ORIGINAL RESEARCH

Association of obesity, diabetes and hypertension with cognitive impairment in older age

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Background: Age-related cognitive impairment is rising in prevalence but is not yet fully characterized in terms of its epidemiology. Here, we aimed to elucidate the role of obesity, diabetes and hypertension as candidate risk factors.

Methods: Original baseline data from 3 studies (OCTOPUS, DECS, SuDoCo) were obtained for secondary analysis of cross-sectional associations of diabetes, hypertension, blood pressure, obesity (body mass index [BMI] ≥30 kg/m²) and BMI with presence of cognitive impairment in log-binomial regression analyses. Cognitive impairment was defined as scoring more than 2 standard deviations below controls on at least one of 5–11 cognitive tests. Underweight participants (BMI<18.5 kg/m²) were excluded. Results were pooled across studies in fixed-effects inverse variance models.

Results: Analyses totaled 1545 participants with a mean age of 61 years (OCTOPUS) to 70 years (SuDoCo). Cognitive impairment was found in 29.0% of participants in DECS, 8.2% in SuDoCo and 45.6% in OCTOPUS. In pooled analyses, after adjustment for age, sex, diabetes and hypertension, obesity was associated with a 1.29-fold increased prevalence of cognitive impairment (risk ratio [RR] 1.29; 95% CI 0.98, 1.72). Each 1 kg/m² increment in BMI was associated with 3% increased prevalence (RR 1.03; 95% CI 1.00, 1.06). None of the remaining risk factors were associated with impairment.

Conclusion: Our results show that older people who are obese have higher prevalence of cognitive impairment compared with normal weight and overweight individuals, and independently of co-morbid hypertension or diabetes. Prospective studies are needed to investigate the temporal relationship of the association.

Keywords: obesity, body mass index, diabetes, hypertension, cognitive impairment, aging, cognitive epidemiology

Introduction

The metabolic syndrome and its complications threaten global health. In most countries, prevalence is high,[1] tends to increase over time[2,3] and generates huge economic costs.[4] Prevalence is largest among older age groups,[5] adding to the relevance of the syndrome as a candidate predictor of and potentially causal contributor to age-related disease including cognitive impairment, which itself is rising in prevalence due to globally ageing societies.[6] It has been estimated that 22% of people aged over 70 years in the USA are currently cognitively impaired,[7] and epidemiological studies have frequently demonstrated associations with the metabolic syndrome.[8–13] Diabetes, hypertension and obesity together contribute to the diagnostic criteria of the metabolic syndrome[14] and have each been assessed in detail for their relationship with cognitive outcome. Links

of diabetes to presence and risk of future cognitive impairment are well established,[15,16] while the evidence is less clear for obesity and hypertension. Here, the direction of associations appears to be dependent on the point of measurement during the lifespan. Whereas in prospective investigations spanning decades, midlife obesity and midlife hypertension increase the risk of later impairment,[17,18] cross-sectional and prospective investigations with shorter follow-up periods have produced mixed results: late-life obesity and hypertension have each been associated with an increased[13,19–22] but also with a reduced risk of impairment[17,23–26] in those types of studies. For obesity, the analysis is further complicated by measurement issues of commonly assessed parameters such as body weight or body mass index (BMI) that do not capture body composition well. The roles of obesity and hypertension in particular thus warrant clarification. Importantly, many previous epidemiological investigations have also failed to consider that diabetes, obesity and hypertension tend to cluster in individuals and are highly correlated.[14,27] Each could therefore confound the other's relationship with cognitive risk.

Here, we used data from 3 large clinical trials with detailed baseline cognitive and metabolic characterization to investigate the relationships of obesity, hypertension and diabetes with presence of cognitive impairment in cross-sectional analyses that additionally considered potential mutual confounding among the metabolic risk factors. Results were pooled across the 3 studies for combined estimates.

Methods
Study design
We analyzed baseline data from 3 randomized controlled trials with primary/secondary outcome post-operative cognitive dysfunction (POCD) in an effectively observational, cross-sectional study design. All clinical and cognitive data were measured at pre-surgery assessment.

Study populations and designs of included studies
Data from the Surgery Depth of Anaesthesia Cognitive Outcome (SuDoCo),[28] Dexamethasone for Cardiac Surgery (DECS)[29,30] and OCTOPUS studies[31,32] were used. Access to original study data resulted from a cross-institutional collaboration. Study designs, inclusion criteria and recruitment procedures have been described in detail previously.[28,30,31] In brief, any patients with neurological deficits that did not allow cognitive testing were excluded in all the 3 studies. In SuDoCo, patients with Mini-Mental State Examination (MMSE) <24 were also excluded; those with diagnosed

mental illness were additionally excluded in DECS. Each trial assessed the effect of an intervention (SuDoCo: monitoring depth of anesthesia during non-cardiac surgery; DECS: dexamethasone administration versus placebo during cardiac surgery; OCTOPUS: on-pump versus off-pump methods for cardiac surgery) on POCD risk. Hence, each study administered neurocognitive assessment before and after surgery. For the purpose of the present cross-sectional analysis, only data collected at pre-surgery baseline assessment were used. Data from participants who completed pre-surgery cognitive testing were included. A total of 19 underweight patients, who could obscure linear associations of obesity with cognitive impairment, and patients with missing data on diabetes, hypertension and obesity were excluded from our analyses.

Physical examination and education
In each study, detailed physical examination and self-reported medical history were used to identify participants with any type of diabetes and those with a history of hypertension. BMI was calculated from participants' height and weight. "Obesity" was defined as BMI of at least 30 kg/m². "Underweight" was defined as BMI <18.5 kg/m². In OCTOPUS and SuDoCo, blood pressure was measured at pre-anesthetic assessment during the days prior to surgery. Blood pressure data were not available for DECS. Participants self-reported on their level of education in OCTOPUS and DECS; data on education were not available for SuDoCo.

Cognitive examination
Trained staff preoperatively administered 11 neuropsychological tests in OCTOPUS, 5 neuropsychological tests in DECS and 6 neuropsychological tests in SuDoCo. In each of the 3 studies, all tests were additionally completed by non-surgical control groups to provide normative data. The respective control groups were matched for age (OCTOPUS), age and sex (DECS), or age and cognitive function (SuDoCo) and had been recruited at a cardiology outpatient clinic (DECS[30]), or in nursing homes and senior citizen clubs (SuDoCo[28]). For OCTOPUS, healthy volunteers served as controls.[33] All neuropsychological tests were age sensitive and covered a range of neurocognitive domains including working memory, attention, processing speed, manual dexterity, executive function and mental flexibility. In OCTOPUS, paper-pencil versions of the Rey Auditory Verbal Learning Test, Grooved Pegboard Test, Subjective Ordering Task, Sternberg Letter Cancellation Task, Trail-Making Test B, Stroop-Color-Word-Test and Symbol Digit Modalities Task were applied. For DECS, paper-pencil versions of the Rey

Auditory Verbal Learning Test, Grooved Pegboard Test, Corsi Blocks, Wechsler Adult Intelligence Scale-Digit Span, Trail-Making Test A and B were used. The SuDoCo trial covered the Motor Screening Test, Pattern Recognition Memory, Spatial Recognition Memory and Choice Reaction Time tests from the CANTAB computerized test battery as well as the paper-pencil based Stroop Color and Word Test and visual Verbal Learning Test.

We first excluded patients with missing cognitive data and performed an outlier correction for extreme values in individual test parameters. Using the respective interquartile range of test scores, 8 out of 2176 single test scores in OCTOPUS and 92 out of 15015 single test scores in SuDoCo were excluded, but no single patient had to be excluded in total due to this outlier correction. There were no outliers to be removed in DECS. Presence of cognitive impairment was then defined as scores of more than 2 SDs below the respective control group on ≥1 test.[34]

Statistical analysis

Multiple log-binomial regression analyses determined associations of each of the parameters of metabolic function (diabetes, obesity, BMI, hypertension, systolic and diastolic blood pressure) with presence of cognitive impairment. The first model estimated unadjusted risk (prevalence) ratios (RRs) (model 0). Age and sex were entered as covariables in model 1. Model 2 additionally controlled for the respective remaining potential metabolic risk factors (e.g., analyses of obesity, hypertension and diabetes were controlled for) in order to evaluate independence of any associations from comorbidity with other components of the metabolic syndrome versus mutual confounding. For 2 of the studies (OCTOPUS; DECS), data on educational level of participants were available; thus, education was additionally adjusted for in a final step (model 3). Estimated risk ratios corresponded to 1-point increments in BMI and 10-point increments in blood pressure values to aid clinical interpretability.

Analyses were performed separately for each of the 3 studies and were then pooled in fixed-effects inverse variance analyses for each of the metabolic parameters. Model estimates of risk ratios and corresponding *p*-values were entered with precision up to the third decimal, and 95% CIs were entered with precision up to the first decimal point. Fixed-effects models were selected on the basis that the same effect was assumed to underlie estimates in all the 3 studies.[35] Fully adjusted models (model 2) were repeated using random-effects models to show the mean distribution of effects (Table S1). The I^2 index determined the proportion of variance between the 3 studies that would remain had we removed

sampling error. These pooled analyses were necessary to combine risk estimates across all 1545 participants of the 3 studies and so should not be understood as a meta-analysis of previous research. The statistical analysis plan was approved by an internal committee before the analyses were performed in IBM© SPSS© Statistics (version 24), The R Project for Statistical Computing (version 3.3.3) and Review Manager (version 5.3).

Ethics

Participants of all the studies gave written informed consent upon enrollment. Ethical approval was obtained for each of the studies and assessments complied with the Declaration of Helsinki. For the present secondary analysis, additional ethical approval was obtained (Ethikkommission der Charité – Universitätsmedizin Berlin, EA1/242/08).

Results
Metabolic and cognitive characterization of study samples

Analyses were based on N=272 patients from DECS, N=272 patients from OCTOPUS and N=1001 patients from SuDoCo (Figure S1). Participant characteristics for each of the 3 studies are summarized in Table 1. Mean sample age ranged from 61 years (OCTOPUS) to 70 years (SuDoCo). Reasons for surgery were severe cardiac disease in DECS and OCTOPUS; patients in SuDoCo underwent any non-cardiac surgery mainly of general surgery, orthopedic or gynecological/ urological type. Mean BMI was in the overweight category in each of the 3 studies (BMI ≥25 kg/m²), with prevalence of obesity (BMI ≥30 kg/m²) ranging between 14.7% (OCTOPUS) and 24.0% (SuDoCo). Cognitive impairment was identified in 8.2% (SuDoCo) to 45.6% (OCTOPUS) of patients. Across all the 3 studies, 285 (18.4%) of 1545 patients had cognitive impairment.

Associations of metabolic syndrome parameters with cognitive impairment

Associations of diabetes, hypertension and obesity with cognitive impairment are shown in Table 2. In pooled analyses, obesity was associated with presence of cognitive impairment and independently of age, sex, diabetes or hypertension. Obese participants were overall 1.29-fold more likely to present with cognitive impairment compared with normal weight and overweight individuals (RR 1.29; 95% CI 0.98, 1.72) with no evidence of statistical heterogeneity among the studies (Chi²=0.55; I^2=0%; Table 2; Figure 1). Similar findings were observed with further adjustment for educational level (RR 1.33; 95% CI 0.94, 1.87). Diabetes and hypertension

Table 1 Sample characteristics of the 3 studies

Sample characteristics	OCTOPUS	DECS	SuDoCo
Country	The Netherlands	The Netherlands	Germany
N	272	272	1001
Age, years, mean ± SD	61.4 ± 9.1	64.1 ± 11.9	69.9 ± 6.5
Male, n (%)	189 (69.5%)	210 (77.2%)	556 (55.5%)
Education, mean ± SD years, or n (%)	9.4 ± 2.6	Primary: n=119 (43.8%)	–
		Secondary: n=70 (25.7%)	
		Further/higher: n=83 (30.5%)	
Systolic blood pressure, mmHg, mean ± SD	138.9 ± 19.6	–	136.3 ± 19.3
Diastolic blood pressure, mmHg, mean ± SD	79.2 ± 10.0	–	73.9 ± 11.6
Diabetes, n (%)	35 (12.9%)	44 (16.2%)	215 (21.5%)
Hypertension, n (%)	112 (41.2%)	150 (55.1%)	683 (68.2%)
Body mass index (kg/m²) mean ± SD	26.6 ± 3.1	27.2 ± 4.5	27.4 ± 5.0
Normal weight (BMI 18.5 to 24.9) n (%)	94 (34.6%)	99 (36.4%)	326 (32.6%)
Overweight (BMI 25.0 to 29.9) n (%)	138 (50.7%)	114 (41.9%)	435 (43.5%)
Class I obesity (BMI 30 to 34.9) n (%)	40 (14.7%)	45 (16.5%)	166 (16.6%)
Class II obesity (BMI 35.0 to 39.9) n (%)		9 (3.3%)	49 (4.9%)
Class III obesity (BMI ≥40) n (%)		5 (1.8%)	25 (2.5%)
Cognitive impairment, n (%)	124 (45.6%)	79 (29.0%)	82 (8.2%)

Note: Data on systolic and diastolic blood pressure available for N=270 in OCTOPUS and N=949 in SuDoCo. % shown of total sample. Surgical procedures were cardiac surgery (OCTOPUS, DECS) or general surgery (SuDoCo). BMI ≥30 kg/m² was used as cutoff for subgroup analyses on obesity. Different sets of cognitive tests were used in each of the studies (see Methods).
Abbreviations: BMI, body mass index; DECS, Dexamethasone for Cardiac Surgery; SD, standard deviation; SuDoCo, Surgery Depth of Anaesthesia Cognitive Outcome.

Table 2 Association of diabetes, hypertension, and obesity with cognitive impairment in each study, and pooled estimates of prevalence ratios

Exposure associations with cognitive impairment	OCTOPUS		DECS		SuDoCo		Pooled estimates
	Estimate (95% CI)	Weight	Estimate (95% CI)	Weight	Estimate (95% CI)	Weight	Estimate (95% CI)
Diabetes and cognitive impairment							
Model 0: no adjustment	0.93 (0.59, 1.34)	38.1%	1.53 (0.97, 2.25)	34.8%	1.18 (0.71, 1.87)	27.1%	1.18 (0.92, 1.52)
Model 1: age, sex	0.82 (0.46, 1.37)	25.1%	1.46 (0.93, 2.16)	42.5%	1.21 (0.73, 1.91)	32.4%	1.19 (0.91, 1.56)
Model 2: +hypertension, obesity	0.77 (0.43, 1.31)	30.5%	1.35 (0.76, 2.30)	31.6%	1.20 (0.71, 1.95)	37.9%	1.09 (0.80, 1.49)
Model 3: +education	0.92 (0.50, 1.57)	47.9%	1.39 (0.79, 2.35)	52.1%	–	–	1.14 (0.77, 1.69)
Hypertension and cognitive impairment							
Model 0: no adjustment	1.22 (0.94, 1.57)	56.0%	1.13 (0.78, 1.67)	26.0%	1.06 (0.69, 1.70)	18.1%	1.16 (0.96, 1.41)
Model 1: age, sex	1.08 (0.75, 1.55)	39.5%	1.06 (0.73, 1.58)	35.4%	0.98 (0.63, 1.57)	25.1%	1.05 (0.83, 1.32)
Model 2: +diabetes, obesity	1.10 (0.76, 1.59)	44.8%	0.95 (0.60, 1.53)	27.9%	0.91 (0.57, 1.49)	27.3%	1.00 (0.78, 1.28)
Model 3: +education	1.07 (0.74, 1.56)	60.6%	1.01 (0.64, 1.62)	39.4%	–	–	1.05 (0.78, 1.40)
Obesity and cognitive impairment							
Model 0: no adjustment	1.25 (0.88, 1.67)	47.2%	1.58 (1.05, 2.28)	32.1%	1.09 (0.66, 1.72)	20.8%	1.31 (1.05, 1.63)
Model 1: age, sex	1.26 (0.77, 1.96)	29.4%	1.56 (1.04, 2.26)	42.5%	1.16 (0.70, 1.83)	28.1%	1.35 (1.05, 1.73)
Model 2: +diabetes, hypertension	1.28 (0.78, 2.00)	36.3%	1.49 (0.89, 2.45)	31.3%	1.14 (0.68, 1.85)	32.4%	1.29 (0.98, 1.72)
Model 3: +education	1.29 (0.79, 2.02)	53.4%	1.38 (0.82, 2.25)	46.6%	–	–	1.33 (0.94, 1.87)

Note: Results from log-binomial regression analyses. For each study, results for Model 2 and Model 3 are based on a single model respectively.
Abbreviations: CI, confidence interval; DECS, Dexamethasone for Cardiac Surgery; RR, risk ratio; SuDoCo, Surgery Depth of Anaesthesia Cognitive Outcome.

were not associated with cognitive impairment in any of the studies or in pooled analyses (Table 2).

Associations of BMI and blood pressure with cognitive impairment are shown in Table 3. A higher BMI was associated with an increased prevalence of impairment across studies. Independently of age, sex, diabetes and hyperten-

sion, each one unit increment in BMI was associated with a 3% increased prevalence of cognitive impairment (RR 1.03; 95% CI 1.00, 1.06). There was no evidence of statistical heterogeneity among the studies (Chi²=0.50; I^2=0%; Table 3; Figure 2), and the finding remained similar following additional adjustment for education (RR 1.03; 95% CI 0.99, 1.07).
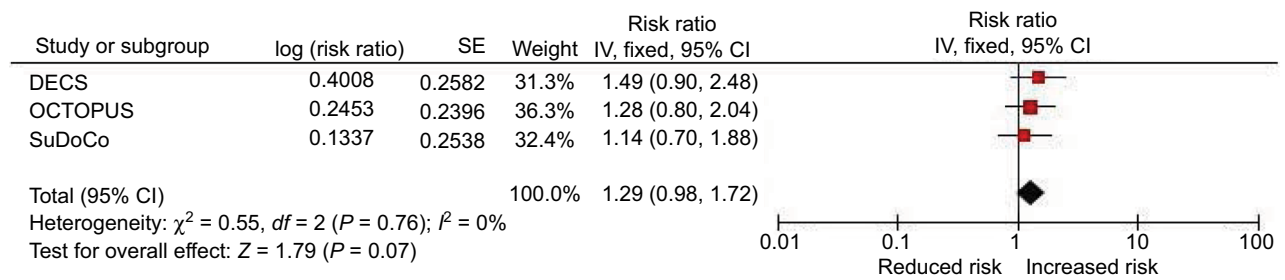
Study or subgroup	log (risk ratio)	SE	Weight	Risk ratio IV, fixed, 95% CI	Risk ratio IV, fixed, 95% CI
DECS	0.4008	0.2582	31.3%	1.49 (0.90, 2.48)	
OCTOPUS	0.2453	0.2396	36.3%	1.28 (0.80, 2.04)	
SuDoCo	0.1337	0.2538	32.4%	1.14 (0.70, 1.88)	
Total (95% CI)			100.0%	1.29 (0.98, 1.72)	

Heterogeneity: $\chi^2 = 0.55$, $df = 2$ ($P = 0.76$); $I^2 = 0\%$
Test for overall effect: $Z = 1.79$ ($P = 0.07$)

0.01 0.1 1 10 100
Reduced risk   Increased risk

Figure 1 Pooled association of obesity with cognitive impairment (model 2).
Abbreviations: CI, confidence interval; DECS, Dexamethasone for Cardiac Surgery; SE, standard error; SuDoCo, Surgery Depth of Anaesthesia Cognitive Outcome.

Table 3 Association of BMI, systolic and diastolic blood pressure with cognitive impairment in each study, and pooled estimates of prevalence ratios

	OCTOPUS		DECS		SuDoCo		Pooled estimates
	Estimate (95% CI)	Weight	Estimate (95% CI)	Weight	Estimate (95% CI)	Weight	Estimate (95% CI)
BMI and cognitive impairment							
Model 0: no adjustment	1.02 (0.97, 1.06)	35.5%	1.04 (1.00, 1.09)	31.2%	1.01 (0.97, 1.05)	33.3%	1.02 (1.00, 1.05)
Model 1: age, sex	1.02 (0.96, 1.08)	22.6%	1.04 (1.00, 1.09)	38.0%	1.02 (0.97, 1.06)	39.4%	1.03 (1.00, 1.06)
Model 2: +diabetes, hypertension	1.02 (0.96, 1.08)	24.3%	1.04 (0.99, 1.09)	37.0%	1.02 (0.97, 1.06)	38.6%	1.03 (1.00, 1.06)
Model 3: +education	1.02 (0.97, 1.09)	38.7%	1.03 (0.98, 1.08)	61.3%	–	–	1.03 (0.99, 1.07)
Systolic blood pressure and cognitive impairment							
Model 0: no adjustment	0.98 (0.89, 1.07)	61.4%	–	–	1.03 (0.91, 1.14)	38.6%	0.99 (0.93, 1.07)
Model 1: age, sex	0.94 (0.85, 1.03)	64.9%	–	–	1.01 (0.89, 1.12)	35.1%	0.96 (0.89, 1.03)
Model 2: +diabetes, obesity	0.94 (0.85, 1.03)	60.7%	–	–	1.00 (0.89, 1.12)	39.3%	0.96 (0.89, 1.03)
Model 3: +education	0.95 (0.86, 1.04)	–	–	–	–	–	–
Diastolic blood pressure and cognitive impairment							
Model 0: no adjustment	0.86 (0.72, 1.03)	54.1%	–	–	0.96 (0.79, 1.17)	45.9%	0.90 (0.79, 1.03)
Model 1: age, sex	0.89 (0.74, 1.07)	52.1%	–	–	0.98 (0.81, 1.19)	47.9%	0.93 (0.81, 1.06)
Model 2: +diabetes, obesity	0.89 (0.74, 1.07)	53.2%	–	–	0.98 (0.81, 1.18)	46.8%	0.93 (0.81, 1.07)
Model 3: +education	0.90 (0.75, 1.08)	–	–	–	–	–	–

Note: Results from log-binomial regression analyses. Estimates correspond to 1 kg/m^2 increment in BMI and 10 mmHg increment in blood pressure. Data on systolic/diastolic blood pressure available for N=270 participants in OCTOPUS and for N=949 participants in SuDoCo. Data on blood pressure not available for DECS. For each study, results for Model 2 and Model 3 are based on a single model respectively.
Abbreviations: BMI, body mass index; CI, confidence interval; DECS, Dexamethasone for Cardiac Surgery; RR, risk ratios; SuDoCo, Surgery Depth of Anaesthesia Cognitive Outcome.
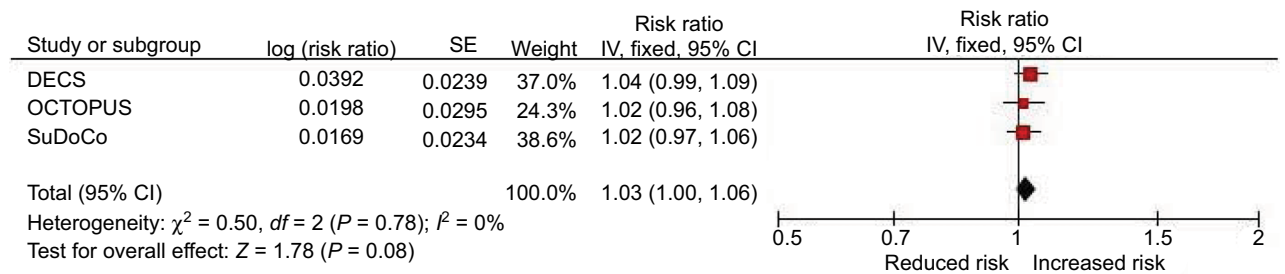
Study or subgroup	log (risk ratio)	SE	Weight	Risk ratio IV, fixed, 95% CI	Risk ratio IV, fixed, 95% CI
DECS	0.0392	0.0239	37.0%	1.04 (0.99, 1.09)	
OCTOPUS	0.0198	0.0295	24.3%	1.02 (0.96, 1.08)	
SuDoCo	0.0169	0.0234	38.6%	1.02 (0.97, 1.06)	
Total (95% CI)			100.0%	1.03 (1.00, 1.06)	

Heterogeneity: $\chi^2 = 0.50$, $df = 2$ ($P = 0.78$); $I^2 = 0\%$
Test for overall effect: $Z = 1.78$ ($P = 0.08$)

0.5 0.7 1 1.5 2
Reduced risk   Increased risk

Figure 2 Pooled association of BMI with cognitive impairment (model 2).
Abbreviations: BMI, body mass index; CI, confidence interval; DECS, Dexamethasone for Cardiac Surgery; SE, standard error; SuDoCo, Surgery Depth of Anaesthesia Cognitive Outcome.

In a post hoc analysis to further elucidate the relationship of BMI and cognitive impairment, model 2 (controlling for age, sex, diabetes, hypertension) was repeated for the "obese" category (BMI ≥30 kg/m^2) rather than the total sample. When effects were pooled across 339 obese participants in this subgroup, each one unit increment in BMI was associated with an 8% increased prevalence of cognitive impairment (RR 1.08; 95% CI 1.01, 1.16).

Systolic and diastolic blood pressures were not associated with cognitive impairment (Table 3).

Of note, there were no associations of sex with cognitive impairment in any of our analyses (data not shown); thus, sex was not further explored as a modifier of the association of obesity or BMI with cognitive impairment.

Discussion

In this secondary analysis of cross-sectional data from 3 studies, prevalence of cognitive impairment as defined by a lower performance compared with controls was relatively high compared with some previous investigations.[36] Overall, 18.4% of patients had cognitive impairment. Though there was substantial heterogeneity in prevalence between the 3 studies that ranged from 8.2% (SuDoCo) to 45.6% (OCTOPUS). When results were pooled across the 3 studies to assess metabolic predictors of cognitive impairment, we found a 29% increased prevalence of cognitive impairment in participants who are obese (BMI ≥30 kg/m^2) compared with normal weight to overweight individuals. Each 1 kg/m^2 increment of BMI was associated with 3% increased prevalence. That estimate even increased to 8% increased prevalence of impairment for each 1 kg/m^2 increment of BMI when analyses of BMI were restricted to participants in the "obese" category. Overall this is suggestive of a non-linear dose–response relationship of BMI with impairment.

Previous epidemiological studies identified diabetes[15,16] and, although less consistently, hypertension and obesity measured in later life[13,17,19,21,22] as risk factors for cognitive impairment. However, many of these studies assessed each of these candidate predictors in isolation or with consideration of few other metabolic factors. Because all correlate strongly with one another,[14,27] the individual contribution of each to cognitive outcome may have been obscured in those analyses. Even in cases where some of these factors have been controlled for, residual confounding is a real possibility.

In one of the first studies to investigate cognitive impairment in later life to consider such confounding, we established that the cross-sectional associations of obesity and a higher BMI with presence of cognitive impairment were independent of comorbid diabetes and hypertension. As we

adjusted for 3 of 4 components of the metabolic syndrome (all except dyslipidemia), it follows that obesity might be one driving force behind the cognitive impairment seen in people with the metabolic syndrome.[8–13] Mediation of the obesity-cognition association by presence of diabetes or hypertension is unlikely, as controlling for mediating factors would have led to a profound reduction in effect size. However, the possibility of an influence of subclinical insulin resistance or subclinical elevated blood pressure remains.

Our cross-sectional data suggest that diabetes and hypertension themselves are not at all or only weakly associated with cognitive impairment. Reasons for disparity from previous epidemiological research that had implicated hypertension and (even more strongly) diabetes in cognitive risk[16,20] are unclear but may stem from the fact that 2 of our studies were of a high-risk (rather than general) population. Further, our definition of "cognitive impairment" may be less sensitive to pathological changes associated with hypertension or diabetes, and none of the 3 studies had set out to determine associations of metabolic risk factors with cognitive impairment, so that data on diabetes and hypertension, in contrast to measurement of participants' cognitive status, height and weight, may not have been collected with sufficient rigor. This could have led to the lack of a finding on diabetes and hypertension.

Obesity – though both preventable and modifiable – is threatening global health through increasing risk of poor health outcomes. Four million deaths per year are currently attributed to a high BMI globally.[37] In our study, we found that older people who were obese were more likely to be cognitively impaired, which highlights the relevance of cognitive impairment as an obesity-related organ dysfunction that is equal in importance to others such as coronary heart or kidney disease, for instance. With BMI as a crude reflection of actual body composition particularly in older people[38,39] effect sizes could have been even larger than reported here had we used more detailed assessments such as body fat. Importantly, we found evidence for a non-linear dose–response relationship that suggests that cognitive risk increases exponentially with increasing BMI among people with normal weight, overweight and obesity. Our study lacked data on BMI change across the life span. This reflects one aspect that complicates research of obesity and cognitive outcome: unless participants are followed up over the course of decades,[40] even studies with prospective designs provide only "snapshots" of adiposity status. Exposure to weight change due to aging and/or disease remains obscure despite evidence from rare long-term prospective investigations of a potential role of weight change in cognitive risk prediction.[24]

The pathophysiology linking obesity with cognitive impairment is poorly understood but may be causal. Obesity constitutes a pro-inflammatory state,[41] which itself has been associated with cognitive impairment,[42] and animal models suggest that elevated triglyceride levels which are common in obese individuals, impair brain function.[43,44] Relatedly, obesity-induced systemic damage of the vasculature could cause cerebral white matter lesions.[45] The apparent non-linear relationship of BMI with cognitive impairment in our analysis may indicate cumulative effects of these mechanisms. Because the effect size of the association of obesity with cognitive impairment was unchanged after adjustment for education, it is unlikely that it was due to confounding by this factor that could have led to exposure of people of low socioeconomic status to an increased risk of both late-life obesity[46,47] and late-life cognitive impairment.[48,49] Reverse causality underlying our findings is also possible, however, due to the cross-sectional study design. Obesity following increased food intake[50] or reduced physical activity[51] might also be the result of beginning cognitive impairment.

We investigated several parameters of metabolic derangement for their cross-sectional association with cognitive impairment. This enabled us to tease out the contribution of each to cognitive risk. We took advantage of comprehensive neuropsychological test batteries that tapped a range of cognitive domains, and combined results across the 3 studies to obtain more reliable parameter estimates.

Limitations

Our study has several limitations. First, analyses were of patients scheduled to undergo surgery within the next few days. Cognitive performance could therefore have been influenced by surgery-related factors such as psychological distress, anxiety and pain, and patients will have been less healthy compared with community-dwelling samples. This is likely reflected in the relatively high prevalence of cognitive impairment. At the same time, self-selection bias for healthier patients to enroll compared with all approached individuals is also likely. These factors all limit the external validity of our findings. Second, we pooled results across 3 studies that were heterogeneous in terms of design and sample characteristics, which complicates the interpretation of our findings. For instance, 2 of the studies included rather sick individuals undergoing cardiac surgery, whereas another focused on less severe (e.g., orthopedic) procedures, and different cognitive test batteries each with a different number of tests were used in each of the 3 studies. This may have influenced prevalence of cognitive impairment.

Also, readers should note that the clinical significance of our findings is unclear due to the definition of "cognitive impairment" that may have captured mild forms of impairment. Third, the metabolic parameters were determined by single-time assessment; none of the studies prospectively investigated their development or change over time, and so we cannot draw conclusions on fluctuations in the severity of hypertension, diabetes or obesity and associated cognitive risk. Fourth, obesity was defined by BMI despite the fact that BMI does not capture body fat and body fat distribution which are likely driving forces behind obesity links to negative health outcomes.[52] The use of BMI in older people for this purpose appears to be particularly limited.[38,39] Fifth, we had no data on dyslipidemia to allow adjustment for the final component of the metabolic syndrome. Sixth, our results are limited by relatively large CIs of estimates due to small sample size. Finally, due to the cross-sectional study design our finding may well reflect reverse causality.

Further studies are needed to evaluate the external validity of our findings through replication in community-dwelling samples, and should examine the underlying pathophysiological mechanisms as well as the influence of body weight trajectories over the life-course on late-life cognition. Comparison among various cognitive domains could determine any domain-specific effects of obesity. Trials modeled on the Action for Health in Diabetes study[53] could further determine the influence of weight loss on cognitive outcome in different weight categories to determine whether weight loss effects on cognition, too, may be non-linear. Once the role of obesity in cognitive impairment is better understood, preventive pharmacological strategies or health programs could reduce cognitive risk in people who are at risk of developing obesity, such as overweight and physically inactive individuals.

Conclusion

Our cross-sectional analysis suggests that among high-risk older people who are scheduled to undergo surgery, those who are obese have a higher likelihood of cognitive impairment compared to normal weight or overweight persons. Among normal weight, overweight and obese persons, a higher BMI is associated with a higher prevalence of cognitive impairment. The association appears to increase in strength with increasing BMI. Further studies are needed to prospectively investigate the temporal relationship of body weight and cognitive risk.

Disclosure

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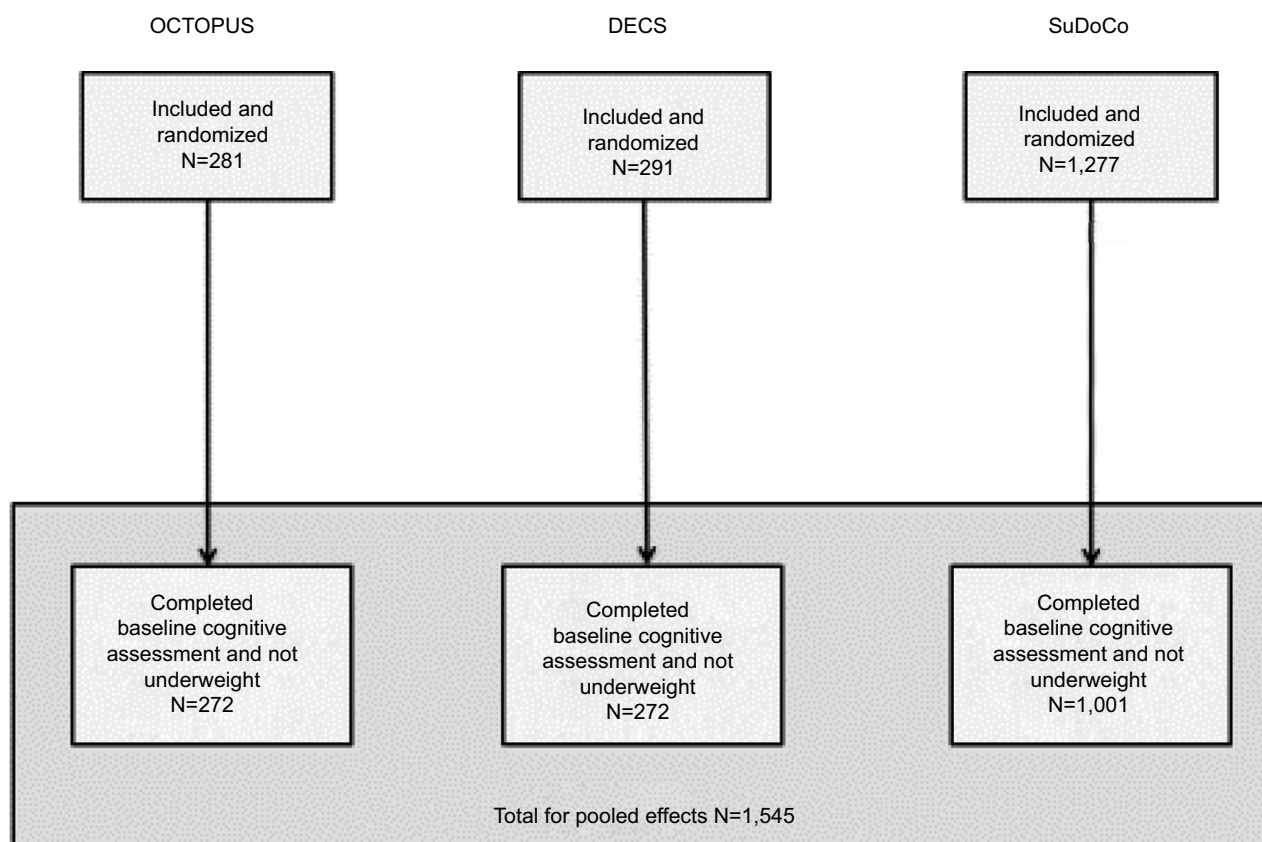
Supplementary materials

OCTOPUS

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Figure S1 Enrollment into the 3 studies.

Table S1 Results for model 2 in fixed-effects model (as described in main manuscript) and random-effects models

Exposure associations with cognitive impairment	Model 2 as fixed-effects model RR (95% CI)	Model 2 as random-effects model RR (95% CI)
Diabetes and cognitive impairment	1.09 (0.80, 1.49)	1.09 (0.79, 1.51)
Hypertension and cognitive impairment	1.00 (0.78, 1.28)	1.00 (0.78, 1.28)
Obesity and cognitive impairment	1.29 (0.98, 1.72)	1.29 (0.98, 1.72)
BMI and cognitive impairment	1.03 (1.00, 1.06)	1.03 (1.00, 1.06)
Systolic blood pressure and cognitive impairment	0.96 (0.89, 1.03)	0.96 (0.89, 1.03)
Diastolic blood pressure and cognitive impairment	0.93 (0.81, 1.07)	0.93 (0.81, 1.07)

Abbreviations: BMI, body mass index; CI, confidence interval; RR, risk ratio.