, 1.18; 95% CI, 0.75–1.85), with less adequate adjustment (RR, 1.23; 95% CI, 0.78–1.95), or those conducted in men only (RR, 1.28; 95% CI, 0.92–1.78) (Appendix E). Finally, on inspection of the underweight funnel plot there was some suggestion of asymmetry owing to missing positive studies for underweight and dementia based on small registry–derived data. However, the formal asymmetry tests were not significant for cohort (Egger's test P value = .158) and in studies that (also) used routinely collected health data ($P = .266$). We noticed no asymmetry inspecting funnel plots, nor were the formal asymmetry tests significant for overweight ($P > .208$) and obesity ($P > .482$) (e-Fig. 2).

4. Discussion

We have conducted the most comprehensive systematic review to date of longitudinal studies that have investigated

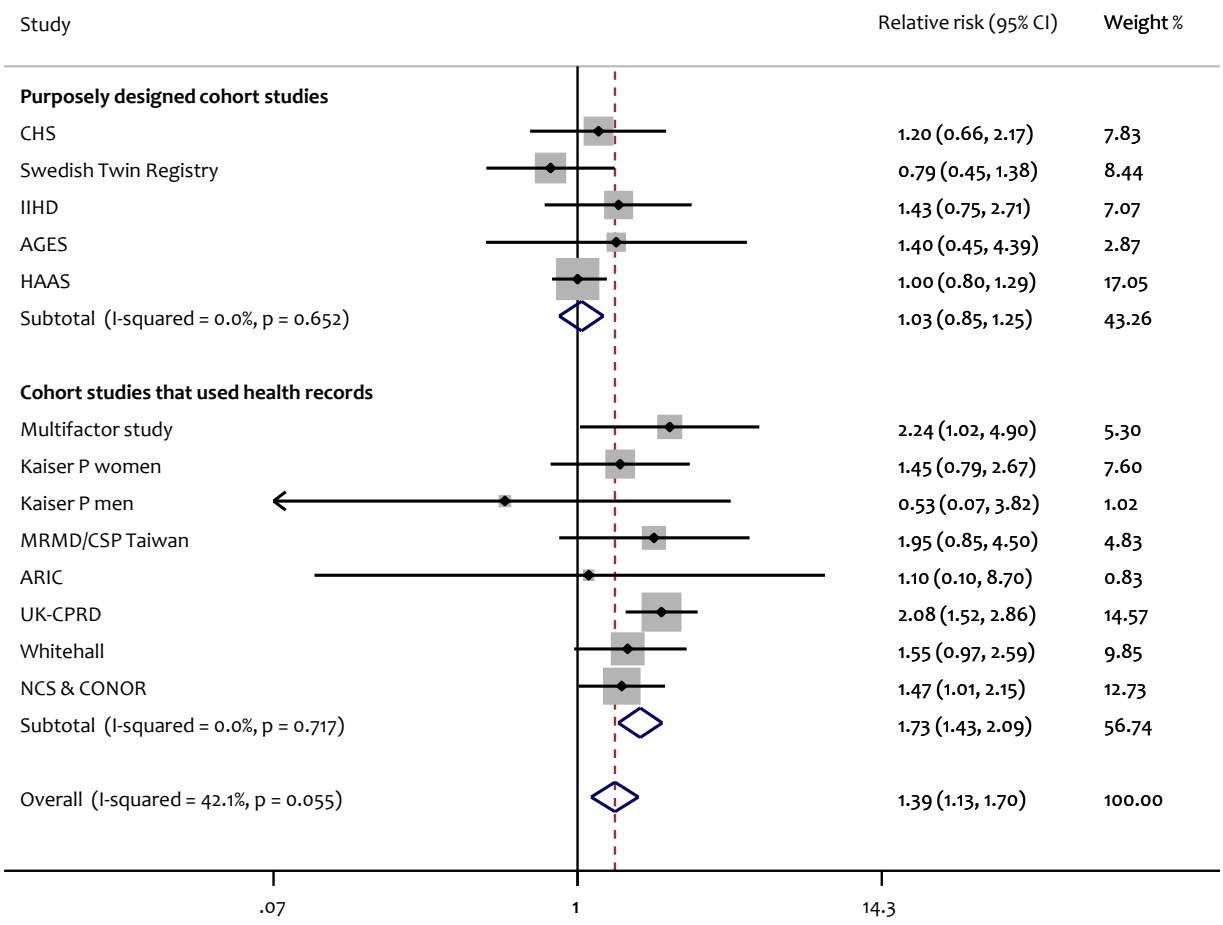

Fig. 2. Adjusted dementia relative risk by midlife underweight compared with normal body mass index.

the association between BMI in midlife and dementia risk. Our results are based on 589,649 participants from up to 19 cohort studies and indicate that while being overweight does not and being obese in midlife does confer a significant increased risk of developing dementia at older ages. The results on the positive association between midlife underweight and dementia were inconsistent across studies.

Excess body weight in midlife may contribute to vascular and neurodegenerative damage that underpins dementia through vascular and dysmetabolic pathways [7], and directly through cell-signaling proteins secreted by the adipose tissue (e.g., leptin and adiponectin) [58]. Yet, mechanistic [59] and epidemiologic evidence [60] suggests that dementia may cause involuntary weight loss well before its clinical onset [25,61], and low BMI may spuriously appear to be detrimental for dementia (and high BMI protective) [62]. Therefore, focusing on midlife exposure was important to assessing any differences in dementia risk, and our meta-regressions suggest that the positive associations between midlife underweight and dementia, which were reported only in studies with follow-up periods less than 20 years [22,45–47,49,53], may be disease-confounded and be explained, at least in part, by reverse causality.

Numerous factors, including depression, diabetes, hypertension, and stroke may confound or mediate the association between BMI and dementia [63], and the covariates in the statistical models varied significantly between the included studies. Although some factors may lay on the causal pathway between obesity and dementia, residual confounding may not be excluded and the lack of adjustment for educational level [22,49,50,53], or type 2 diabetes [44–46,50,52], which are strongly associated with both BMI [64,65], and dementia [66,67], may have contributed to the heterogeneity of findings.

Ascertainment procedures for dementia varied significantly across studies from multiphase clinical consensus approaches (Launer LJ, personal communication, 2015) [10,20,29,30,47,48,51] to routinely recorded health data and death certificates [31,44,50]. The use of medical records and administrative data presents both great opportunities and challenges for dementia research [24,26], because the use of these records as proxies for dementia is hampered by underreporting and measurement variability that may move the risk estimates toward the null effect [68,69], and the diagnosis may be more likely in obese subjects who tend to be sicker and make more

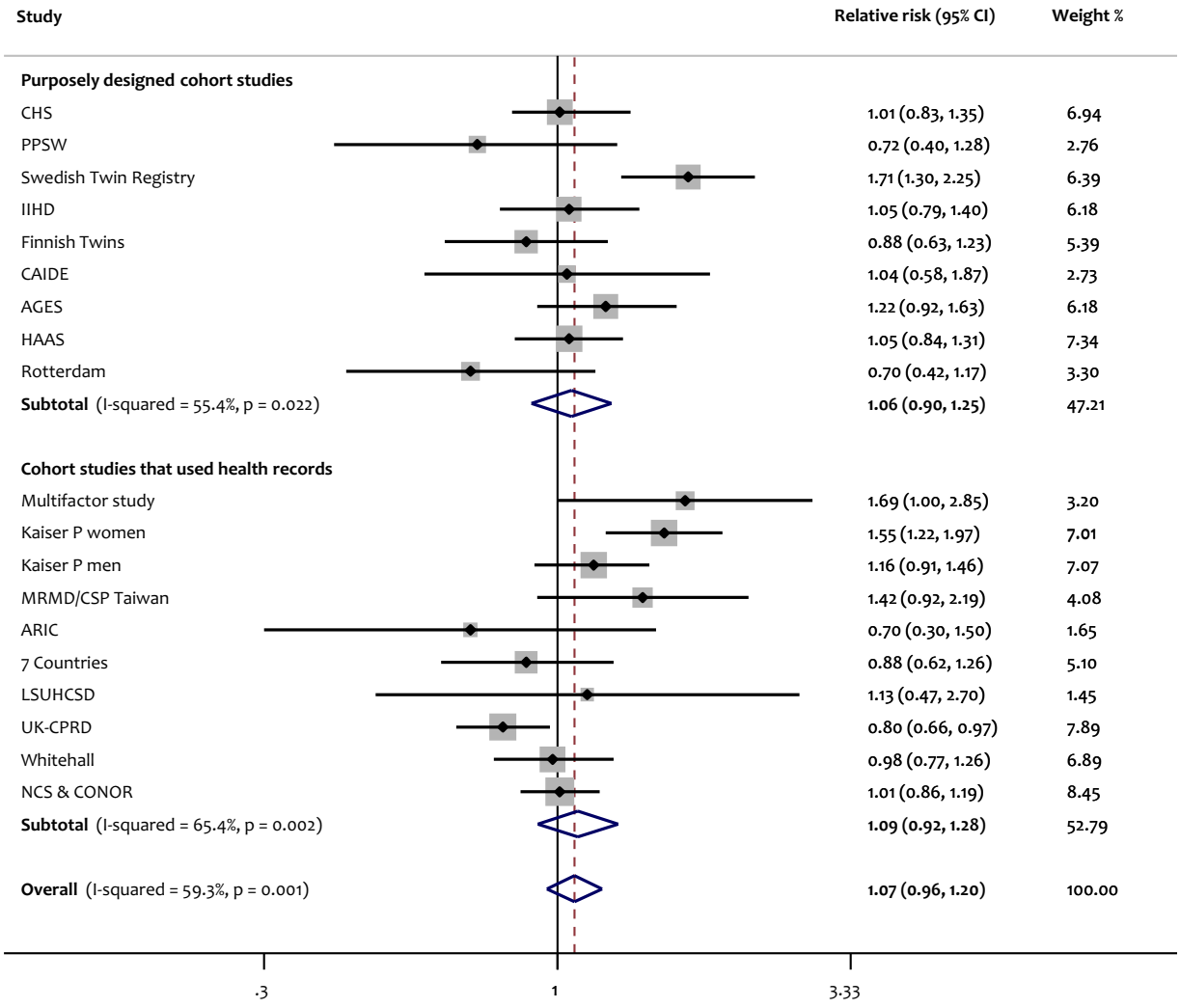

Fig. 3. Adjusted dementia relative risk by midlife overweight compared with normal body mass index.

use of health services. This potential surveillance bias may explain some of the most extreme positive results among some of the studies included in our review [18,19,46,53]. A subtle length/survival bias may not be excluded either [70]. Obesity increases mortality risk and may significantly reduce survival in those with dementia because of poorer health [1]. The use of routine data for dementia diagnosis is biased by the severity of the disease [71]; therefore, the shorter survival in those with dementia and obesity-related comorbidities make them less likely to receive a diagnosis before they die. Participants may be systematically misclassified as disease-free, and competing risks model may not counteract this misclassification error because the assumption of nondifferential effects of exposure status on the analytic sample derivation may not hold [72].

Other sources of bias may exist. Underweight and obesity are plausibly related to access and use of primary care services, and they may influence data collection [24]. Lack of clinical measures and missing values were more likely in those with worse cardiovascular risk profiles who were thus excluded from the analytic samples [20,30], and an unknown number of people who were obese or underweight in midlife and at higher risk of dementia could have been systematically excluded because of differential study enrollment, and differential attrition and survival after enrollment. Both length and selection biases could explain some recent findings on a seeming protective effect of excess body weight in midlife for dementia risk [22]. Nevertheless, across cohort studies there was a significant and consistent 47% higher dementia risk associated with obesity in midlife compared with normal BMI, and the magnitude of the overall effect in the main analysis (i.e., 33%) may be only a slight underestimate.

Some limitations are worth noting. We focused on "all dementia" diagnosis as a proxy of the prevalence of the dementia syndrome in general populations and did not explore separately AD, VaD, and other dementia subtypes. However, clear distinctions and differential diagnoses require a more

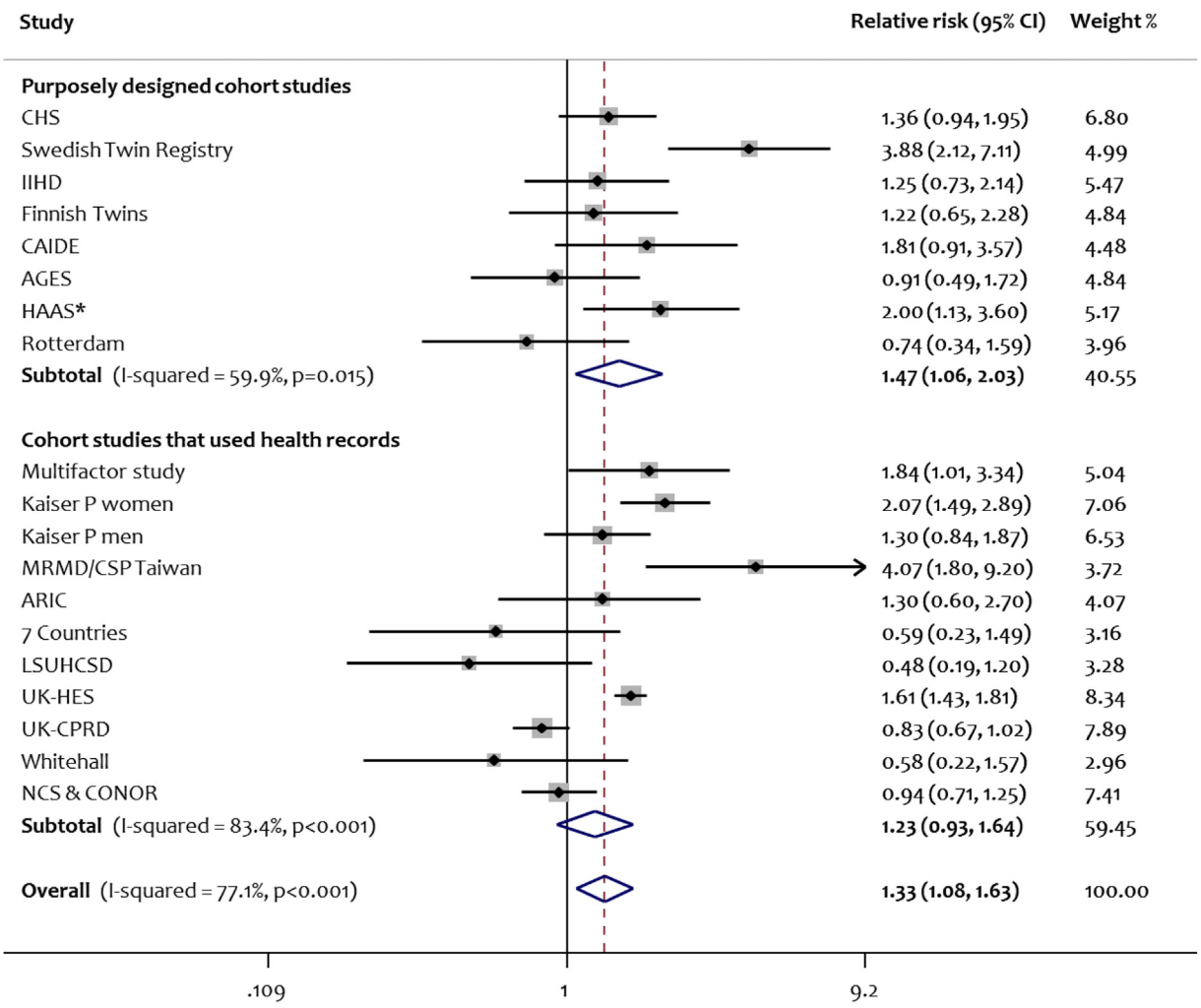

Fig. 4. Adjusted dementia relative risk by midlife obesity compared with normal body mass index.

detailed clinical evaluation over time, which is not usually possible in epidemiologic studies. We used standard World Health Organization categories of midlife BMI in our analysis. BMI is a surrogate measure of global adiposity and has limitations, although particularly in older adults [73]. However, BMI can accurately distinguish between categories of percentage of body fat, it performs similar to other anthropometric measures in the population (including waist circumference) [74], and is associated with mortality greater than and less than the conventional normal range of 22.5 to 25 kg/m^2 [1]. Thus, we integrated our searches contacting several authors, retrieved, and included twice the number of reports compared with previous reviews [13,15], and gathered missing information to harmonize results of primary studies on dementia risk by midlife BMI categories are all major strengths of our review along with the formal exploration of the sources of heterogeneity of results.

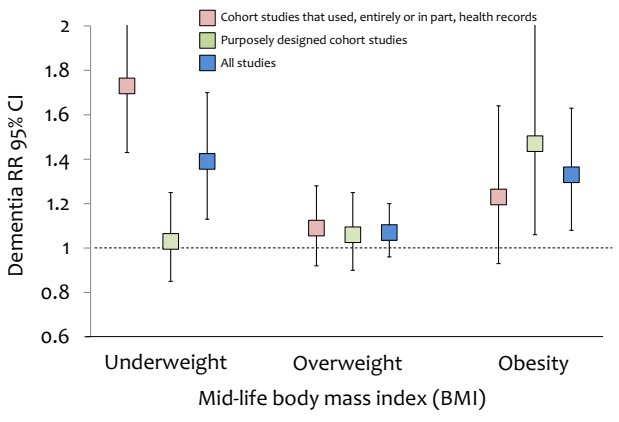

Fig. 5. Pooled dementia risks by midlife underweight, overweight, and obesity.

Although comparisons are not straightforward, because among the 19 studies that met our inclusion criteria 12 were published only recently (Launer LJ, personal communication, 2015) [20,22,29–31,47,49–53], our findings on midlife obesity are in line with those of previous reviews [13,14]. Namely, a meta-analysis of three studies found a 64% significantly higher all-dementia risk associated with

Box 1
Future directions, a roadmap to further explore the link of adiposity and dementia

1. *Life course observational epidemiologic research* aimed at providing clues to the etiology of dementia, building and testing theoretical models of causal pathways to dementia in late life that account for the timing and duration of exposure to high and low adiposity throughout the life course, and for the concomitant potential modifying or mediating effect of other exposures.
2. *Basic science research* to explore biologically plausible mechanisms and pathways through which high (and low) adiposity may modulate the risk of dementia, its biological underpinnings and its clinical expression, at both the induction and latency phase of the disease.
3. *Clinical-translational and implementation research* aimed at designing complex interventions for brain and cognitive health promotion, and prevention and treatment of impairment, in patients and target populations, testing their efficacy and effectiveness, and the scalability of their provision through health and social care services.

midlife obesity compared with healthy body weight [13], and a similar magnitude (i.e., 60%) was found combining the results of five cohort studies for Alzheimer's disease risk by others [75]. An increased risk of dementia by midlife overweight was found in a previous meta-analysis [13] of three cohort studies [18,19,48]. Our results are based on 14 additional data points, which became available only in recent years, and indicate that there is no association between midlife overweight and any dementia, which is consistent with the findings of other systematic reviews [15–17]. As outlined earlier, weight loss in people with dementia begins decades before clinical onset and accrues gradually through stages of dementia [59,76,77], such that midlife to late-life trajectories of body weight have been found to vary by dementia status at older ages [25,61,78,79]. However, the biological plausibility of the link between underweight in midlife and risk of dementia in late life remains a matter of debate, and the scanty epidemiologic evidence limits comparisons with our results. Evidence is urgently needed particularly from low and middle income countries, where prevalence of underweight is highest.

Our main findings are consistent with the hypothesis of a causal link between obesity and dementia [8]. Because the prevalence of obesity exceeded 10% in most countries in 2014 [4], and the steepest increases in obesity prevalences are occurring in those regions where populations are also more rapidly aging [80], the detrimental contribution of obesity to the catastrophic projections of dementia prevalence in the coming years [81] seems destined to accrue heftily, particularly in low and middle income countries [6]. In addition, because dementia risk may further increase with longer duration and accumulation of exposure to high adiposity throughout the life course [7], there is an urgent need to investigate the association of obesity in childhood and throughout adulthood with dementia in late life. Future directions in research could also include the use of individual-participant data meta-analysis [1] and Mendelian randomization designs (that exploit gene polymorphisms of known function to examine the causal effect of a modifiable exposure on disease in nonexperimental studies) [82], which may have the potential to advance significantly our knowledge on modifiable risk and protective factors of dementia. Mechanistic studies are also warranted to identify the pathways through which obesity (and underweight) may increase dementia risk, and translational research should investigate whether weight loss in midlife can influence metabolic flexibility and vascular reactivity through long-term positive effects on intermediate metabolism, endothelial function, inflammation, and oxidative stress (Box 1). Nonetheless, we maintain that the lack of any such evidence should not delay public health actions on a global scale aimed at reducing the population exposure to interrelated vascular risk factors (including obesity, diabetes, high blood pressure, and physical inactivity), and that these actions should target young, middle aged, and older people alike to reduce dementia risk and to attain better and longer lasting health results for individuals, and greater benefits to societies at large.

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Authors' contributions: E.A. conceived the study and drafted the manuscript. E.A. and K.I. designed the systematic review and meta-analysis methods with M.E. E.A. and K.I. conducted the systematic review, extracted data, and performed the statistical analyses with assistance from M.E. and P.G. L.J.L. and F.J.W. extensively revised the manuscript and provided relevant inputs at all stages, including the interpretation of the results. M.J.P., M.E., and P.G. revised the manuscript. All authors approved the final version of the manuscript.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.dadm.2017.05.007.

RESEARCH IN CONTEXT

1. Systematic review: We retrieved prospective, population-based studies of midlife body mass index and dementia risk using PubMed and contacted authors to maximize the comprehensiveness of the analysis. The evidence is highly conflicting and has rapidly expanded in recent years.
2. Interpretation: Our findings resolve the current uncertainty about the detrimental role of obesity in midlife for dementia risk at old ages and question the potential harm of low body mass index, thus suggesting that the obesity paradox does not extend to dementia.
3. Future directions: Future studies should focus on whether sensitive periods and/or cumulative effects of exposure to obesity throughout the life course exist; mechanistic and observational studies are needed to explore the potential role of underweight in midlife in dementia risk modulation. Finally, the effectiveness of public health actions aimed at tackling the global obesity epidemic in lessening the global burden of dementia should be formally investigated.

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