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Metabolic risk factors for cognitive impairment in the perioperative setting

Metabolische Risikofaktoren für kognitive Dysfunktion im perioperativen Verlauf

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List of Abbreviations

Aβ, beta amyloid

ACI, age-related cognitive impairment

AD, Alzheimer's disease

ADL, activities of daily living

APOE, apolipoprotein E

BBB, blood-brain-barrier

BioCog, Biomarker Development for Postoperative CI in the Elderly Study

CSF, cerebrospinal fluid

CRP. C-reactive protein

DECS, Dexamethasone for Cardiac Surgery Study

DSM-V, Diagnostic and Statistical Manual of Mental Disorders, 5th edition

IL-6, interleukin-6

LAR, leptin:adiponectin ratio

MCI, mild CI

MetS, metabolic syndrome

MMSE, Mini-Mental State Examination

NCD, neurocognitive disorder

PCA, principal component analysis

POCD, post-operative cognitive dysfunction

POD, post-operative delirium

RCT, randomized controlled trial

ROC, receiver operating characteristics

SAT, subcutaneous adipose tissue

SuDoCo, Surgery Depth of Anaesthesia Cognitive Outcome Study

TIA, transient ischemic attack

VaD, vascular dementia

VAT, visceral adipose tissue

1. Background and current state of the art

1.1 Introduction

Postoperative cognitive dysfunction (POCD) is characterized by a cognitive decline from pre- to post-surgery assessment and is relatively under-researched as a health outcome. Age-related cognitive impairment (ACI) is – like POCD – characterized by cognitive deficits but occurs in the general population independently of surgery. Previous epidemiological studies have identified metabolic dysfunction as a candidate risk factor for ACI. It is currently unclear however, whether metabolic dysfunction may also be associated with an increased risk of POCD. Therefore, in the work presented here, we evaluated metabolic dysfunction as a candidate risk factor for cognitive impairment with onset before surgery (ACI) and after surgery (POCD) in part using the same cohorts. Ultimately, determining whether POCD and ACI share risk factors will help elucidate the similarities versus differences between the conditions and will provide insight into potential underlying pathophysiological processes, which are not entirely clear at present. Risk stratification of older adults in the general population (ACI) or surgical patients (POCD) also becomes a possibility. Finally, with metabolic dysfunction a modifiable risk factor, knowledge of associations with ACI/POCD risk (if found to reflect causality in future studies) could pave way to preventive measures.

1.2 Age-related cognitive impairment (ACI)

Cognitive function is subject to a decline during ageing with large individual differences in onset, rate and – also depending on survival – endpoint. As the most severe form of ACI, dementia involves substantial cognitive deterioration that impact on a person's activities of daily living (ADL) such as personal hygiene and management of finances. Dementia is highly relevant to public health, because it compromises the quality of life of older adults [1] as well as their carers [2] and is a cause of worry to many during ageing [3]. Due to a demographic change towards an older population, the prevalence of dementia is increasing in Germany [4] and other developed [5] as well as in developing countries [6]. Resultant economic and societal costs are already immense and are further increasing accordingly [7].

Alzheimer's disease (AD) is the most common form of dementia and is neuropathologically mainly characterized by a deposition of sticky amyloid peptides that aggregate to neurotoxic plaques in the brain [8]. Strictly speaking, a diagnosis with AD is only certain after post-mortem examination, but some diagnostic tools have been developed that can be used in clinical practice to identify patients with a high probability of having AD. Brain imaging of beta amyloid (Aβ) deposits and measurement of Aβ concentration in cerebrospinal fluid (CSF) have been found to have good diagnostic accuracy and can supplement neuropsychological evaluation of individuals [9]. However, these methods are costly and/or invasive, and are used infrequently in clinical practice as a result [10]. Interestingly, Aβ can also be detected in blood, albeit at much lower concentrations compared with CSF [11], but its measurement is extremely difficult [12,13]. Recently developed analysis methods [14-16] are often

limited by a lack of information on diagnostic accuracy for AD in real-world samples and the fact that many are in-house methods that cannot be upscaled for use in routine clinical practice.

During ageing, people can also experience ACI that remains short of frank dementia. They can experience slight decrements in neuropsychological (or, "cognitive") test performance ("normative cognitive decline"), they can enter paths towards steeper trajectories that commonly lead up to dementia, such as mild cognitive impairment (MCI) (characterized by mild cognitive deficits but intact ADL), or they can lie anywhere "in between" on the continuum of cognitive decline. To capture the full spectrum of impairment, "ACI" is used as a summary term for any severity of cognitive ageing that exceeds normative decline, including constructs such as MCI and dementia, as well as more subtle cognitive decrements (see Figure 1).

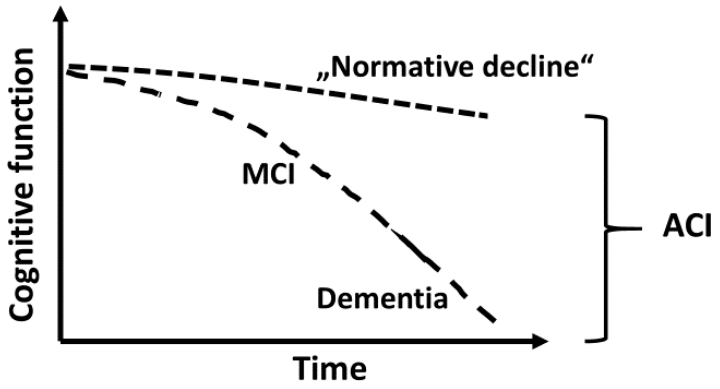

Figure 1. Continuum of cognitive ageing (based on [17])

ACI (often also referred to as "[age-related] cognitive decline/deficit", "cognitive ageing" or similar) is typically operationalized in epidemiological research studies including in the work presented here from a person's cognitive test performance or (for prospective studies) the change in performance over time relative to the respective total sample under investigation, rather than any clinical diagnoses (e.g., [18,19]). This approach is advantageous, because it does not rely on prevalent or incident MCI/dementia in a given cohort, which may be rare depending on sample age, to define ACI.

In sum, ACI in epidemiological research settings is a heterogenous construct that includes various degrees of impairment and is often sample-specific.

1.3 Post-operative cognitive dysfunction (POCD)

Post-operative cognitive dysfunction (POCD) is the type of cognitive impairment that occurs after surgery. It is not a clinical diagnosis and currently only used for research purposes, but can be loosely defined as a cognitive deficit that becomes apparent after the surgical event as compared with a patient's level of pre-surgery cognitive function. During the first few months after surgery, research studies have shown that POCD can be found in around 10 to 38% of patients [20]. Although not all patients with POCD necessarily report cognitive problems, POCD has been recognized as a relevant health outcome, because it impacts on the quality of life of patients years after surgery [21] and has also been linked to an increased mortality risk [22]. POCD can affect patients of any age and can occur following any type of surgery though advanced age, more extensive surgery, presence of ACI before surgery [23] and a lower education [24] are clear risk factors.

POCD research is relatively young. To illustrate, <20 studies on POCD were published per year in the 1990s; compared with >200 studies in 2013 [25]. However, the field is extremely heterogeneous in terms of study designs and – because POCD is not a clinical diagnosis – definitions of POCD, complicating interpretation, cross-study comparison of results and meta-analysis. For instance, studies of POCD vary in terms of number of cognitive testing sessions after surgery and in terms of the specific cognitive tests used (which can range from simple screening tests such as Mini-Mental State Examination, MMSE, e.g., [26] to extensive batteries e.g., [27]). Additionally, studies use various follow-up periods (1 day [28] to 5 years after surgery [29]) which is relevant in view of the fact that POCD can be transient: following the acute 'hit' of surgery, prevalence in a given cohort may be initially relatively high but reduces with increasing length of follow-up, because patients may cognitively recover [23]. To define POCD, most commonly, a patient's change in cognitive test performance from pre- to post-surgery assessment is compared to a non-surgical control group using reliable change indices (RCI) (e.g., [22]). Various methods for RCI calculation are in use [30]. Other calculations which do not include control groups are also common. One prominent example is the 20/20 rule ("20% decline on at least 20% of tests"; e.g., [31]). There has been a recent attempt by the Nomenclature Consensus Working Group to streamline POCD definition and terminology [32]. They suggested the terms "delayed neurocognitive recovery", "mild neurocognitive disorder (NCD) postoperative" and "major NCD postoperative" depending on time since surgery, ADL function and cognitive test performance [32]. While this suggestion is likely beneficial to future research in the field, virtually all previous research had used the term "POCD" with, as aforementioned, various definitions. Here, for consistency with prior research and because much of the work presented here was performed prior to the 2018 consensus statement, the term "POCD" will be used. It will refer to a heterogenous syndrome that encompasses all definitions used in the field, independently of follow-up period, severity, type and number of cognitive tests, and consideration of ADL.

1.4 ACI and POCD: similarities and differences

On the one hand, given that patients with ACI before surgery are at an increased risk of POCD [23] and the fact that neuropsychological symptoms can be identical in ACI and POCD, it is reasonable to assume that both are caused by similar pathophysiological mechanisms. Surgery could simply accelerate neurodegenerative processes that would have otherwise occurred over the course of decades. It would follow logically that POCD itself would also increase the risk of later ACI including dementia, because it would lead patients on a path towards greater severity of impairment in the future. However, while some studies have identified POCD as a risk factor for dementia [33] others have not [34] and a meta-analysis published in 2011 determined that general anesthesia (which could be considered an indicator of POCD in this context) was not associated with later dementia risk [35]. Thus, the evidence on POCD as a risk factor for later ACI is ambiguous. Additionally, some differences in disease course for ACI versus POCD speak against a neuropathological similarity of the conditions. Whereas POCD can be transient so that patients may cognitively recover [23], ACI can fluctuate but generally moves towards an increasing severity. For instance, overall progression from MCI to dementia in long-term studies is around 32% [36] whereas reversion from MCI back to a cognitively normal state is possible, but rarer [37].

Comparison of the epidemiology of ACI and POCD can improve our knowledge of their similarities and differences, and through multivariate statistical adjustment for potential confounding factors can provide insight into potential pathophysiological mechanisms underlying the two conditions. Additionally, knowledge of their epidemiology will allow risk stratification. For POCD, this is particularly relevant in elective surgical settings, where patients may opt out based on their post-operative cognitive risk. A person's cognitive risk could also be reduced by tackling any modifiable risk factors provided that factor is found to be causally related to ACI/POCD.

Epidemiological studies have shown that metabolic dysfunction, which is a modifiable risk factor, may increase risk ACI as outlined below. Its relationship with POCD is almost entirely unclear as yet and warrants evaluation.

1.5 Metabolic dysfunction

1.5.1 Prevalence, complications and measurement issues

Prevalence of metabolic dysfunction, which includes the conditions obesity, dyslipidemia, hypertension and hyperglycemia, is high and further increasing. For example, prevalence of obesity, defined by the World Health Organization as an abnormal or excessive fat accumulation [38] and typically measured by body mass index (BMI$\geq$30kg/m^2) [39], has seen a steady increase in prevalence in the US and other developed countries over the course of the past century. Today around 8% of US adults and around 2% of adults in Germany [40] suffer from severe obesity (BMI$\geq$40kg/m^2). The increasing prevalence of metabolic dysfunction can be attributed to a combination of a sedentary

lifestyle with a high-calorie diet that have seen a rise over the course of the past century [41]. Alarmingly, this applies not only to developed but also to developing countries which observe a similar increase in prevalence [42,43] and are even less able to deal with the economic and population health consequences stemming from their complications which can include a number of chronic diseases [44,45]. The immensity of the problem was recently determined by the Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration, who reported that metabolic dysfunction parameters were responsible for 10% (dyslipidemia), 15% (obesity), 15% (hyperglycemia) and 40% (hypertension) of deaths due to cardiovascular disease, kidney disease and diabetes respectively [46].

The various parameters of metabolic dysfunction are deeply intertwined. They initiate similar processes such as a systemic low-grade pro-inflammatory response, and they predispose to one another, i.e. cluster within individuals [47,48]. To describe this pattern, Reaven (1988) coined the term "metabolic syndrome" (MetS). Various definitions of MetS were applied during the decades to follow [49] though the usefulness of concept is not entirely undebated [50,51]. A single set of criteria for MetS was eventually agreed upon by a number of institutions including the American Heart Association [52]. According to that definition, MetS requires the presence of at least 3 of the 5 components: central obesity, elevated triglyceride concentrations, reduced high-density lipoprotein (HDL) cholesterol concentrations, elevated blood pressure and elevated glucose concentrations. The prevalence of MetS is high in developed countries and particularly so in the USA [49]. In Germany, 18-28% of adults can be classified as having MetS [53]. MetS is also a problem to developing countries; for instance, 18% of adults ≥16 years old in sub-Saharan Africa have MetS [54]. Because its components are vascular risk factors, MetS itself is well-established as a vascular risk factor [55] and as such is a fundamental determinant of population health. Risk of MetS increases with advancing age [56].

Four of the 5 MetS components can be assessed relatively easily. "Elevated triglyceride concentrations", "reduced HDL concentrations" and "elevated glucose concentrations" are determined in standardized lab analyses; "elevated blood pressure" is determined from routine blood pressure measurement. Cut-off values for each of the components (e.g., for "elevated blood pressure", systolic ≥130 and/or diastolic ≥85 mmHg, or drug treatment) apply to all adults, with the exception of the "reduced HDL concentrations" component, which has a sex-specific cut-off.

The component "central obesity", however, comes with some measurement issues. "Central obesity" is used to capture excessive visceral adipose tissue (VAT), which is stored around the abdomen and has been found to be the culprit for associations with negative health outcomes compared with subcutaneous adipose tissue (SAT) stored under the dermal layers for instance around the hips [57-59]. In the MetS consensus definition, central obesity is defined by a high waist circumference, but the cut-off values are not only sex- but also ethnicity-specific (e.g., Caucasian males ≥94 cm, Caucasian females ≥80 cm [52,60]). As a result, total body obesity (BMI≥30 kg/m^2 [39]) is frequently relied

upon as a surrogate for "central obesity" in research settings. This is despite the fact that BMI performs less well as compared with waist circumference in the prediction of cardiometabolic risk [61] which can be considered a goal of diagnosing MetS. Moreover, data on BMI are often collected through self-report of height and weight during interview. Self-report is prone to weight-dependent reporting bias [62] introducing systematic error to statistical analyses in research studies. Even when ascertained using body weight scales and measurement of height, BMI is further problematic, because it does not distinguish between fat mass and lean body mass. Thus muscular body types may be misclassified as "obese" based on BMI, complicating patient care (i.e., a muscular person could be advised to lose weight based on BMI) and also introducing error, or "noise", into analyses associating obesity or MetS (with obesity as a surrogate for "central obesity") with health outcomes in research settings. This is particularly the case in samples of older adults: aging is characterized by muscle loss and an increase in adipose tissue mass [58,60,63] (particularly VAT [64]) and these changes can occur without a change in BMI.

1.5.2 Adipokines

Adipose tissue is a metabolically active producer of "adipocytokines", which include adipocyte-derived cytokines as well as peptides of the class adipokines and function as signaling compounds to regulate the body's energy metabolism and immune response [65]. The present work will focus on the most abundant adipokines, the hormones adiponectin and leptin. Whereas leptin concentration correlates positively with adipose tissue mass, a higher adipose tissue mass is associated with lower adiponectin concentrations. Thus, obesity is characterized by an adipokine imbalance involving high leptin concentrations but low adiponectin concentrations in the circulation [65]. Whereas leptin is positively associated with deficits in the body's vascular system function and insulin sensitivity as well as with increased systemic inflammation, the opposite pattern of associations is found for a higher adiponectin concentration [66,67]. These associations appear to reflect a causal relationship: adiponectin has anti-atherogenic effects, improves insulin sensitivity and inhibits pro-inflammatory processes, while inducing production of anti-inflammatory compounds [65,68]. Leptin, in contrast, initiates pro-inflammatory processes, for instance by activating macrophages and initiating the production of cytokines [65], and has atherogenic effects [69] although its relationship with glucose metabolism is complex and points to both positive and negative effects of the compound [70]. Based on these described effects, adipokines have been suggested to lie on the biological pathway linking obesity with cardiovascular disease [67]. The leptin-to-adiponectin ratio (LAR) can be calculated to reflect the relative positive versus negative effects of the compounds [71].

Leptin and adiponectin are therefore not only useful molecular biomarkers of metabolic dysfunction, but they may causally affect systemic vascular health, glucose metabolism and inflammation of the body. In the context of cognitive impairment, effects on brain function are possible. It is currently unclear whether or not adiponectin is able to cross the blood-brain barrier (BBB) [72,73]. If it does

(which is likely considering that adiponectin receptors can be found, among other tissues and organs, in the brain [74]), it would be reasonable to assume that its beneficial effects for instance on vascular health extend to the vasculature of the brain. Leptin is a large molecule that appears to cross the blood-brain barrier (BBB) through a transport system [75,76] and so it appears likely that leptin-induced vascular dysfunction, for instance, too would take hold in the brain. However, presence of leptin in the brain is also necessary for proper functioning of the body: through an interaction with its receptors in the brain, leptin regulates thermogenesis, homeostasis, reproduction, neurogenesis and breathing [75,77]. Most importantly in the context of metabolic dysfunction, leptin also serves as an indicator of caloric reserves and through effects on the hypothalamus suppresses appetite to reduce calorie intake [75,76]. It would follow logically that obese individuals (i.e., high-leptin) reduce their food intake, but this is not the case due to a systemic leptin resistance in these individuals. The mechanisms underlying leptin resistance are unclear. Potential mechanisms may include, among others, reduced leptin signaling, inflammatory processes and impaired transport of leptin across the BBB following long-term exposure to elevated leptin concentrations [78]. Leptin resistance may have developed evolutionarily to ensure that food is ingested despite high fat mass [75].

1.5.3 Terminology

Metabolic dysfunction can be considered a continuum rather than a dichotomous construct that is absent or present. Therefore, throughout this text, "metabolic dysfunction" refers to alterations in adipokine concentrations (higher leptin levels/lower adiponectin levels relative to the respective sample under investigation), to MetS as well as each of the 5 MetS components and their subclinical expression. Specifically, the term "hyperglycemia" will be used to refer to diabetes as well as impaired glucose tolerance, impaired fasting glucose, and a higher glucose or HbA1c level relative to a total given sample used in a research study. "Dyslipidemia" will be used as a summary term to describe diagnosed hypercholesterolemia, diagnosed hypertriglyceridemia as well as their subclinical expressions, i.e. higher triglyceride levels, lower HDL cholesterol levels, higher low-density lipoprotein (LDL) cholesterol levels and/or higher total cholesterol levels relative to a total sample. The term "obesity" will refer to BMI$\geq$30 kg/m^2 as a categorical measure as well as to a relatively higher BMI within a given sample. The term "central obesity" will refer to an elevated waist circumference or a relatively higher waist circumference within a given sample (this applies to the discussion of previous research only, as the work presented here does not include data on waist circumference).

1.5.4 Association with ACI

Metabolic dysfunction is a promising candidate risk factor for adverse health outcomes including cognitive impairment, primarily because it is modifiable. Its use in epidemiological research has scope not only for risk stratification (as for any risk factor) but additionally (if found to be causally related to

cognitive impairment) for intervention in individuals and at population health level (i.e., through strategic promotion/prevention of certain health behaviors).

1.5.4.1 Conventional metabolic dysfunction parameters

What could be termed "conventional metabolic dysfunction parameters", i.e. MeS and each of its 5 components and their subclinical expression, have been identified as risk factors for ACI and, unsurprisingly, given their roles as vascular risk factors, particularly for the type of impairment stemming from cerebrovascular damage (e.g., [79]). However, the relationship of metabolic dysfunction with ACI is complex. Associations with ACI have been observed for MetS itself [80,81], for its individual components (e.g., [82-85]), for the number of MetS components (range 0 to 5; [86]) and for lifestyle correlates such as low physical inactivity [87] typically even after multivariate adjustment for potential confounding factors. The evidence is not entirely consistent however (e.g., for MetS [88-90]). Overall, associations of these metabolic dysfunction parameters with ACI are most commonly found when they are assessed during mid-life, i.e. typically decades prior to the measurement of ACI, rather than in older age [83,84,91-93]. Midlife obesity for instance increases the risk of ACI in older age (e.g., [94]). Results of a US study of around 1000 adults suggest a particular role of midlife *central* obesity. Here, an association of midlife central obesity with an increased dementia risk in older age was independent of BMI [95]. When metabolic dysfunction is measured a few years before or at the same time as the cognitive assessment in older age (rather than midlife), the evidence is less consistent however (e.g., [96]) and may occasionally even point toward an association of metabolic dysfunction with a *reduced* cognitive risk [97-99]. For instance, in around 2700 participants of the Advanced Cognitive Training for Independent and Vital Elderly Trial with mean age 74 years, those who were overweight (BMI 25.0 to 29.9 kg/m^2) or obese (BMI≥30 kg/m^2) had faster processing speed compared with normal-weight individuals (BMI 18.5 to 24.9 kg/m^2) [100]. In the UK Whitehall II study of over 10 000 adults, obesity around age 50 was identified as a risk factor for dementia during 28-year follow-up, but at age 60 or 70 in the same participants was not associated with dementia risk [101]. Similar observations of metabolic dysfunction particularly at midlife as associated with later ACI have also been reported for dyslipidemia, hypertension [83,102] and occasionally for hyperglycemia (e.g., [103]). For MetS itself, too, a meta-analysis determined that an association with ACI was limited to <70 year olds [104].

The evidence thus overall suggests that once older age has been reached, the role of metabolic dysfunction as a risk factor for ACI may reverse, leading to null findings or even findings of metabolic dysfunction as associated with a reduced risk of ACI. Findings for obesity in particular as associated with a reduced ACI risk in older age have also been observed for other health outcomes such as mortality in what has been termed "obesity paradox" [97,105]. For cognitive outcomes, the importance of timing has only relatively recently been recognized and requires further in-depth analysis. It is noteworthy at this point that among the parameters of metabolic dysfunction, hyperglycemia

somewhat stands out as most consistently associated with ACI irrespective of study design and sample age: it is frequently associated with ACI both in long-term prospective studies recruiting participants at midlife (e.g., [106]) and in studies with briefer follow-up periods or cross-sectional designs in older age [107-109].

1.5.4.2 Adipokines

The research literature on adipokines and ACI is sparse since these compounds have only been discovered during the past few decades and are not measured using routine lab methods. The balance of evidence as it currently stands suggests mixed results. Some investigations had reported a higher level of adiponectin to be associated with higher cognitive function (e.g., [110,111]), whereas others found opposite results (e.g., [112,113]). Higher leptin too has been previously implicated as associated with ACI (e.g., [114]) but also with reduced cognitive risk (e.g., [115,116]). This inconsistency is perhaps unsurprising given that the relationship of conventional metabolic dysfunction parameters such as obesity– which adipokines are biomarkers of – with ACI is complex and may reverse with progressing age, as described above (see Section 1.5.4.1). The totality of evidence on adipokines and ACI is extremely limited however and does not allow conclusions as to their roles in midlife versus older age. Preliminary reports of associations of a higher adiponectin/lower leptin concentration with a higher mortality risk in older age [64] may indicate that the relationship of these adipokines with health outcomes may be similarly age-dependent as has been observed for the conventional parameters of metabolic dysfunction.

1.5.4.3 Possible explanations for the epidemiological link of metabolic dysfunction with ACI

From a pathophysiological perspective, it is reasonable that an assumed causal risk factor (metabolic dysfunction) would precede the health outcome (ACI) by some time. At midlife, metabolic effects for instance on vasculature, glucose metabolism and inflammation have decades to develop, as typically there is no major fluctuation within individuals, i.e. obese people tend to remain obese. The observed link of metabolic dysfunction with a reduced health (including cognitive) risk in older age appears counterintuitive at first and needs to be interpreted cautiously to avoid causal inference that is most likely incorrect (e.g., “obesity is beneficial to brain function”). For obesity in particular, such reports could be explained by BMI as an inappropriate measure of obesity in older adults [97] (see Section 1.5.1). Further, the observations for any metabolic dysfunction parameter as producing null findings or as associated with a reduced ACI risk could reflect survival bias: “healthier” individuals with metabolic dysfunction being more likely to survive to older age. Frailty and poor health including ACI may also influence metabolism and food intake. Older adults with metabolic dysfunction in a way demonstrate a resilience toward frailty and that do not suffer from sensory impairment or reduced appetite for instance due to prodromal dementia. Consistent with this potential explanation, one study found that a decline in cholesterol levels between mid-life and older age was associated with an increased dementia risk [117]. Another study reported that within a sample of patients with AD, those

who also had diabetes declined at slower rates compared with patients who did not have diabetes [118]. Such observations could be seen to support the aforementioned mechanisms contributing to paradoxical observations of metabolic dysfunction as associated with reduced ACI risk when both are measured in older age.

1.5.5 Association with POCD

1.5.5.1 Conventional metabolic dysfunction parameters

Compared with ACI, relatively little is known of the epidemiology of POCD. Only a limited number of studies has analyzed metabolic dysfunction as a potential risk factor and the research literature on this topic had never been systematically reviewed. To gain a full picture of the evidence, we performed four systematic reviews and meta-analyses on POCD associations with obesity, dyslipidemia, hypertension, and hyperglycemia. Each meta-analysis was based on between 6 and 24 studies [20,119-121].

We found that across 14 studies patients with diabetes were at 26% increased risk of POCD; additional preliminary evidence suggested a higher HbA1c was associated with an increased POCD risk in patients with diabetes [119]. The evidence was unclear for obesity mainly owing to a very small number of included studies though a trend for higher POCD risk in obese patients was observed [20]. Dyslipidemia and hypertension were not identified as risk factors [120,121]. A single small study has investigated MetS and POCD risk and found that MetS patients had higher POCD risk compared patients without MetS [122]. Crucially, what became clear from this work is that a majority of studies was of small sample size, often with <100 included patients. In addition, almost all had reported univariate analyses typically presented as “baseline characteristics” tables comparing patients who developed POCD with those who did not. This means that their findings could be interpreted in terms of risk prediction, which does not require multivariate adjustment (i.e. knowing that patients with diabetes are at increased risk of POCD may suffice), but they do not allow any conclusion as to potential pathophysiological processes or confounding factors that may statistically drive any observed associations. To illustrate, if a study found associations of diabetes with POCD but did not control for obesity, then we cannot determine whether diabetes may potentially contribute to POCD development or whether its association with POCD only arose from its function as a correlate of obesity.

1.5.5.2 Adipokines

For adipokines, the evidence on associations with POCD is even sparser. To illustrate, I provide a brief summary of two systematic searches of the PubMed database performed 23rd Dec 2020. The search “leptin” AND ((“post-operative cognit*” OR “postoperative cognit*” OR POCD) OR (("surgery" OR "operation") AND ("cognit*" OR "intelligence" OR "MMSE" OR "Mini Mental" OR "dementia" OR "Alzheim*" OR "mild cognitive impairment" OR "MCI")))” returned 41 studies. Of these, one study found that pre-surgery leptin concentration was lower in patients who developed POCD at 7 days compared to a group without POCD [123]. One study on obese patients undergoing

bariatric surgery found that a decline in serum leptin concentrations across surgery was associated with improved cognitive function pre- to post-surgery [124]. Another study with similar design did not find any associations between leptin change and cognitive change across surgery [125]. A review article suggested that leptin administration could be used to treat POCD [126]. Another search using the term "adiponectin" instead of "leptin" led to 16 results: two studies measured adiponectin and POCD but did not statistically associate the two [127,128]. Another study found that patients with POCD had lower *post-surgery* adiponectin compared with a group without POCD [129]. The remaining studies were unrelated, respectively.

This preparatory work highlighted the need for further well-designed epidemiological studies that build multivariate models associating metabolic dysfunction parameters with risk of POCD with consideration of potential confounding factors and inter-relationships among the parameters.

1.6 Excursus: The importance of pre-morbid IQ in epidemiological studies on cognitive outcomes

In epidemiological studies of cognitive outcomes, individual differences in cognitive reserve capacity [130] are a highly relevant but often neglected potential confounding factor. Cognitive reserve can be operationalized by a person's pre-morbid IQ, i.e. their level of cognitive function plateau reached early in life before the onset of age-related declines around age 30. Only rare birth cohort studies (e.g., [131]) include repeat cognitive testing across the lifespan, but alternatively pre-morbid IQ can also be *estimated* at any point during the lifespan from its proxies education or occupation, and from vocabulary as the only cognitive domain immune to age-related declines [132,133]. In the context of ACI, these easily ascertainable proxies of pre-morbid IQ are only infrequently used for statistical adjustment of analyses associating metabolic dysfunction with ACI (e.g., [134]). This is despite pre-morbid IQ as a potential common cause to metabolic dysfunction and ACI. For instance, a lower pre-morbid IQ predicts overweight in older age [96,135,136]. Potential mechanisms could include a poor lifestyle stemming from low health education/literacy and/or lack of opportunity to afford healthy choices. At the same time, a person with a low pre-morbid IQ carries that low IQ into older age and is thus likely be captured by research definitions of ACI comparing cognitive scores to published norms or the total sample. A low pre-morbid IQ also predisposes to an increased risk of clinical forms of ACI such as dementia [92]. Spurious associations of metabolic dysfunction with ACI that are confounded by pre-morbid IQ could therefore be found. For instance, a contribution of pre-morbid IQ can mislead researchers to understand associations of diabetes with ACI in older age as reflective of a causal relationship with diabetes leading to ACI when in fact both could be driven by pre-morbid IQ as a common cause. This was impressively demonstrated in an analysis of the Lothian Birth Cohort [137]: a cross-sectional association of diabetes with ACI at age 70 was found, but when IQ at age 11 (pre-

morbid IQ) was controlled for, diabetes was no longer associated with ACI. A lower pre-morbid IQ predisposed participants to diabetes and also to a lower cognitive function in older age in that study.

In the context of POCD, pre-morbid IQ too is only infrequently controlled for in analyses associating metabolic dysfunction with POCD (e.g., [138]) although we have recently shown that patients with a lower pre-morbid IQ are – similar to ACI – at increased POCD risk [24].

Based on this evidence, pre-morbid IQ should be controlled for in any epidemiological study that goes beyond risk prediction and attempts to tease out any potential causal relationships linking metabolic dysfunction with ACI or POCD.

1.7 Summary of present gaps in knowledge in the research field

Despite intensive research efforts during the past century (ACI) and during the past few decades (POCD), their relationships with metabolic disturbance have not been fully elucidated as yet.

For ACI, further evidence is needed to add to the emerging pattern of epidemiological evidence indicating an association of conventional metabolic dysfunction parameters with later impairment particularly when the exposure is measured in mid-life, whereas this relationship is weaker and may even reverse in older age (see Section 1.5.4.1). Adipokines are correlates of adipose tissue mass but also function as risk factors with potential for causal effects on the brain. Their relationship with ACI warrants evaluation, because those few studies that have investigated these markers in the context of ACI have produced conflicting results (see Section 1.5.4.2). Concurrent investigation of several parameters of metabolic dysfunction in multivariate analyses is needed to determine the independence of the respective associations. This can help compare the parameters of metabolic dysfunction in terms of their associated ACI risk and, through statistical adjustment, can allow conclusions as to potential mechanisms underlying any observed unadjusted associations. Pre-morbid IQ for instance should be controlled for throughout. Finally, metabolic dysfunction and ACI has never been investigated in the perioperative setting before using samples of older adults who are scheduled for surgery during the next few days.

For POCD, the evidence on adipokines as candidate risk factors is virtually absent and for conventional parameters metabolic dysfunction as candidate risk factors is limited (see Section 1.5.5). The few epidemiological studies in this field have mainly not aimed to investigate the epidemiology of POCD, but simply reported unadjusted “baseline characteristics” tables in their manuscripts and had small sample size. We therefore need to add to this limited evidence in multivariate, sufficiently powered analyses, again ideally with adjustment for pre-morbid IQ.

Finally, current diagnostic procedures for AD continue to rely on costly and/or invasive methods such as brain imaging and CSF collection (see Section 1.2). To date, no high-throughput measurement method for plasma Aβ with high diagnostic accuracy has been developed.

1.8 Goal of the present work

The present work aimed to add to the observational evidence on metabolic dysfunction and cognitive impairment. Initially, the cross-sectional associations of conventional parameters of metabolic dysfunction with presence of ACI were tested specifically in samples of middle-aged to older adults who were scheduled for surgery. Baseline data of 3 randomized controlled trials (RCTs) and of the multi-center Biomarker Development for Postoperative Cognitive Impairment in the Elderly (BioCog) study were used. Findings are reported in the articles *Association of obesity, diabetes and hypertension with cognitive impairment in older age* (see Section 2.1.1) and *Associations of the metabolic syndrome and its components with cognitive impairment in older adults* (see Section 2.1.2). In addition, in the BioCog cohort, associations of circulating adipokine concentration with ACI were statistically tested, as reported in the article *Plasma leptin, but not adiponectin, is associated with age-related CI* (see Section 2.1.3). We next used prospective data from the 3 RCTs to evaluate obesity, diabetes and hypertension as potential risk factors for POCD as reported in the article *Diabetes, but Not Hypertension and Obesity, Is Associated with Postoperative Cognitive Dysfunction* (see Section 2.2).

In a final set of analyses, we aimed to take one step forward in identifying a potential blood-based biomarker to AD diagnosis. For this purpose, we evaluated the diagnostic accuracy of a novel, commercial, high-throughput assay for measurement of plasma Aβ using a sample of AD patients and controls attending a memory clinic. Results are reported in the article *Plasma amyloid concentration in Alzheimer's disease: Performance of a high-throughput amyloid assay in distinguishing Alzheimer's disease cases from controls* (see Section 2.3).

1.9 Expected implications

Ultimately, the work described here could have an immediate impact on the research field and could additionally provide preliminary evidence that – if supported by further studies – could aid population health. Firstly, direct comparison of risk factors between ACI and POCD will help determine whether both conditions represent similar syndromes and are only differentiated by the fact that POCD is induced by surgery, or whether clear distinctions have to be made. Secondly, identification of metabolic risk factors for ACI and POCD can help shed light on potential underlying pathophysiological mechanisms leading up to the conditions. Inclusion of potential confounders in multivariate models can approach the issue of causality underlying any associations; inclusion of several parameters of metabolic dysfunction can determine which of the parameters are the most informative and may statistically explain observations of associations of others with ACI. Thirdly, the results of this work could be used for risk stratification and initiation of, for instance, cognitive monitoring programs in older adults at risk of ACI. For POCD, our results could additionally aid decision-making on elective surgical procedures. Eventually, if metabolic dysfunction is found to be causally related to these cognitive outcomes, preventive strategies could follow. Validation of an assay

for measurement of plasma Aβ could aid future AD diagnosis with a potential to revolutionize clinical practice.

1.10 Hypotheses

As a starting point for this work, we hypothesized that ACI and POCD each were correlated with (ACI) or predicted by (POCD) metabolic dysfunction (see Figure 2). We did not expect an association of metabolic dysfunction with reduced odds of ACI, which has previously been reported for older age groups (e.g., "obesity paradox"), based on sample age of cohorts included in this analysis.

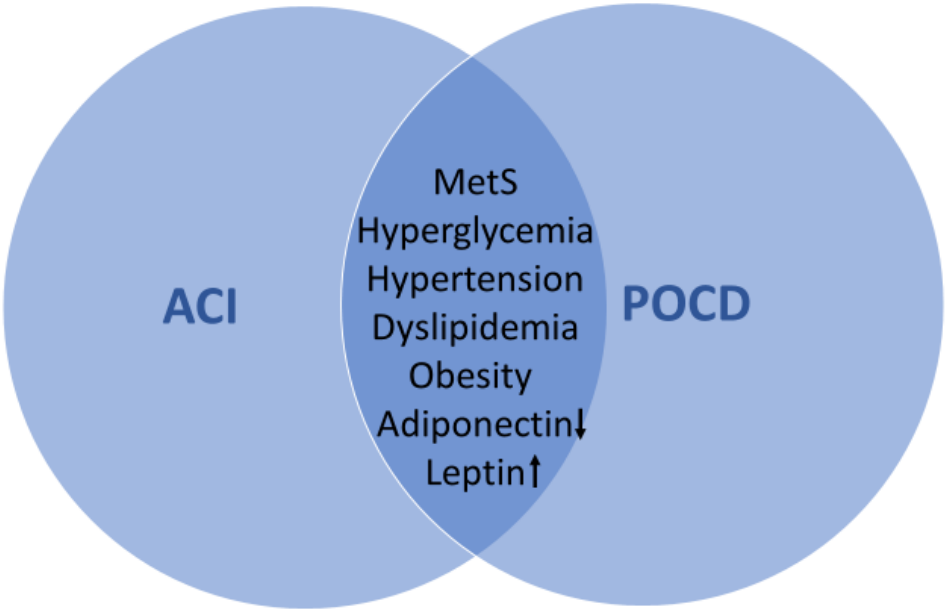

Figure 2: Hypothesized full overlap of metabolic risk factors for ACI and for POCD. Metabolic risk factors include the respective continuous counterpart (e.g., "hyperglycemia" includes diabetes, pre-diabetes and higher blood glucose/HbA1c relative to total samples). ACI, age-related cognitive impairment; MetS, metabolic syndrome; POCD, post-operative cognitive dysfunction.

We hypothesized that the plasma Aβ assay would have high diagnostic accuracy in distinguishing confirmed AD patients from controls.

2. Own contributions

2.1 Metabolic dysfunction and ACI

2.1.1 Conventional metabolic parameters and ACI in “3 RCTs”

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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

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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/m^2. "Underweight" was defined as BMI <18.5 kg/m^2. 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/m^2), with prevalence of obesity (BMI ≥30 kg/m^2) 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 (Chi^2=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/m^2) 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 hypertension, 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 (Chi^2=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).

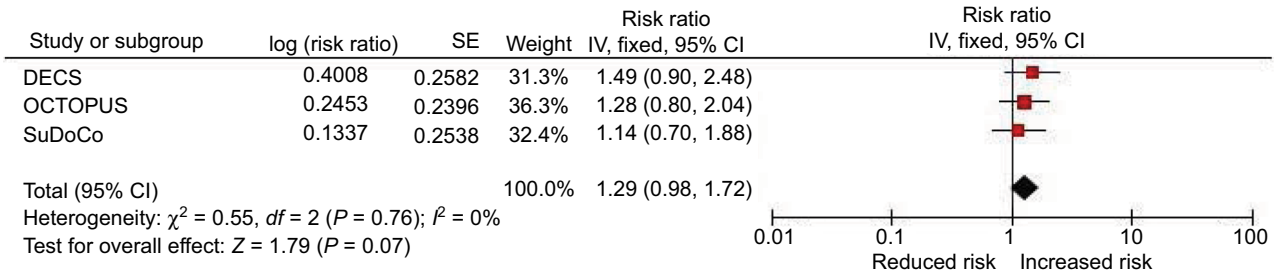

Figure 1 Pooled association of obesity with cognitive impairment (model 2).
Abbreviations: CI, confidence interval; DECS, Dexamethasone for Cardiac Surgery; SE, standard error; SuDoCo, Surgery Depth of Anaesthesia Cognitive Outcome.

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.

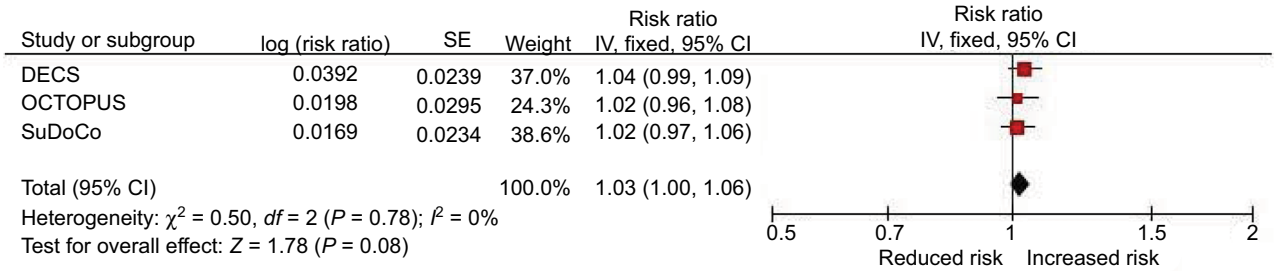

Figure 2 Pooled association of BMI with cognitive impairment (model 2).
Abbreviations: BMI, body mass index; CI, confidence interval; DECS, Dexamethasone for Cardiac Surgery; SE, standard error; SuDoCo, Surgery Depth of Anaesthesia Cognitive Outcome.

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

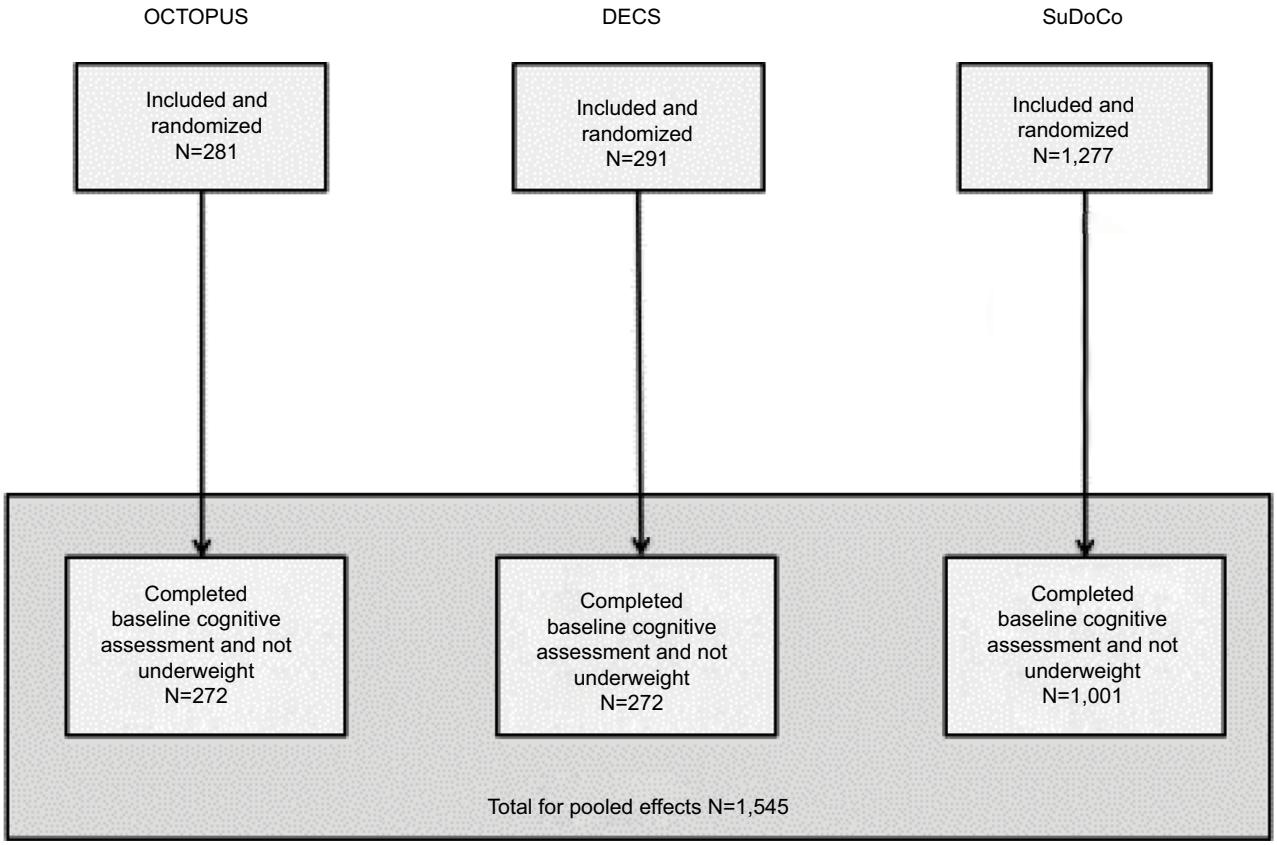

Figure S1 Enrollment into the 3 studies.

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.

To add to the evidence on associations of metabolic dysfunction with ACI, as a first step, we ran a pooled analysis using original baseline (pre-surgery) data from 3 RCTs of surgical patients. Each study had evaluated the effect of an intervention (Dexamethasone for Cardiac Surgery, DECS: dexamethasone versus placebo during surgery; OCTOPUS: on-pump versus off-pump method for cardiac surgery; Surgery Depth of Anaesthesia Cognitive Outcome Study, SuDoCo: monitoring of depth of anesthesia versus no monitoring) on the risk of developing post-operative delirium (POD) and POCD. The studies stemmed from the Netherlands (DECS; OCTOPUS) and Berlin (SuDoCo) and recruited a total of >1500 middle-aged to older adults. Each of the 3 RCTs had been fully published in terms of their intervention effects on primary and secondary outcomes, but their data had not previously been assessed from an observational perspective.

Metabolic parameters are frequently only used as categorical variables in epidemiological research. This approach aids interpretation by clinicians (who are accustomed to working with binary disease status variables) as well as translation to lay terms for communication with patients on their own individual risk. However, dichotomization comes with reduced statistical power. Here, in order to preserve statistical power and to elucidate any potential linear dose-response relationships, which can support an argument for causality, dichotomous metabolic parameters as well as their continuous counterparts were used as available. Thus associations of obesity (BMI≥30 kg/m^2), diabetes and hypertension with presence of ACI were supplemented by analyses of BMI, systolic blood pressure and diastolic blood pressure. Data on HDL cholesterol, triglyceride and adipokine concentrations were not available. ACI was defined within each of the 3 RCTs through comparison of patients' scores on 11 (OCTOPUS), 5 (DECS) and 6 (SuDoCo) age-sensitive cognitive tests with scores on the same tests by a study-specific, non-surgical control group respectively. Specifically, within each study, patients who scored ≥2 standard deviations below the respective control group on ≥1 cognitive test were considered to have ACI.

ACI was found in 18.4% of patients. Pooled across the 3 studies, BMI was overall associated with ACI such that each 1 kg/m^2 higher BMI was associated with a 3% increased odds of ACI with age, sex, diabetes and hypertension controlled for. Within the obese group (BMI≥30 kg/m^2), the association was even stronger with an 8% increased odds of ACI per 1 kg/m^2 higher BMI. This suggests a non-linear relationship of BMI with cognitive risk. When education as a proxy of pre-morbid IQ was entered into the model of BMI and ACI for DECS and OCTOPUS (SuDoCo did not have data on education), a trend remained for an association of higher BMI with higher odds of ACI that was just short of statistical significance. Diabetes, hypertension, systolic blood pressure and diastolic blood pressure were each not associated with ACI.

Thus, we showed in a cross-sectional analysis of samples of middle-aged to older surgical patients that among the exposure variables under investigation, only a higher BMI was independently associated

with increased odds of ACI. This study lacked data on other metabolic dysfunction parameters such as dyslipidemia and, consequently, MetS. Considering the fact that the research literature on metabolic dysfunction and ACI is not entirely consistent, and because this was the first time that metabolic dysfunction and ACI had been investigated in a sample of surgical patients, we next aimed to replicate these findings in another, independent cohort of surgical patients.

2.1.2 Conventional metabolic parameters and ACI in BioCog

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Associations of the metabolic syndrome and its components with cognitive impairment in older adults

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Abstract

Background: The metabolic syndrome (MetS) is an established cardiovascular risk factor. Here, we investigated its role in cognitive impairment.

Methods: Baseline data from 202 participants (aged 65 to 87 years) of the BioCog study were used. All were free of clinical dementia (MMSE≥24/30). Cognitive impairment was defined as the lowest tertile of a cognitive summary score. Multiple logistic regression analyses examined associations of body mass index (BMI), triglycerides (TG), high-density lipoprotein (HDL-C), glucose and glycated hemoglobin A1c (HbA1c) levels with the odds of cognitive impairment. MetS was defined as ≥3 of its 5 components obesity (BMI ≥ 30 kg/m^2), elevated TG (TG ≥1.7 mmol/L), reduced HDL-C (males: < 1.0 mmol/L; females: < 1.3 mmol/L), elevated glucose (glucose ≥5.5 mmol/L and/or diagnosed diabetes) and elevated blood pressure (history of hypertension). Analyses controlled for age, sex and smoking history.

Results: Lower HDL-C was significantly associated with a higher odds of cognitive impairment (OR 2.70 per 1 mmol/L reduction; 95% CI 1.25, 5.56; $p = 0.011$), whereas BMI, TG, glucose and HbA1c were not (all $p > 0.05$). Results for HDL-C were similar when HDL-C, glucose, BMI and TG were entered into a single model (OR 2.56 per 1 mmol/L reduction, 95% CI 1.09, 5.88, $p = 0.031$) and when cerebrovascular disease and coronary heart disease were additionally controlled for (OR 2.56 per 1 mmol/L reduction, 95% CI 1.06, 6.25, $p = 0.036$). Among the 5 MetS components, participants with elevated TG were at 2-fold increased odds of impairment (OR 2.09, 95% CI 1.08, 4.05, $p = 0.028$) including when the remaining 4 MetS components were entered (OR 2.23, 95% CI 1.07, 4.65, $p = 0.033$), but the finding was no longer statistically significant when cerebrovascular disease and coronary heart disease were additionally controlled for ($p = 0.11$). Presence of MetS and of obesity, reduced HDL-C, elevated glucose or elevated blood pressure were not significantly associated with impairment (all $p > 0.05$).

Conclusion: Our findings support low HDL-C as an independent risk marker of cognitive impairment in older age. The need for research into mediatory and confounding factors, and re-evaluation of traditional cut-off points is highlighted.

Trial registration: The study was registered on 15th October 2014 at clinicaltrials.gov (NCT02265263).

Keywords: Cognitive impairment, Epidemiology, High-density lipoprotein, Glucose, Metabolic syndrome, Triglycerides

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Background

The metabolic syndrome (MetS) is a cluster of metabolic abnormalities, including abdominal obesity, elevated blood pressure (BP), elevated blood glucose levels, low high-density lipoprotein cholesterol (HDL-C) levels, and elevated triglyceride (TG) levels, and is suggested to play a major role in the development of cardiovascular disease (CVD) and type 2 diabetes mellitus [1]. Although its definition had been a matter of debate [1], MetS is now a widely accepted concept [2], and has been used across multiple populations to assess cardiovascular and mortality risk [3]. For example, it was estimated that 11 million deaths world-wide can be attributed to MetS annually [3]. Although MetS has traditionally primarily been linked to CVD, studies suggest that MetS [4–7] and metabolic abnormalities more generally [7–9] may also be related to cognitive impairment as a type of organ dysfunction that burdens the global economy to extents similar to CVD [10]. Chronically elevated blood glucose levels, for instance, have consistently been associated with an increased risk of future cognitive impairment [11].

MetS [12] and its contributing parameters of metabolic dysfunction (e.g., [13]) are hugely prevalent in Western societies and on a global scale, but all are modifiable. This implies a potential for strategic improvement of public health that warrants clarification. We therefore examined associations of MetS, of each of its 5 components and of associated continuous parameters of metabolic dysfunction with cognitive impairment in a community-based sample of older adults without clinical dementia.

Method

Study design

We analyzed cross-sectional associations of MetS with cognitive impairment in the Biomarker Development for Postoperative Cognitive Impairment in the Elderly (BioCog) study (http://www.biocog.eu). The primary aim of the study is to identify biomarkers predictive of post-operative cognitive impairment in patients undergoing elective surgery at study sites in Utrecht, the Netherlands, and Berlin, Germany. Details on recruitment procedures and study protocol have been reported elsewhere [14] and the study was registered on 15th October 2014 at clinicaltrials.gov (NCT02265263). In brief, patients were eligible to participate if they were aged ≥65 years, Caucasian, scheduled for elective surgery of any type with operative time ≥ 60 min and with an expected post-operative hospital treatment period of at least 7 days, and if they scored normal on a screening tool for dementia (Mini Mental State Examination, MMSE≥24/30). Of 7727 patients screened for inclusion, 933 were recruited between November 2014 and April 2017. Here, we report on baseline metabolic and cognitive data that were collected before surgery from the first 400 of those patients. Participants with missing data on any of the 5 MetS components or any missing cognitive data were excluded from our analysis.

Clinical interview and physical examination

Participants self-reported on smoking history and sociodemographic parameters. Arterial hypertension, diabetes, a history of transient ischemic attacks (TIA), a history of stroke and coronary heart disease (CHD) were ascertained from a combination of self-report and local hospital records on pre-existing conditions and medication. Weight and height were measured to calculate body mass index (BMI).

Biomarker measurement

Blood was collected immediately before induction of anesthesia in a supine position and following an overnight fast. HbA1c was measured in a laboratory adjacent to the respective hospital site. Blood was additionally centrifuged and serum samples stored at − 80 °C for shipment to a central biobank repository. Samples were later retrieved from that biobank for measurement of glucose, TG and HDL-C levels. Those analyses were performed at a single laboratory. Because samples stored at the biobank were insufficient for $N = 16$ participants of our analysis sample, data on glucose, TG and HDL-C were used from the immediate laboratory adjacent to the hospital site for those 16 participants. Sensitivity analyses revealed no influence of analysis laboratory on any of the results reported here (data not shown). For one participant, blood was collected after induction of anesthesia but before incision. Their data were not excluded.

Definition of metabolic syndrome

In accordance with standardized criteria [15], we used a slightly modified definition of MetS (Table 1). BMI was used to define obesity instead of waist circumference, since waist circumference was not measured in our study.

Cognitive examination

Participants underwent neuropsychological testing in a quiet hospital room usually on the day before surgery. The MMSE was used to screen for clinical dementia for inclusion into the study, before a series of computer-based (Cambridge Neuropsychological Test Automated Battery, CANTAB®; Cambridge Cognition Ltd.) and paper-pencil tests were performed: Paired Associates Learning (PAL), Verbal Recognition Memory (VRM), Spatial Span (SSP), Simple Reaction Time (SRT), Trail-Making Test-B (TMT-B), and Grooved Pegboard (GP). Principal component analysis (PCA) with extraction of factors with

Table 1 Definition of metabolic syndrome[a]

Component	Standard criteria[b]	Criteria used in present study
Elevated waist circumference	Population- and country-specific definitions	BMI ≥ 30 kg/m^2
Elevated TG	TG ≥ 150 mg/dL (1.7 mmol/L), or drug treatment	Fasting TG ≥150 mg/dl (1.7 mmol/L)
Reduced HDL-C	HDL-C < 40 mg/dL (1.0 mmol/L) in males; HDL-C < 50 mg/dl (1.3 mmol/L) in females; or drug treatment	HDL-C < 40 mg/dl (1.0 mmol/L) in males HDL-C < 50 mg/dl (1.3 mmol/L) in females
Elevated blood pressure	Systolic ≥130 and/or diastolic ≥85 mmHg, or drug treatment	Hypertension based on self-report and/or local hospital records
Elevated glucose	≥100 mg/dL in plasma, or drug treatment	1. Fasting blood glucose[c] ≥100 mg/dL (5.5 mmol/L) (if not fasted, HbA1c ≥42 mmol/mol[d]) and/or 2. Diabetes based on self-report and/or local hospital records

[a]The metabolic syndrome is defined as the presence of at least 3 of the 5 components
[b]Consensus statement [15]
[c]Glucose measured in serum (nearly identical to plasma; [59])
[d]In the present sample, all participants were fasted

Eigenvalue > 1 was applied to the 6 cognitive tests to derive a score of global cognitive ability ('*g*') [16]. *G* is unaffected by test-specific measurement error, produces more reliable results compared with individual cognitive tests and typically accounts for around 40% of variance [17]. *G* is independent of cognitive test battery [18], and all aforementioned tests have been used to calculate *g* in the past (e.g., [18]). Visual inspection of a scree plot confirmed presence of a single factor (Eigenvalue 2.37) explaining 39.53% of variance in the data. Standardized residuals of that factor were saved to obtain an operant latent variable *g* (factor loadings TMT-B, 0.77; PAL, 0.71; GP, 0.67; VRM, 0.56; SSP, 0.54; SRT, 0.49). 'Cognitive impairment' was defined as scoring in the lowest tertile of *g* and was the outcome of interest in our analysis. As a screening tool for dementia [19], the MMSE was not used to calculate *g*.

Statistical analysis

Data for MMSE, TMT-B, SRT and GP were log transformed prior to analysis to approximate normal distribution. An initial univariate analysis of variance (ANOVA) compared MMSE scores across tertiles of *g*; a chi^2 test compared associations of MMSE< 27 (indicative of prodromal dementia) with presence of cognitive impairment.

Participants were divided into quartiles based on the respective distributions of HbA1c, glucose, TG, HDL-C and BMI. We then used multiple logistic regression to examine the association of each with odds of cognitive impairment using the lowest quartile as the reference category. In addition, we used each on a continuous scale. For each analysis, we ran three regression models: Model 1 was adjusted for age, sex and smoking. Model 2 included age, sex, smoking, BMI, TG, HDL-C, and either glucose or HbA1c. Model 3 additionally included CHD, TIA and stroke. To check for non-linearity in the association with cognitive impairment, we subsequently added quadratic terms into the respective final model (Model 3).

We next categorized MetS and each of its components based on established definitions (Table 1) and studied their association with odds of cognitive impairment using multiple logistic regression. Again, Model 1 was adjusted for age, sex and smoking, Model 2 included age, sex, smoking and all 5 MetS components, and Model 3 additionally controlled for CHD, TIA and stroke.

We then studied the association of the number of abnormal MetS components with the odds of cognitive impairment using 0 abnormal components as reference category. For the purpose of this analysis, the groups with 4 or 5 components were merged due to small participant numbers in these groups. Finally, the number of MetS components (range 0 to 5) was entered into a multiple logistic regression model. For these analyses, Model 1 controlled for age, sex and smoking, and Model 2 additionally controlled for CHD, TIA and stroke. All results remained unchanged following exclusion of 2 underweight participants (BMI ≤ 18.5 kg/m^2) and 1 participant with very high TG (28.9 mmol/L) in a separate analysis unless stated otherwise. SPSS version 18.0 (IBM Corporation, New York) was used.

Results

Sample characteristics

A total of 202 participants enrolled into the study had complete cognitive and MetS data. Demographic, metabolic and cognitive characterization of the analysis sample is shown in Table 2. Participants were most commonly scheduled for orthopedic, gynecologic/urologic or general surgery and a majority had elevated BP

Table 2 Demographic, metabolic and cognitive sample characteristics

	Means ± SD, median (interquartile range) or n of total $N = 202$ analysis sample	% of N
Study site		
UMC Utrecht, n (%)	33	16.3%
Charité Berlin Campus Virchow, n (%)	114	56.4%
Charité Berlin Campus Mitte, n (%)	55	27.2%
Male, n (%)	121	59.9%
Age, years, mean ± SD	72.12 ± 4.74	
Smoking history, n (%)		
Missing	28	13.9%
Never smokers	54	26.7%
Former smokers	93	46.0%
Current smokers	27	13.4%
History of coronary heart disease, n (%)	28	13.9%
History of stroke, n (%)	9	4.5%
History of transient ischemic attack, n (%)	6	3.0%
History of diabetes, n (%)	39	19.3%
Non-insulin dependent diabetes, n (%)	23	11.4%
Insulin-dependent diabetes, n (%)	16	7.9%
History of dyslipidemia, n (%)	40	19.8%
Body mass index (BMI; kg/m^2), mean ± SD	27.12 ± 4.39	
Serum glucose (mmol/L), median (interquartile range)	5.77 (5.27–6.49)	
HbA1c[a] (mmol/mol), mean ± SD	39.68 ± 8.20	
Triglycerides (TG) (mmol/L), median (interquartile range)	1.31 (1.04–1.79)	
Total cholesterol[a] (mmol/L), mean ± SD	4.88 ± 1.12	
Low-density lipoprotein[a] (LDL-C) (mmol/L), mean ± SD	3.11 ± 0.98	
High-density lipoprotein (HDL-C) (mmol/L), mean ± SD	1.27 ± 0.43	
BMI categories, n (%)		
Underweight (BMI ≤ 18.5 kg/m^2), n (%)	2	1.0%
Normal/overweight (BMI 18.6–29.9 kg/m^2), n (%)	155	76.7%
Obesity (BMI ≥30 kg/m^2), n (%)	45	22.3%
Elevated blood pressure[b], n (%)	123	60.9%
Elevated fasting glucose[b], n (%)	125	61.9%
Elevated TG[b], n (%)	60	29.7%
Reduced HDL-C[b], n (%)	69	34.2%
Metabolic syndrome (MetS)[b], n (%)	72	35.6%
Number of MetS components[b]		
0	27	13.4%
1	41	20.3%
2	62	30.7%
3	41	20.3%
4	21	10.4%
5	10	5.0%
Factor of global ability *g*, mean ± SD	−0.06 ± 1.01	
Mini Mental State Examination (MMSE)[a], median (interquartile range)	29 (28–30)	
MMSE< 27[a], n (%)	12	6.0%

[a]for HbA1c, $N = 155$; for total cholesterol, $N = 158$; for LDL-C, $N = 157$; for MMSE, $N = 200$
[b]for definition, see Table 1

(60.9%) and elevated fasting glucose (61.9%) respectively (Table 1). Obesity was present in 22.3%, TG were elevated in 29.7%, and HDL-C was reduced in 34.2% of participants. Seventy-two participants (35.6%) fulfilled the criteria for MetS.

Comparison of Mini-Mental State Examination (MMSE) scores across tertiles of *g*

Scores on the MMSE differed statistically significantly across tertiles of *g* (F (2, 197) = 12.38; $p < 0.001$; $\eta p^2 = 0.11$). Participants with cognitive impairment (those scoring in the lowest tertile *g*) had lower MMSE (geometric mean 28.1, 95% CI 27.8, 28.4) relative to the second (geometric mean 28.7, 95% CI 28.4, 29.0) and third tertiles (geometric mean 29.1, 95% CI 28.8, 29.4) (pairwise comparison range $p < 0.001$ to $p = 0.110$). Of 12 participants with MMSE< 27, 8 had cognitive impairment when defined from *g* (chi^2 (1, $N = 200$) = 5.42; $p = 0.020$).

Age- and sex associations with cognitive impairment

Age was directly associated with cognitive impairment. Each 5-year increase in age was associated with a 1.79-fold increased odds of impairment (OR 1.79 per 5-year increment, 95% CI 1.30, 2.47; $p < 0.001$). Sex was unrelated to impairment in the same model (male versus female, OR 0.70, 95% CI 0.38, 1.28; $p = 0.25$).

Continuous metabolic parameters and odds of cognitive impairment

The odds of cognitive impairment according to each of the continuous metabolic parameters and their quartiles are shown in Table 3. HDL-C quartiles were significantly associated with cognitive impairment (p_{trend} across quartiles adjusted for age, sex, smoking = 0.004). Thus, persons in the highest versus lowest quartile of HDL-C had a 0.28-fold odds (95% CI 0.11–0.71). The association also survived addition of BMI, TG, glucose, CHD, TIA and stroke into the model (p_{trend} across quartiles = 0.023). On a continuous scale, in the fully adjusted model, each 1 unit mmol/L higher HDL-C concentration was associated with a 0.39-fold odds (OR 0.39; 95% CI 0.16, 0.94; $p = 0.036$) of cognitive impairment.

Higher glucose levels were also related to a higher odds of cognitive impairment in the fully adjusted model (p_{trend} across quartiles = 0.045). On a continuous scale, 1 mmol/L higher glucose levels were associated with a statistically non-significant trend for a 1.21-fold odds (95%-CI 0.97–1.51; $p = 0.086$) of cognitive impairment. BMI, TG levels, and HbA1c concentrations were not substantially related to cognitive impairment in these analyses. To test for non-linearity we added quadratic terms of the metabolic parameters to each of the fully adjusted models; however, none of these quadratic terms were statistically significant (HDL-C, $p = 0.407$; TG, $p = 0.556$; BMI, $p = 0.788$; glucose, $p = 0.282$; HbA1c, $p = 0.849$), suggesting that non-linear models did not improve model fit.

Metabolic syndrome, the 5 MetS components and odds of cognitive impairment

Participants with elevated TG were at 2.09-fold odds of cognitive impairment in analyses controlling for age, sex and smoking (OR 2.09, 95% CI 1.08, 4.05, $p = 0.028$) and when obesity, reduced HDL-C, elevated glucose and elevated BP were additionally adjusted for (OR 2.23, 95% CI 1.07, 4.65, $p = 0.033$; Table 4). Addition of CHD, TIA and stroke into the model led to statistically non-significant results, however (OR 1.86; 95% CI 0.87, 4.00; $p = 0.110$). Obesity, reduced HDL-C, elevated glucose and elevated BP were each not associated with cognitive impairment (all $p > 0.05$; see Table 4). The presence of MetS was not significantly related to cognitive impairment (OR adjusted for age, sex, smoking 1.38; 95% CI 0.74, 2.60; $p = 0.310$; Table 4). The number of MetS components was also not significantly associated with impairment (OR per number of component increment, adjusted for age, sex, smoking, 1.16, 95% CI 0.92, 1.45; $p = 0.212$; Table 5). Pairwise comparison showed a lower odds of cognitive impairment in the group with 1 MetS component compared with the reference group with 0 components in the fully adjusted model (OR 0.29; 95% CI 0.09, 0.95; $p = 0.041$) though no significant differences in the odds of cognitive impairment in participants with 2, 3 or 4/5 MetS components compared with the reference group were found (all $p > 0.05$; Table 5).

Discussion

In this cross-sectional analysis of a sample of older surgical patients without clinical dementia, participants with lower HDL cholesterol (HDL-C) and those with elevated triglycerides (TG) were at increased likelihood of being cognitively impaired. Individuals with higher glucose levels also had a higher odds of cognitive impairment, although these results became apparent only in quartile analyses. Importantly, the associations for HDL-C and glucose, but not for elevated TG, were largely independent of one another, of other parameters of metabolic dysfunction, and of age, sex, smoking and a history of macrovascular disease. Obesity and elevated blood pressure were not substantially associated with cognitive impairment.

Associations of mid-life obesity [8], mid-life dyslipidemia [20, 21] and mid-life hypertension [22] with later cognitive impairment including increased risk of Alzheimer's disease and presence of Alzheimer's-type neuropathology [23, 24] are well-established. In later life, these risk factors are more difficult to evaluate partly due to an influence of

Table 3 Odds of cognitive impairment according to continuous metabolic parameters

	Quartiles				p_{trend}	Continuous parameters	
	1	2	3	4		OR (95% CI) per unit increment	*p*-value
Body mass index							
Cut-point (kg/m^2)	≤24.15	24.16–26.70	26.71–29.35	≥29.36			
n with cognitive impairment / N total	19 / 51	18 / 51	18 / 50	17 / 50			
Model 1 OR (95% CI)	1.00 (Reference)	0.96 (0.41, 2.25)	1.17 (0.50, 2.75)	1.02 (0.43, 2.41)	0.971	0.99 (0.92, 1.06)	0.772
Model 2 OR (95% CI)	1.00 (Reference)	1.06 (0.41, 2.70)	1.11 (0.43, 2.87)	0.64 (0.23, 1.80)	0.707	0.95 (0.88, 1.03)	0.205
Model 3 OR (95% CI)	1.00 (Reference)	0.98 (0.37, 2.64)	1.18 (0.44, 3.13)	0.59 (0.20, 1.75)	0.602	0.95 (0.88, 1.03)	0.238
Triglycerides							
Cut-point (mmol/L)	≤1.04	1.05–1.31	1.32–1.79	≥1.80			
n with cognitive impairment / N total	17 / 53	14 / 49	23 / 50	18 / 50			
Model 1 OR (95% CI)[a]	1.00 (Reference)	0.92 (0.38, 2.24)	2.20 (0.94, 5.19)	1.58 (0.66, 3.77)	0.167	1.11 (0.93, 1.32)	0.241
Model 2 OR (95% CI)[a]	1.00 (Reference)	1.07 (0.39, 2.91)	2.22 (0.82, 5.98)	0.91 (0.31, 2.73)	0.259	1.02 (0.88, 1.18)	0.835
Model 3 OR (95% CI)[a]	1.00 (Reference)	1.08 (0.38, 3.07)	2.08 (0.75, 5.76)	0.73 (0.23, 2.31)	0.237	1.02 (0.88, 1.18)	0.791
High-density lipoprotein cholesterol							
Cut-point (mmol/L)	≤1.01	1.02–1.27	1.28–1.55	≥1.56			
n with cognitive impairment / N total	28 / 54	10 / 52	21 / 52	13 / 44			
Model 1 OR (95% CI)	1.00 (Reference)	0.23 (0.09, 0.57)	0.65 (0.29, 1.48)	0.28 (0.11, 0.71)	0.004	0.37 (0.18, 0.80)	0.011
Model 2 OR (95% CI)	1.00 (Reference)	0.25 (0.09, 0.65)	0.57 (0.22, 1.44)	0.26 (0.09, 0.80)	0.017	0.39 (0.17, 0.92)	0.031
Model 3 OR (95% CI)	1.00 (Reference)	0.28 (0.10, 0.75)	0.53 (0.20, 1.41)	0.22 (0.07, 0.70)	0.023	0.39 (0.16, 0.94)	0.036
Glucose							
Cut-point (mmol/L)	≤5.27	5.28–5.77	5.78–6.49	≥6.50			
n with cognitive impairment / N total	21 / 54	14 / 48	14 / 52	23 / 48			
Model 1 OR (95% CI)	1.00 (Reference)	0.56 (0.23, 1.35)	0.56 (0.24, 1.33)	1.62 (0.71, 3.70)	0.053	1.19 (0.99, 1.43)	0.068
Model 2 OR (95% CI)	1.00 (Reference)	0.66 (0.26, 1.66)	0.42 (0.16, 1.10)	1.58 (0.61, 4.08)	0.062	1.19 (0.97, 1.46)	0.094
Model 3 OR (95% CI)	1.00 (Reference)	0.62 (0.23, 1.66)	0.45 (0.16, 1.21)	1.84 (0.69, 4.91)	0.045	1.21 (0.97, 1.51)	0.086
HbA1c							
Cut-point (mmol/mol)	≤35.5	35.6–38.8	38.9–42.1	≥42.2			
n with cognitive impairment / N total	15 / 46	14 / 37	12 / 38	17 / 34			
Model 1 OR (95% CI)	1.00 (Reference)	1.26 (0.49, 3.27)	0.65 (0.24, 1.75)	2.15 (0.83, 5.54)	0.142	1.03 (0.99, 1.08)	0.137
Model 2 OR (95% CI)	1.00 (Reference)	1.24 (0.44, 3.46)	0.54 (0.18, 1.63)	1.71 (0.61, 4.80)	0.235	1.03 (0.99, 1.08)[b]	0.137
Model 3 OR (95% CI)	1.00 (Reference)	0.75 (0.24, 2.39)	0.55 (0.18, 1.73)	1.47 (0.49, 4.36)	0.420	1.04 (0.99, 1.09)[b]	0.115

Results shown for logistic regression analyses with outcome cognitive impairment. *p*-value for trend (2-sided) based on the respective median within quartiles, used as a continuous variable, and analyzed using the Wald chi^2 statistic. CI, confidence interval; OR, odds ratio

[a]results largely unchanged following exclusion of $N = 1$ outlier with high TG levels (28.9 mmol/L)

[b]in these models, HDL-C was significantly associated with cognitive impairment (Model 2: OR 0.27, 95% CI 0.09, 0.79, $p = 0.016$; Model 3: OR 0.28, 95% CI 0.09, 0.83, $p = 0.022$; for TG and BMI, all $p > 0.05$ in these models)

Model 1: adjusted for age, sex, smoking

Model 2: Model 1 + TG quartiles, HDL-C quartiles, BMI quartiles, glucose quartiles (for quartile analyses) or Model 1 + TG, HDL-C, BMI and glucose (for continuous parameters) (analysis $N = 202$), or for HbA1c: Model 1 + TG quartiles, HDL-C quartiles, BMI quartiles (for HbA1c quartile analyses) or Model 1 + TG, HDL-C and BMI (for analysis of HbA1c as continuous parameter) (analysis $N = 155$)

Model 3: Model 2 + CHD, TIA, stroke

frailty [25], and previous studies of dyslipidemia in older age and cognitive impairment have produced mixed results. Null findings for diagnosed dyslipidemia [26] and for levels of total cholesterol [9], HDL-C [27] and TG [27, 28] are contrasted with studies showing an increased risk of cognitive impairment in people with low HDL-C [29, 30] or elevated TG in later life [31, 32]. Here, our data suggest a contribution of low HDL-C to cognitive impairment that

Table 4 MetS, each of the 5 MetS components and odds of cognitive impairment

	Model 1		Model 2		Model 3	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Metabolic syndrome	1.38 (0.74, 2.60)	0.310	–	–	1.25 (0.65, 2.42)	0.503
Obesity	1.07 (0.52, 2.23)	0.852	1.00 (0.46, 2.17)	0.997	1.08 (0.48, 2.43)	0.845
Elevated triglycerides	2.09 (1.08, 4.05)	0.028	2.23 (1.07, 4.65)	0.033	1.86 (0.87, 4.00)	0.110
Reduced high-density lipoprotein	1.19 (0.63, 2.23)	0.600	0.86 (0.42, 1.77)	0.691	0.87 (0.41, 1.82)	0.704
Elevated blood pressure	1.11 (0.60, 2.07)	0.740	1.04 (0.54, 2.00)	0.911	0.86 (0.44, 1.71)	0.668
Elevated glucose	1.12 (0.60, 2.08)	0.721	0.98 (0.51, 1.88)	0.948	1.09 (0.55, 2.14)	0.811

Results shown for logistic regression analyses for odds of cognitive impairment. CI, confidence interval; OR, odds ratio. For definitions of metabolic syndrome components, see Table 1. Model 1: separate models associated each exposure variable with cognitive impairment with adjustment for age, sex and smoking ($N = 202$). Model 2: single model including age, sex, smoking, obesity, elevated TG, reduced HDL-C, elevated blood pressure, elevated glucose ($N = 202$). Model 3: single model including age, sex, smoking, obesity, elevated TG, reduced HDL-C, elevated blood pressure, elevated glucose, CHD, TIA, stroke ($N = 200$). Model 3 is a separate model for MetS. Results largely unchanged following exclusion of $N = 1$ outlier with high TG levels (28.9 mmol/L)

could indicate a causal relationship. Indeed, HDL-C has vasoprotective and anti-inflammatory properties [33] so that reduced inflammation could be a plausible mediator of the association in our sample. TG levels correlate with atherogenic and pro-inflammatory triglyceride-rich lipoproteins (TRL) [34] which may directly promote cognitive impairment. Our findings also suggest a contribution of macrovascular disease to the association of elevated TG with cognitive impairment. Cerebrovascular disease could be a mediator in the relationship, for instance. We are unable to determine this from the present study. Nonetheless, irrespective of the issue of causality and mediatory processes, elevated TG and HDL-C both appear to be useful risk markers with potential for utility in clinical settings and could contribute to screening tool development.

The disparate findings on HDL-C as a continuous metabolic parameter versus the dichotomized MetS component 'reduced HDL-C' suggest that the latter at-risk group may not necessarily be well-captured by the standardized, sex-specific cut-off points that are currently in use [15]. Their reevaluation and update, including determination whether sex-specific cut-offs are necessary, may be warranted. We found no significant association when we used TG as a continuous variable or as quartiles in our analysis. In contrast, when based on the standardized cut-off point [15], elevated TG were significantly associated with cognitive impairment at least in largely unadjusted analyses, suggesting that this threshold is appropriate for cognitive risk prediction. Nevertheless, given the relatively small sample size, the results of our analysis need to be interpreted cautiously and require replication in larger samples.

Previous epidemiological research has consistently implicated hyperglycemia as detrimental to cognition. Irrespective of whether measured at midlife or later life, diabetes, pre-diabetes [35–37], and poorer glycemic control in people with diabetes [37] have been linked to increased risk of vascular-type impairment as well as Alzheimer's disease [38]. Neurotoxic effects of glucose on the brain [39] and hyperglycemia-induced vascular damage [40] which appear to generate vascular impairment as well as facilitate neurodegeneration characteristic of Alzheimer's disease [41] have been suggested as underlying the relationship. In our sample, we found evidence for a more complex role of glucose in cognitive impairment that became apparent only in quartile analyses and was not supported by analyses of HbA1c as an index of long-term glycemic control. The marginally significant result could thus reflect Type I error. The fact

Table 5 Number of MetS components and odds of cognitive impairment

Number of components	Model 1		Model 2	
	OR (95% CI)	*p*	OR (95% CI)	*p*
0	1.00 (Reference)[a]	–	1.00 (Reference)[b]	–
1	0.36 (0.11, 1.15)[a]	0.084	0.29 (0.09, 0.95)[b]	0.041
2	1.02 (0.38, 2.77)[a]	0.965	0.93 (0.34, 2.52)[b]	0.878
3	0.94 (0.32, 2.77)[a]	0.902	0.76 (0.26, 2.28)[b]	0.629
4/5[c]	1.23 (0.40, 3.77)[a]	0.713	0.99 (0.31, 3.12)[b]	0.982
Number of components (continuous)[d]	1.16 (0.92, 1.45)	0.212	1.11 (0.88, 1.41)	0.387

Model 1: adjusted for age, sex and smoking ($N = 202$). Model 2: adjusted for age, sex, smoking, CHD, TIA, stroke ($N = 200$)
[a]single model; [b]single model
[c]due to small N in each, groups with 4 or 5 components were merged in this analysis
[d]range 0 to 5

that – for consistency with standard definitions of MetS [15] – diagnosis of diabetes qualified for inclusion in the 'elevated glucose' group, may also have 'diluted' that group leading to non-significant results. Alternatively, the standardized cut-off point for 'elevated glucose' [15] may not be appropriate for our sample of surgical patients who may have had extended periods of fasting prior to blood collection or for whom fasting status may not have been recorded with sufficient rigor. The high prevalence of 'elevated glucose' (61.9%, albeit as aforementioned this included participants with diabetes) supports the latter possibility. The precise role of glucose in cognitive impairment thus remains to be explored further.

The evidence for obesity in older age as a risk factor for cognitive impairment is limited [8] with occasional implication of overweight, obesity and elevated waist circumference as protective factors [29, 42, 43]. Here, obesity and BMI both were not related to cognition. At the lower end of the body weight spectrum, the relationship may be affected by frailty [25] but results on obesity and BMI did not change when underweight participants were excluded from our analysis or when quadratic terms were added into the model. Elevated blood pressure, too, was unrelated to cognitive impairment contrasting with some other cross-sectional and longitudinal studies of older adults [22].

Previous studies of the MetS construct and cognitive impairment have occasionally produced null results similar to our own [44, 45]. However, others did report associations with impairment [7, 29, 30, 46, 47]. For instance, in the Singapore Longitudinal Ageing Study, participants with MetS were at 1.46-fold increased risk of mild cognitive impairment (MCI) during 6-year follow-up [7]. In the French Three-City Study of more than 7000 older adults, MetS – in line with its status as a vascular risk factor – was selectively associated with a 2.42-fold increased risk of impairment of vascular origin [29]. Finally, women with MetS were at 2.47-fold increased risk of poor memory 12 years later in a Finnish investigation [30] and a pooled analysis of three studies reported that MetS was overall associated with 2.95-fold increased risk of progression from MCI to dementia [48]. The Finnish study [30] and some others [49] additionally reported a linear relationship of the number of MetS components with cognitive risk, but we and others [29, 47] found no such evidence. Disparity of our results from previous studies could stem from our slightly modified definition of MetS, the cross-sectional study design, the surgical nature of our sample, and the high prevalence of MetS (35.6%) compared with those studies (12.9% [30]; 15.8% [29]; 22.4% [7]) but is in line with a recent systematic review of 25 studies which concluded that the evidence on associations of MetS with cognitive impairment in older age is insufficient at present [49]. A recent report of accumulation of beta amyloid in the brains of people with MetS [50] demonstrate the need for further research into the cognitive and neuropathological consequences of the syndrome.

Each MetS component (except obesity) can be modified through pharmaceutical treatment and the potential benefit of concurrent tackling of several components is being increasingly recognized. Thus, the ACCORD-MIND trial recently tested the effect of antidiabetic, lipid lowering and blood pressure lowering therapy, in a double 2×2 factorial design; however, neither improved glycemic control [51], nor improved lipid levels or blood pressure [52] affected the rate of cognitive decline during 40-month follow-up, suggesting that the epidemiological evidence linking elevated glucose, dyslipidemia and elevated blood pressure to cognitive impairment may be confounded. Further similarly complex trials are needed for clarification of the effects of strategic targeting of different metabolic parameters, as well as benefits of concurrent treatment, on cognitive risk.

Strengths of our study include a multi-center design and the use of a comprehensive cognitive test battery that was validated through comparison with an instrument commonly used to assess cognitive status. Consideration of several metabolic parameters in a single analysis was able to evaluate relative independence of each from one another in their relationship with cognition. Thus far the 5 MetS components have mainly been investigated in isolation. Only a few studies directly compared the components in terms of their association with cognitive risk and had implicated low HDL-C [30], elevated TG [29], hypertension [46] and, most frequently, hyperglycemia [26, 44] as independent risk markers. However, some limitations need to be considered. Surgical patients are at risk of developing post-operative cognitive impairment [53] and so are of special interest in terms of their cognitive status. To our knowledge the present study is the first to assess MetS and cognitive impairment in this type of sample. At the same time, the focus on surgical patients as well as self-selection bias preventing unwell patients to enroll limits the generalizability of our findings to the general population that includes healthy, community-dwelling individuals. Further, we used BMI as a proxy for central obesity [12] though strictly speaking central obesity can only be determined through direct measurement. We also did not consider MetS-related complications such as retinopathy in our analysis. The possibility of confounding of our statistically significant findings by unmeasured factors such as diet or physical activity, too, remains. Because 'cognitive impairment' was defined from a cognitive summary score, our results are not

necessarily comparable to studies that used standardized constructs such as MCI. Due to the cross-sectional study design we were unable to evaluate participants' metabolic function during the decades prior to enrolment and did not consider anti-hyperglycemic, anti-hypertensive and lipid-lowering treatment in our analysis. Associations of elevated blood pressure with cognitive impairment may thus have become apparent had we controlled for or stratified by treatment. We deem confounding of our findings on HDL-C by anti-dyslipidemia drugs unlikely given the balance of epidemiological and trial evidence which suggests a limited role of drugs such as statins or fibrates in cognitive decline [54–56]. In any event, the fact that we observed associations of HDL-C with cognitive impairment despite lacking data on treatment indicates that the underlying processes may be mechanistic and dose-dependent on lipid concentrations irrespective of whether they are treated. Finally, our sample was relatively small and so the fact that we did not find significant associations for some of the MetS components does not rule out that studies with larger sample size may be able to detect smaller effects. Further prospective, epidemiological studies comparing the contributions of each of the 5 components to cognitive risk are needed and should take advantage of a range of different types of samples to gain a full understanding of any sample-specific relationships of MetS with cognitive impairment. Researchers should additionally consider analysis of inflammatory markers, which may interact with MetS in determining cognitive outcome [57], as well as pre-morbid cognitive ability (which affects both cognitive ability and metabolic risk in older age [58]) to explore mediation and confounding.

In conclusion, in this cross-sectional analysis of older adults who were all free of clinical dementia and scheduled to undergo surgery, lower HDL-C and elevated TG were each associated with presence of cognitive impairment defined as reduced cognitive performance relative to the total sample. For HDL-C, but not for elevated TG, the finding was independent of age, sex, smoking, the remaining parameters of metabolic dysfunction, as well as of macrovascular disease. This suggests potential for a causal relationship. The MetS construct per se was not associated with cognition. Prospective studies should compare the cognitive risk associated with different parameters of metabolic dysfunction in view to identify at-risk individuals and to shed light on underlying pathophysiological mechanisms considering that the evidence for metabolic parameters as effective targets for intervention is currently limited.

Abbreviations

BMI: Body mass index; BP: Blood pressure; CHD: Coronary heart disease; HbA1c: Glycated hemoglobin; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; MCI: Mild cognitive impairment; MetS: Metabolic syndrome; TG: Triglycerides; TIA: Transient ischemic attack

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Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to threats to subject privacy but are available from the corresponding author on reasonable request.

Authors' contributions

Study concept and design: AS, GW, CS, TP. Data collection: DH, JJ, IF. Statistical analysis and interpretation: IF. Drafting of initial manuscript: TP, IF. Review of manuscript for critical intellectual content: IF, JJ, DH, AS, GW, CS, TP. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was conducted in compliance with the Declaration of Helsinki. All participants gave written informed consent. The study protocol was approved by the institutional ethics review boards (Ethikkommission, Ethikausschuss 2 am Campus Virchow-Klinikum, Charité Universitatsmedizin Berlin, Reference EA2/092/14; Medisch Ethische Toetsingscommissie, UMC Utrecht, Reference 14/469).

Consent for publication

Not applicable.

Competing interests

GW is coordinator of the BioCog consortium and is chief executive of the company Pharmaimage Biomarker Solutions GmbH (http://www.pi-pharmaimage.com). Among other academic and private partners, the company is a partner of the BioCog study. CS and TP are project leaders in BioCog. CS, TP, AS, JJ, DH and IF declare that they have no conflicts of interest related to this article.

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In another cross-sectional analysis, we assessed the relationship of dichotomous conventional metabolic parameters (MetS, obesity, dyslipidemia, hyperglycemia, hypertenion) and their continuous counterparts (BMI, triglycerides, HDL, glucose, HbA1c, blood pressure) with ACI using baseline (pre-surgery) data from an interim sample of the BioCog study of older surgical patients. BioCog is a multi-center cohort established in 2014 with recruitment of 1033 surgical patients aged ≥65 years at three study sites in Utrecht, the Netherlands, and Berlin, Germany [139]. Aim of the study was to develop prediction models for POD and POCD. Here, we used the first 202 participants (age range 65 to 87) with complete data on conventional metabolic parameters and baseline cognitive testing. MetS was defined in accordance with the consensus definition [52] with the exception that "central obesity" was substituted by "obesity" defined as BMI≥30kg/m^2 (waist circumference was not measured). ACI was defined relative to the total sample as the lowest tertile of a global ability score calculated from performance on 6 age-sensitive cognitive tests [140] using principal component analysis (PCA) [141]. The ACI outcome thus captured those participants who had lower global cognitive ability relative to their peers.

35.6% of patients had MetS. Among the 5 MetS components, "elevated triglycerides" was the only parameter significantly associated with ACI in a model controlling for age, sex, smoking and the remaining 4 individual MetS components. However, the finding was rendered statistically non-significant when macrovascular disease including a history of stroke and transient ischemic attack was controlled for. HDL cholesterol was inversely associated with ACI such that higher quartiles of the HDL distribution were at reduced odds of ACI even in the fully adjusted model; though on this occasion, analyses were not adjusted for education as a proxy for pre-morbid IQ to preserve analysis N (a large proportion of data on education were missing). The binary MetS variable, "number of MetS components" (range 0 to 5), BMI, HbA1c, glucose and triglyceride levels were each not associated with ACI even with minimal adjustment.

In sum, we were not able to replicate our finding from the 3 RCTs showing an association of a higher BMI with increased odds of ACI, but instead implicated dyslipidemia (which was not measured in the 3 RCTs) as increasing the odds of ACI. Up to this point, we had only used conventional metabolic dysfunction parameters and so next used the BioCog study to additionally determine the relationship of ACI with metabolic dysfunction when measured by circulating adipokine concentration.

2.1.3 Adipokines and ACI in BioCog

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Plasma leptin, but not adiponectin, is associated with cognitive impairment in older adults

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ABSTRACT

Background: Leptin and adiponectin are adipose-tissue derived hormones primarily involved in glucose, lipid, and energy metabolism, inflammation, and atherosclerosis. Both adipokines may cross the blood-brain barrier but evidence on their roles in cognitive impairment is limited and conflicting. Here, we determined associations of plasma adipokine concentration with cognitive impairment in older adults.

Methods: Cross-sectional analysis of baseline data from 669 participants aged ≥65 years of the Biomarker Development for Postoperative Cognitive Impairment in the Elderly (BioCog) study were recruited 2014–2017 at study sites in Berlin, Germany and Utrecht, the Netherlands. Cognitive impairment was defined as the lowest tertile of a cognitive summary score derived from six neuropsychological tests.

Results: After adjustment for age, sex, fasting, BMI, diabetes, hypertension, cerebrovascular disease, and coronary heart disease, higher leptin concentrations and a higher leptin/adiponectin ratio (LAR) were associated with a higher odds of cognitive impairment (OR per 1 SD higher leptin concentration, 1.33; 95 % CI 1.05, 1.69; p = 0.02; OR per 1 SD higher LAR, 1.26; 95 % CI 1.01, 1.57; p = 0.04). Sensitivity analyses determined that these findings were driven by the non-obese group (BMI < 30 kg/m^2), whereas leptin and LAR were not associated with cognitive impairment in the obese group (BMI ≥ 30 kg/m^2). Soluble leptin receptor, leptin/soluble leptin receptor ratio, total adiponectin and high-molecular weight adiponectin concentrations were each not associated with impairment.

Conclusions: With leptin as a known promoter of atherosclerosis and inflammation, our findings point to a pathogenic role of leptin in age-related cognitive impairment that may be limited to non-obese individuals and warrants further investigation.

1. Introduction

The adipokines leptin and adiponectin are secreted by adipocytes and contribute to metabolic homeostasis (Grassmann et al., 2017; Lopez-Jaramillo et al., 2014; Nimptsch et al., 2019; Stern et al., 2016) but have opposing effects on vascular function and inflammation. Leptin (which circulates at levels proportional to adipose tissue mass and is thus a signal for adiposity (McGuire and Ishii, 2016)) promotes atherosclerosis, endothelial dysfunction and inflammation. In contrast, adiponectin (which circulates at levels inverse to adipose tissue mass (Aleksandrova et al., 2018)) has vascular health-promoting, anti-inflammatory and insulin-sensitizing properties (Grassmann et al., 2017; Nimptsch et al., 2019). Both adipokines may cross the blood-brain barrier (BBB) (Adya et al., 2015; Bloemer et al., 2018) (though the evidence on adiponectin is conflicting (Forny-Germano et al., 2018)), and may influence cerebrovascular function and neuroinflammation (Adya et al., 2015; Forny-Germano et al., 2018). Effects of leptin and adiponectin on the pathogenesis of cognitive impairment could thus be

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expected. Nonetheless, epidemiological investigations on their associations with cognition are often limited by small sample size and a focus on patient populations (Gustafson et al., 2015; Labad et al., 2012), children (Buck et al., 2019; Li et al., 2019) or younger adults (Bove et al., 2013) and they have produced mixed results (e.g., Albala et al., 2016; Bednarska-Makaruk et al., 2017; Bove et al., 2013; Cezaretto et al., 2018; Gilbert et al., 2018; Gunstad et al., 2008; Gustafson et al., 2012, 2015; Holden et al., 2009; Kitagawa et al., 2016; Labad et al., 2012; Lieb et al., 2009; Oania and McEvoy, 2015; Sang et al., 2018; Warren et al., 2012). For instance, reports of an inverse relationship of leptin concentration with cognitive function (Gunstad et al., 2008; Gustafson et al., 2015; Labad et al., 2012 Gorska-Ciebiada et al., 2016) are contrasted with studies implicating higher leptin concentration or higher leptin bioavailability (indicated by lower levels of its soluble receptor, sOB-R; (Gruzdeva et al., 2019)) in reducing cognitive risk (Albala et al., 2016; Gilbert et al., 2018; Holden et al., 2009; Khemka et al., 2014; Lieb et al., 2009; Yin et al., 2018) as well as null results (Bednarska-Makaruk et al., 2017). Similarly, whereas some reported a positive correlation of adiponectin with cognitive test performance (Cezaretto et al., 2018; Teixeira et al., 2013), others found a higher adiponectin concentration in patients with dementia compared with healthy or less severely impaired controls (Bednarska-Makaruk et al., 2017; Gilbert et al., 2018; Khemka et al., 2014) or inverse associations with cognitive function (Sanz et al., 2019).

Of note, adiponectin occurs in trimer, hexamer, and multimeric (high–molecular weight, HMW) form of which the latter appears to be biologically particularly active (Aso et al., 2006). Only a few studies have measured HMW adiponectin (Arnoldussen et al., 2018; Gustafson et al., 2015; Kitagawa et al., 2016) but surprisingly found no association with cognition despite the fact that adiponectin-induced improvement in cerebrovascular function and neuroinflammation would likely depend on the biological activity of the compound. Clarification of the roles of total versus HMW adiponectin in cognition is therefore needed.

Here, our goal was to determine the associations of leptin and its receptor, and of total and HMW adiponectin with cognitive impairment in a large sample of older adults. To operationalize the antagonistic effects of leptin and adiponectin, we additionally calculated the leptin/adiponectin ratio as an 'atherosclerotic index' that has previously been shown to correlate with metabolic health (Finucane et al., 2009) and health outcomes (Park et al., 2013) as well as the leptin/sOB-R ratio as an index of free, unbound leptin in circulation (Herrick et al., 2016).

2. Materials and methods

2.1. Study design

We used a cross-sectional study design based on data from the Biomarker Development for Postoperative Cognitive Impairment in the Elderly (BioCog) study, an observational study on post-operative cognitive impairment. The full study protocol has been reported elsewhere (Winterer et al., 2018). In brief, BioCog recruited 1033 participants in Berlin, Germany, and Utrecht, the Netherlands, who were ≥65 years old, scheduled for elective surgery of any type (expected duration ≥60 min), were Caucasian, free of clinical dementia (Mini Mental State Examination, MMSE ≥ 24 (Folstein et al., 1975)), and had no history of neuropsychiatric disease or addiction disorder. Only baseline data collected during the days before surgery were used.

2.2. Ethical consideration

The BioCog study has full institutional ethical approval at Charité Universitätsmedizin Berlin (EA2/092/14) and UMC Utrecht (No. 14-469), and is registered on clinicaltrials.gov (NCT02265263). Assessments complied with the Declaration of Helsinki and participants provided informed consent.

2.3. Clinical assessment

Sociodemographic data and medical history including history of hypertension, diabetes, coronary heart disease (CHD), transient ischemic attack (TIA) and stroke were ascertained using a combination of self-report and clinical records. Current smoking and level of education were self-reported. Height and weight were measured to derive body mass index (BMI). Obesity was defined as BMI ≥ 30 kg/m^2. Underweight was defined as BMI < 18.5 kg/m^2 (NCD Risk Factor Collaboration, 2016).

2.4. Adipokine measurement

Blood was collected on the day of surgery in a supine position, following an overnight fast and before incision, and was centrifuged after 30 − 40 min at room temperature at 2500 x g for 10 min to obtain serum. Plasma was collected into ethylenediaminetetraacetic acid (EDTA) tubes which were placed on a rocking mixer for at least 30 s for anticoagulation and was centrifuged at 2500 x g for 10 min. Samples were frozen at -80 °C, and following a single thaw/refreeze cycle, were shipped from a central coordinating lab to analysis laboratories for measurement of leptin and receptor (sOB-R) and of total adiponectin and HMW adiponectin from plasma. For logistical reasons, leptin and sOB-R were measured at two laboratories (37 % of samples at Lab 1; 63 % at Lab 2). Allocation of samples to labs was unrelated to study site, outcome or any other potentially confounding factor. The first sets of samples arriving at the central lab were allocated to Lab 1 and later samples to Lab 2. Both labs used identical ELISA kits (BioVendor GmbH, catalogue # RD191001100 for leptin; catalogue # RD194002100 for sOB-R). Total and HMW adiponectin were measured at a single laboratory (Lab 2) using a kit manufactured by Alpco (Salem, USA; catalogue # 47-ADPHU-E01). Assays were performed according to the manufacturers' protocols. Mean intra-assay coefficients of variation (CV) for pool plasma (controls) were 6.43 % for total adiponectin and 7.41 % for HMW adiponectin; inter-assay CV were 12.51 % and 14.09 % respectively. Mean intra-assay CV were 3.39 % (Lab 1) and 2.45 % (Lab 2) for leptin, and 4.81 % (Lab 1) and 3.63 % (Lab 2) for sOB-R. Inter-assay CVs were 11.03 % (Lab 1) and 2.63 % (Lab 2) for leptin and 4.76 % (Lab 1) and 4.28 % (Lab 2) for sOB-R. Measurements which were below or above the limits of quantification were set as the respective lower or upper limit of quantification (leptin, n = 22; sOB-R, n = 6; HMW adiponectin, n = 1 across both labs). For a small number of samples, Lab 2 additionally produced values that were outside of the limits of quantification (leptin, n = 22; total adiponectin, n = 2; sOB-R, n = 1). These were included as those measured values for the purpose of this analysis. We derived the leptin/adiponectin ratio (LAR) and the leptin/sOB-R ratio (free leptin index; FLI). Additionally, plasma C-reactive protein (CRP) and interleukin-6 (IL-6) were measured.

2.5. Cognitive examination

Participants performed six age-sensitive neuropsychological tests tapping the domains of processing speed, executive function and verbal and non-verbal memory during the days before surgery. Four tests (Paired Associates Learning; Verbal Recognition Memory; Spatial Span; Simple Reaction Time) were from the Cambridge Neuropsychological Test Automated Battery (CANTAB®; Cambridge Cognition Ltd.) and two were conventional tests (Grooved Pegboard; Trail-Making Test-B). From performance on those six tests, the latent '*g*' factor was calculated as an index of participants' global cognitive ability (Spearman, 1904) as reported in detail elsewhere (Feinkohl et al., 2019). Use of *g* is advantageous, because it reflects only the variance shared by all six cognitive tests; thus it is immune to test-specific measurement error and so interpretations of analyses based on *g* may have higher reliability compared with analyses of observed test scores (Penke and Deary, 2010). *G* is a standardized score with mean 0 and standard deviation 1

in the total sample. Here, we defined cognitive impairment as the lowest *g* tertile. We have previously cross-validated this definition of cognitive impairment with the more commonly used cognitive screening instrument Mini-Mental State Examination (MMSE) (Folstein et al., 1975) by showing that MMSE scores were lower in the lowest *g* tertile compared with the upper tertiles (Feinkohl et al., 2019).

2.6. Statistical analysis

669 participants had complete data on sociodemographic and cognitive parameters, and on leptin and HMW adiponectin, and provided our analysis sample. Data on total adiponectin were missing for n = 1 and on sOB-R for n = 25 participants.

Participants were divided into quartiles based on the distribution of each adipokine. Characteristics were compared across quartiles using analyses of variance (ANOVA) for continuous variables and chi^2 tests for categorical variables. The associations of each adipokine with one another and with age and BMI were examined in univariate Spearman rank correlation analyses.

Multiple logistic regression analyses determined the association of quartiles of each adipokine with the odds of cognitive impairment using the lowest quartile as the reference category. In addition, we estimated the odds ratio associated with a 1 standard deviation higher adipokine concentration on a continuous scale. In the respective first model (Model 1) we adjusted for age, sex, fasting status and (for analyses of leptin, sOB-R, LAR, FLI) for analysis lab. Model 2 additionally adjusted for BMI, diabetes, hypertension, CHD, TIA and stroke. To test for non-linearity, we subsequently added quadratic terms to the multivariable models (Model 2) of adipokines as continuous parameters. Finally, multivariate models (Model 2) of continuous adipokines were repeated with additional adjustment for CRP, IL-6, education and smoking, and, separately, with exclusion of underweight participants. For those adipokine exposures with statistically significant results in Model 2, multiple linear regression analyses additionally explored their associations with scores on the six individual cognitive tests used to generate *g*.

In post-hoc analyses, we repeated all multivariable models (Model 2) associating continuous adipokines with odds of cognitive impairment stratified by obesity status (BMI $<$ 30 versus $\geq 30\,kg/m^2$), and across the total sample tested for effect modification by including interaction terms (adipokine x BMI). In cases where information was missing on a covariate, we assigned the respective covariate as 'absent' (hypertension, n = 13; diabetes, n = 13; stroke, n = 16; CHD, n = 18; TIA, n = 19; smoking n = 16). Missing data on CRP were replaced by the median of the distribution (n = 6). Missing data on education were not imputed (n = 53). Data on all remaining variables were complete.

3. Results

3.1. Sample characteristics

Participants were aged between 65 and 90 years (mean 72.2 $\pm$ 4.9 years) and ten participants were not fasted. Those with high leptin concentrations as compared to those with low concentrations had higher BMI, were more likely to have a history of hypertension and diabetes, and less likely to be male and to have a history of CHD (Table 1). Participants with high as compared to those with low adiponectin concentrations had a lower BMI, were older, less likely to be male, and less likely to have a history of hypertension, diabetes, and CHD (Table 2). The covariate structure according to quartiles of sOB-R and HMW adiponectin is shown in Supplemental Tables S1 and S2.

In correlation analyses, leptin concentrations were positively correlated to BMI and inversely associated with sOB-R (Table 3). sOB-R was inversely correlated to BMI, modestly positively correlated with total and HMW adiponectin, and weakly positively correlated with age. Total and HMW adiponectin were inversely correlated with BMI and weakly positively associated with age. Total adiponectin was highly correlated with HMW adiponectin.

3.2. Adipokines and cognitive impairment

In multiple logistic regression analyses, we found that higher quartiles of leptin and higher quartiles of LAR were each associated with higher odds of cognitive impairment (Table 4). The association for leptin but not for LAR remained following multivariable adjustment (Model 2). For instance, participants in the highest quartile of leptin concentration were at 2.9-fold increased odds of impairment relative to the lowest quartile (OR 2.86; 95 % CI 1.43, 5.72). Quartiles of sOB-R, total and HMW adiponectin, and FLI were unrelated to cognitive impairment throughout (Table 4).

Next we assessed the adipokines as continuous parameters in further multiple logistic regression analyses. Higher leptin concentration and higher LAR were each associated with increased odds of cognitive impairment (Table 4). Each standard deviation higher leptin and each standard deviation higher LAR were associated with 1.30-fold (OR 1.30; 95 % CI 1.07, 1.57) and 1.28-fold (OR 1.28; 95 % CI 1.07, 1.54) increased odds of cognitive impairment, respectively, with age, sex, fasting and analysis lab controlled for. In absolute numbers, each 1 ng/mL higher leptin concentration was associated with a 0.9 % higher odds of impairment (OR 1.01; 95 % CI 1.00, 1.02). These results were unchanged following multivariable adjustment in Model 2 (for leptin, OR per 1 standard deviation increment 1.33, 95 % CI 1.05, 1.69; for LAR, OR per 1 standard deviation increment in LAR 1.26, 95 % CI 1.01, 1.57). Addition of quadratic terms did not produce statistically significant estimates (quadratic term for leptin, $P = 0.11$; quadratic term for LAR, $P = 0.41$) indicating that non-linearity did not underlie the aforementioned associations. Quadratic terms for all of the remaining adipokines were also statistically non-significant (sOB-R, $P = 0.54$; total adiponectin, $P = 0.10$; HMW adiponectin, $P = 0.12$; FLI, $P = 0.07$).

Addition of CRP, IL-6, education and smoking into the respective Model 2, or exclusion of seven underweight participants, did not change any of the results (data not shown). Associations of leptin and LAR with cognitive impairment appeared to be driven by the timed tests of processing speed and executive function (Simple Reaction Time, Grooved Pegboard, Trail-Making Test-B), as trends were observed for higher leptin and higher LAR associated with slower performance on these tests (Supplemental Table S3).

3.3. Sensitivity analyses

BMI was not associated with cognitive impairment in any of the multivariable models presented above and in Table 5 (data not shown; all $P > 0.20$) and in analyses controlling only for age and sex (OR per 1 kg/m^2 increment 1.03; 95 % CI 0.99, 1.07; $P = 0.16$), but due to its close relationship with adipokine concentrations we explored a potential interaction of adipokines with BMI in determining odds of cognitive impairment. As a first step, the respective Model 2 with adipokines as continuous parameters were repeated separately for obese ($BMI \geq 30 kg/m^2$) and non-obese participants ($BMI < 30\,kg/m^2$; Table 5). In the non-obese group, higher leptin (OR per 1 standard deviation increment 2.09, 95 % CI 1.44, 3.02), higher LAR (OR per 1 standard deviation increment 1.72, 95 % CI 1.23, 2.41), lower sOB-R (OR per 1 standard deviation reduction 1.28, 95 % CI 1.01, 1.61) and higher FLI (OR per standard deviation increment 1.54, 95 % CI 1.03, 2.30) were each associated with higher odds of cognitive impairment. There were no findings for the obese group (all $P > 0.20$; Table 5). As a second step, we repeated the analyses across the total sample with addition of adipokine x BMI interaction terms. Differential relationships with cognitive impairment according to BMI were indicated by interaction terms for leptin (multivariable-adjusted $P = 0.002$), LAR (multivariable-adjusted $P = 0.03$) and FLI (multivariable-adjusted $P = 0.05$; Table 5).

Table 1
Characteristics of total study sample and by quartiles of leptin.

	Total sample	Leptin				*P*-value
		Quartile 1	Quartile 2	Quartile 3	Quartile 4	
N	669	166	164	174	165	
Leptin concentration, range, ng/mL	0.2–159.9	0.2 – 5.7	5.8 – 13.4	13.4 – 30.6	30.7 – 159.9	
Age, years, mean	72.2	72.7	71.9	72.2	71.8	0.33
Male sex, %	58.3 %	84.3	62.2	52.3	34.5	< 0.001
Body mass index, kg/m^2, mean	27.0	24.2	26.6	27.3	30.1	< 0.001
Hypertension, %	61.6	55.4	56.7	58.6	75.8	< 0.001
Diabetes, %	20.2	13.3	20.7	17.8	29.1	0.003
Coronary heart disease, %	18.4	25.3	18.9	14.9	14.5	0.04
Stroke, %	4.8	4.8	4.9	5.2	4.2	0.98
Transient ischemic attack, %	3.3	4.2	3.0	2.3	3.6	0.78
Cognitive impairment, %	33.3	22.0	23.4	23.8	30.2	0.06

Precise range is not shown due to rounding. N = 669. P-value for comparison among leptin quartiles in analyses of variance (ANOVA) or chi^2 tests.

4. Discussion

We found in a sample of older adults that higher levels of total (bound and unbound) leptin and a higher leptin/adiponectin ratio (LAR) were each associated with higher odds of being cognitively impaired. The associations were independent of sociodemographics, vascular risk factors, macrovascular disease and inflammation as well as BMI. Neither total nor HMW adiponectin alone were associated with impairment. Our data overall suggest that higher leptin concentrations are related to a higher odds of cognitive impairment, while they do not support the hypothesis that adiponectin concentrations are related to this outcome.

Metabolic dysregulation and obesity are candidate risk factors for age-related cognitive impairment (Pedditizi et al., 2016; Van den Berg et al., 2009), but fewer studies have evaluated adipokine concentrations as potential contributors to the relationship.

Previous investigations had reported a higher level of adiponectin as a correlate of higher cognitive function in middle-aged (Cezaretto et al., 2018) and older adults (Teixeira et al., 2013) and lower adiponectin in patients with mild cognitive impairment or Alzheimer's disease (AD) compared with controls (Teixeira et al., 2013;Gorska-Ciebiada et al., 2016). In direct contrast, others implied higher adiponectin as associated with presence ofcognitive impairment (Bednarska-Makaruk et al., 2017; Gilbert et al., 2018; Khemka et al., 2014 Sanz et al., 2019 Wennberg et al., 2016) . Here, we found no relationship of adiponectin with cognition even with minimal adjustment and are thus unable to resolve this inconsistency.

Higher circulating leptin had previously been associated with a reduced cognitive risk in a number of epidemiological investigations (Gilbert et al., 2018; Holden et al., 2009; Johnston et al., 2014; Khemka et al., 2014; Lieb et al., 2009; Littlejohns et al., 2015; Zeki Al Hazzouri et al., 2013;Yin et al., 2018). Such reports appear counterintuitive in the face of leptin as a promoter of atherosclerosis, endothelial dysfunction and inflammation, but can be explained by an additional role of leptin as a cognitive enhancer. Leptin receptors are expressed in several regions of the brain, where it not only acts as a satiety signal (Banks et al., 2006; Letra et al., 2014), but is also involved in neurogenesis and brain growth (Banks et al., 2006), the clearance of beta amyloid (a neuropathological hallmark of Alzheimer's disease) (Fewlass et al., 2004), and in hippocampal synaptic plasticity (Forny-Germano et al., 2018; McGregor and Harvey, 2018).

Yet, in our analysis, and in several other studies of older adults, higher leptin was associated with cognitive impairment (Gorska-Ciebiada et al., 2016; Gunstad et al., 2008; Labad et al., 2012). For instance, in male participants of the Edinburgh Type 2 Diabetes Study (ET2DS) after controlling for a range of covariates including age, BMI, waist-hip ratio, estimated pre-morbid cognitive ability, inflammation, vascular risk factors and macrovascular disease, higher plasma leptin was associated with a lower global cognitive function and with a poorer performance on a verbal fluency test and the Trail-Making Test-B as a measure of processing speed and executive function (Labad et al., 2012). Here, we observed a trend for poorer performance on this test as associated with higher leptin concentration albeit the trend fell short of statistical significance and was of smaller effect size compared with ET2DS results. In any event, associations of higher leptin with cognitive impairment are corroborated by reports of associations of higher leptin concentration with brain atrophy (Rajagopalan et al., 2013) and may reflect the aforementioned beneficial effects of leptin on brain function being outweighed by its effects on atherosclerosis, endothelial dysfunction and inflammation (Forny-Germano et al., 2018). Although in our analysis the association of leptin with cognitive impairment remained after adjustment for CRP and IL-6, speaking against mediation

Table 2
Characteristics of study participants by quartiles of total adiponectin.

	Total adiponectin				*P*-value
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
N	174	167	168	159	
Adiponectin concentration, range, ng/μL	2.7 – 9.0	9.1 – 12.7	12.8 – 18.0	18.0 – 61.1	
Age, years, mean	71.2	72.4	72.2	72.8	0.02
Male sex, %	70.1	60.5	54.2	47.2	< 0.001
Body mass index, kg/m^2, mean	28.1	27.6	27.2	25.2	< 0.001
Hypertension, %	68.4	64.1	59.5	53.5	0.04
Diabetes, %	28.7	28.1	13.7	9.4	< 0.001
Coronary heart disease, %	25.3	12.6	17.9	17.0	0.02
Stroke, %	4.0	6.6	4.2	4.4	0.66
Transient ischemic attack, %	4.0	1.8	4.2	3.1	0.60
Cognitive impairment, %	23.0	22.1	24.3	40.2	0.12

Precise range is not shown due to rounding. N = 668. P-value for analyses of variance (ANOVA) or chi^2 tests.

Table 3
Correlations among adipokines and of adipokines with age and body mass index.

	Age	Body mass index	Total adiponectin[2]	HMW adiponectin	sOB-R[1]
Leptin	−0.03 (0.44)	0.51 (< 0.001)	−0.07 (0.06)	−0.02 (0.60)	−0.50 (< 0.001)
sOB-R[1]	0.09 (0.02)	−0.43 (< 0.001)	0.23 (< 0.001)	0.28 (< 0.001)	–
HMW adiponectin	0.13 (0.001)	−0.24 (< 0.001)	0.77 (< 0.001)	–	–
Total adiponectin[2]	0.09 (0.02)	−0.24 (< 0.001)	–	–	–

HMW, high molecular weight; sOB-R, soluble leptin receptor.
Values are Spearman rank correlation coefficients (*P*-values). Analysis n = 669, except [1]n = 644 and [2]n = 668; analysis of total adiponectin and sOB-R,n = 643.

Table 4
Adjusted odds and 95 % CI of cognitive impairment for quartiles of adipokine concentration, and for continuous adipokine concentration.

h		Quartiles of plasma concentration					Continuously[3]	
		I	II	III	IV	P_{trend}	OR (95 % CI) per 1 SD increment	P_{OR}
Leptin	Model 1	1.0 (Ref)	1.34 (0.81, 2.20)	1.30 (0.77, 2.20)	2.58 (1.45, 4.58)	0.007	1.30 (1.07, 1.57)	0.009
	Model 2	1.0 (Ref)	1.35 (0.80, 2.28)	1.39 (0.80, 2.45)	2.86 (1.43, 5.72)	0.02	1.33 (1.05, 1.69)	0.02
sOB-R [1]	Model 1	1.0 (Ref)	0.95 (0.58, 1.54)	0.90 (0.55, 1.48)	0.83 (0.50, 1.37)	0.90	0.86 (0.71, 1.04)	0.12
	Model 2	1.0 (Ref)	0.94 (0.57, 1.54)	0.91 (0.54, 1.53)	0.85 (0.49, 1.49)	0.95	0.87 (0.71, 1.06)	0.17
Total adiponectin[2]	Model 1	1.0 (Ref)	0.98 (0.61, 1.56)	0.82 (0.51, 1.32)	0.88 (0.54, 1.42)	0.83	0.90 (0.75, 1.07)	0.21
	Model 2	1.0 (Ref)	0.97 (0.60, 1.56)	0.91 (0.56, 1.49)	1.05 (0.63, 1.75)	0.95	0.95 (0.79, 1.15)	0.61
HMW adiponectin	Model 1	1.0 (Ref)	0.67 (0.42, 1.07)	0.62 (0.39, 1.01)	0.76 (0.47, 1.24)	0.22	0.98 (0.82, 1.16)	0.80
	Model 2	1.0 (Ref)	0.69 (0.42, 1.11)	0.72 (0.44, 1.19)	0.95 (0.57, 1.59)	0.31	1.06 (0.88, 1.27)	0.55
FLI[1]	Model 1	1.0 (Ref)	1.30 (0.79, 2.14)	1.30 (0.77, 2.20)	1.83 (1.05, 3.19)	0.21	1.11 (0.93, 1.33)	0.24
	Model 2	1.0 (Ref)	1.32 (0.78, 2.22)	1.35 (0.77, 2.39)	1.93 (0.98, 3.81)	0.30	1.10 (0.90, 1.34)	0.37
LAR[2]	Model 1	1.0 (Ref)	0.94 (0.57, 1.53)	1.14 (0.69, 1.89)	1.86 (1.10, 3.16)	0.04	1.28 (1.07, 1.54)	0.008
	Model 2	1.0 (Ref)	0.88 (0.53, 1.47)	1.10 (0.63, 1.91)	1.76 (0.93, 3.33)	0.10	1.26 (1.01, 1.57)	0.04

BMI, body mass index; CI. confidence interval; FLI, free leptin index; HMW, high molecular weight; LAR, leptin/adiponectin ratio; SD, standard deviation; sOB-R, leptin receptor.
Analysis n = 669, except [1]n = 644 and [2]n = 668.
p-value for trend (two-sided) across quartiles is based on the median adipokine concentrations within quartiles, used as a continuous variable and analyzed using the Wald chi[2] statistic.
Model 1: adjusted for age, sex, fasting (and for leptin, sOB-R, FLI, LAR additionally for analysis lab).
Model 2: Model 1 + body mass index, diabetes, hypertension, stroke, transient ischemic attack, coronary heart disease.
[3]adipokines were standardized for these analyses, so that OR estimates show the change in odds of cognitive impairment for each SD increment in adipokine concentration.

of the relationship by inflammation, these markers were measured in peripheral blood and so may not have captured the degree of leptin-induced neuroinflammation in our participants. Macrovascular disease as another potential causal intermediate also did not contribute to the relationship though we measured only symptomatic macrovascular disease; thus subclinical atherosclerosis remains a potential mediator. Finally, cognitive reserve is a determinant both of leptin (Labad et al., 2012) and cognitive ability in older age (Opdebeeck et al., 2016), and an important potential confounder as a result. Here, we showed that the associations of leptin with cognitive impairment was independent of education as a proxy of cognitive reserve thus corroborating potential causal effects.

Several previous studies found that (in those cases, inverse) associations of leptin with 5- to 8-year cognitive risk were limited to non-obese (BMI < 30 kg/m^2) (Lieb et al., 2009) or non-overweight/obese individuals (BMI < 25 kg/m^2) (Zeki Al Hazzouri et al., 2013). Due to this and the close relationship of leptin and adiponectin with BMI, we not only controlled for BMI but had additionally included interaction

Table 5
Adjusted odds and 95 % CI of cognitive impairment stratified by obesity status, and results for adipokine x BMI interaction terms across total sample.

	Obese subgroup (BMI ≥ 30 kg/m^2)		Non-obese subgroup (BMI < 30 kg/m^2)		$P_{interaction}$
	OR (95 % CI) per 1 SD increment	*P*-value	OR (95 % CI) per 1 SD increment	*P*-value	
Leptin	0.87 (0.60, 1.26)	0.460	2.09 (1.44, 3.02)	< 0.001	0.002
sOB-R[1]	1.40 (0.76, 2.57)	0.284	0.78 (0.62, 0.99)	0.04	0.60
Total adiponectin[2]	0.85 (0.49, 1.49)	0.570	0.96 (0.78, 1.17)	0.65	0.30
HMW adiponectin	1.17 (0.66, 2.06)	0.597	1.04 (0.86, 1.27)	0.67	0.30
FLI[1]	0.90 (0.68, 1.19)	0.466	1.54 (1.03, 2.30)	0.03	0.05
LAR[2]	0.95 (0.67, 1.35)	0.761	1.72 (1.23, 2.41)	0.002	0.03

BMI, body mass index; CI, confidence interval; FLI, free leptin index; HMW, high molecular weight; LAR, leptin/adiponectin ratio; sOB-R, leptin receptor.
Analysis n = 669. Of these, n = 142 (21.1 %) in the 'obese' group and n = 527 (78.8 %) in the 'non-obese' group.
1Analysis n = 644. Of these, n = 137 (21.3 %) in the 'obese' group and n = 507 (78.7 %) in the 'non-obese' group.
[2]Analysis n = 668. Of these, 142 (21.3 %) in the 'obese' group and n = 526 (78.7 %) in the 'non-obese' group.
All analyses adjusted for age, sex, fasting (and for leptin, sOB-R, FLI, LAR additionally for analysis lab), body mass index, diabetes, hypertension, stroke, transient ischemic attack, coronary heart disease.
Adipokines were standardized, so that OR estimates show the change in odds of cognitive impairment for each SD increment in adipokine.
Interaction terms from analysis of (adipokine x body mass index) in separate logistic regression models of each adipokine and cognitive impairment in total sample.

terms and also stratified analyses by obesity status. Associations of leptin with cognitive impairment were restricted to non-obese individuals (BMI $< 30\ kg/m^2$), which further supports our interpretation of leptin as a direct promoter of cognitive impairment: leptin transport from circulation across the BBB is in fact compromised in obesity (Banks et al., 2006), which can account for obesity failing to induce satiety despite high circulating leptin (Banks et al., 2006) as well as for an attenuation of correlations of CSF with plasma leptin in obese relative to non-obese individuals (Johnston et al., 2014). We assume that in our sample participants in the non-obese group were exposed to a steadily increasing cognitive risk with higher circulating (and therefore brain) leptin concentration, whereas for obese individuals circulating leptin did not reflect leptin concentration in the brain, leading to null findings for that group. Alternatively, analyses of the obese group may have been limited by reduced statistical power due to low participant number, though on inspection of effect estimates combined with the statistical significance of the interaction terms, we deem this possibility unlikely. We urge readers to interpret the results from these subgroup analyses with caution nonetheless. Of note, BMI itself was unrelated to cognitive impairment in our analysis and in a previous investigation of a subsample of this cohort (Feinkohl et al., 2019) so that a recent report of leptin as a mediator of the relationship of higher BMI with lower cognitive function (Smith et al., 2019) was not supported by our data.

Irrespective of the role of leptin in the pathogenesis of cognitive impairment, we have demonstrated that it has potential as a biomarker of cognitive impairment and could be used for risk stratification of older adults. Measurement of total (bound and unbound) leptin appears to suffice for this purpose. Combined measurement with levels of its receptor or adiponectin did not add any valuable additional information over and above leptin.

4.1. Strengths and limitations

Our study has several strengths. We used a large sample of older adults who were all free of clinical dementia and defined cognitive impairment from performance on a large battery of cognitive tests using principal component analysis to account for measurement error. Yet, a number of limitations should be considered. Because we defined 'cognitive impairment' relative to the sample, we are unable to generalize our findings to clinically relevant cognitive outcomes such as dementia. Given that blood-based diagnostic biomarkers of dementia are lacked (Feinkohl et al., 2020; Hampel et al., 2010), further research is needed in that direction. We used a cross-sectional design and included only participants of the BioCog cohort who had complete data on adipokines and cognition. This will have introduced a selection bias; the analysis sample was unlikely representative of the full BioCog cohort. Because participants were scheduled for surgery within a few days of providing these data, our sample was presumably of a relatively low health status and unlikely representative of the general older population. At the same time, the surgical nature of the sample is also an asset to our study, because it allowed recruitment of patients who would otherwise not be enrolled into a study that required active travel to a study site. Leptin and sOB-R were measured in two different labs and although we controlled our analysis for this factor, residual confounding by analysis lab is a possibility. An influence by unmeasured variables too cannot be ruled out. We ran a large number of statistical analyses thus increasing the risk of Type I error.

4.2. Future directions

Further research is needed to tease out the beneficial versus detrimental effects of leptin on brain function. Separate investigation of obese and non-obese groups, or, in sufficiently large samples, of underweight, normal weight, overweight and obese groups is advisable. Long-term prospective studies could further account for reverse causality of prodromal dementia impacting on adipose tissue mass and, consequently, adipokine levels, which may also in part drive reports of reduced cognitive risk in high-leptin individuals in older age. Here, we used a surgical patient sample. Whether the association of higher leptin concentration with higher odds of cognitive impairment before surgery extends to an increased risk of post-operative cognitive dysfunction (POCD) remain to be explored.

5. Conclusion

In one of the largest studies on adipokine concentration and cognition performed to date, higher plasma leptin concentrations were associated with increased odds of cognitive impairment and independently of sociodemographics, vascular risk factors, macrovascular disease, inflammation, as well as BMI. Underlying mechanisms warrant further assessment.

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CRediT authorship contribution statement

Insa Feinkohl: Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing - original draft, Writing - review & editing. **Jürgen Janke:** Investigation, Methodology, Writing - review & editing. **Arjen J.C. Slooter:** Conceptualization, Funding acquisition, Methodology, Writing - review & editing. **Georg Winterer:** Conceptualization, Funding acquisition, Methodology, Writing - review & editing. **Claudia Spies:** Conceptualization, Funding acquisition, Methodology, Writing - review & editing. **Tobias Pischon:** Resources, Conceptualization, Funding acquisition, Methodology, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

GW is coordinator of the BioCog consortium and is chief executive of the company Pharmaimage Biomarker Solutions GmbH (http://www.pi-pharmaimage.com). Among other academic and private partners, the company is a partner of the BioCog study. CD, AS and TP are project leaders in BioCog. IF, JJ, AS, CS and TP declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2020.104783.

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The relationship of plasma adipokine concentration with ACI was assessed in a cross-sectional analysis of 669 participants of the full BioCog cohort with complete data. Leptin and adiponectin were measured and their ratio (LAR) was derived. ACI again was defined as the lowest tertile of a global ability factor derived from the 6 age-sensitive cognitive tests.

In analyses controlling for sociodemographics, macrovascular disease including stroke and TIA, and conventional metabolic parameters including BMI, a higher leptin concentration and higher LAR were each associated with increased odds of having ACI. For instance, participants in the highest quartile of leptin distribution were at almost 3-fold odds of ACI compared with the lowest tertile. Importantly, the finding also remained statistically significant following adjustment for inflammatory markers, smoking and pre-morbid IQ indexed by educational level. Post-hoc sensitivity analyses determined that the findings appeared to be specific to the non-obese group (BMI<30kg/m^2); within the obese group (BMI≥30 kg/m^2) leptin was not associated with ACI. No associations were found for adiponectin.

This investigation concluded our set of cross-sectional analyses on metabolic dysfunction and ACI using baseline, pre-surgery data from surgical samples. We next went on to determine the role of pre-surgery metabolic dysfunction in POCD risk in a prospective analysis of the 3 RCTs.

2.2 Metabolic dysfunction and POCD risk

Dementia
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Original Research Article

Diabetes, but Not Hypertension and Obesity, Is Associated with Postoperative Cognitive Dysfunction

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Keywords
Diabetes · Hypertension · Obesity · Postoperative cognitive dysfunction

Abstract
Background/Aims: Older people undergoing surgery are at risk of developing postoperative cognitive dysfunction (POCD), but little is known of risk factors predisposing patients to POCD. Our objective was to estimate the risk of POCD associated with exposure to preoperative diabetes, hypertension, and obesity. ***Methods:*** Original data from 3 randomised controlled trials (OCTOPUS, DECS, SuDoCo) were obtained for secondary analysis on diabetes, hypertension, baseline blood pressure, obesity (BMI ≥30 kg/m^2), and BMI as risk factors for POCD in multiple logistic regression models. Risk estimates were pooled across the 3 studies. ***Results:***

Gunnar Lachmann, Insa Feinkohl, Claudia Spies, and Tobias Pischon contributed equally to this work. Preliminary results of this study were presented at the Annual Meeting of the American Society of Anesthesiologists (ASA) in Boston, USA (October 2017), and at the Annual Meeting of the German Epidemiological Society (DGEpi) in Lübeck, Germany (September 2017).

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Analyses totalled 1,034 patients. POCD occurred in 5.2% of patients in DECS, in 9.4% in SuDoCo, and in 32.1% of patients in OCTOPUS. After adjustment for age, sex, surgery type, randomisation, obesity, and hypertension, diabetes was associated with a 1.84-fold increased risk of POCD (OR 1.84; 95% CI 1.14, 2.97; $p = 0.01$). Obesity, BMI, hypertension, and baseline blood pressure were each not associated with POCD in fully adjusted models (all $p > 0.05$). ***Conclusion:*** Diabetes, but not obesity or hypertension, is associated with increased POCD risk. Consideration of diabetes status may be helpful for risk assessment of surgical patients.

Introduction

Patients undergoing surgery are at risk of developing a postoperative neurocognitive disorder or postoperative cognitive dysfunction (POCD) – a condition that is defined by a decline in performance on neuropsychological tests from pre-surgery to post-surgery assessment. Large individual differences in POCD spanning cognitive recovery during the first few months to persistent cognitive impairment have been reported [1–5]. Although it has been the subject of extensive research during the past two decades, many questions remain unanswered, and a lack of uniform diagnostic criteria [6] and differences in length of follow-up period hamper comparability between studies. Little is currently known about potential risk factors, which help to identify at-risk patients and shed light on underlying pathophysiology. In recent systematic reviews and meta-analyses [7–10], we have shown that patients with metabolic derangement may be at an increased risk of POCD. Indicators of metabolic derangement include classical vascular risk factors such as elevated blood glucose, elevated blood pressure, and obesity, which all tend to correlate [11]. In line with its well-established role as a predictor of age-related cognitive impairment [12–16], we found in our meta-analysis that diabetes was associated with a 26% increased risk of POCD [8]. Findings were less clear for obesity [17], and hypertension was overall not associated with POCD [10]. However, studies included in those meta-analyses were largely exploratory and frequently failed to apply statistical adjustment for potential confounders, which is considered a major limitation. Detailed assessment of exposure to these candidate risk factors and subsequent risk of POCD on the basis of primary data is thus needed, particularly in view of their modifiable nature that leaves scope for risk alteration at individual patient level.

Here, we therefore aimed to estimate the risk of POCD associated with preoperative exposure to diabetes, hypertension, and obesity, with focus on potential mutual confounding among the risk factors in determining POCD risk. Data were provided by 3 large randomised controlled trials (RCTs) targeting factors and procedures potentially influencing POCD risk. In a secondary analysis of their primary data, we evaluated risk of POCD associated with each exposure of interest and additionally provide pooled risk estimates combined across the 3 studies.

Materials and Methods

Study Design

In a quasi-observational, secondary analysis of 3 studies, the Surgery Depth of Anaesthesia Cognitive Outcome (SuDoCo) [18], Dexamethasone for Cardiac Surgery (DECS) [19, 20], and OCTOPUS [21] studies, associations of exposure to diabetes, hypertension, and obesity with POCD risk were determined. None of the 3 studies had previously been used to investigate this research question. Access to their original data resulted from a cross-institutional collaboration.

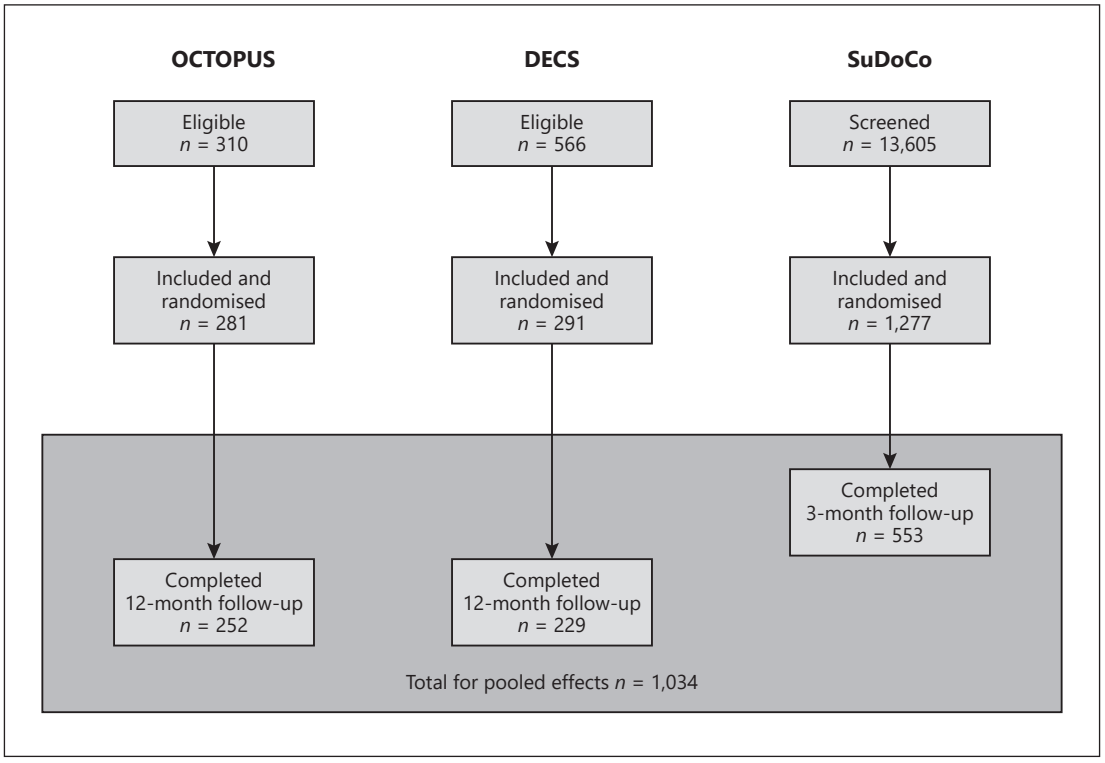

Fig. 1. Enrolment flow chart and data used for present analysis (grey).

Setting

All 3 studies were RCTs with primary or secondary outcome POCD. Each trial evaluated intervention effects (SuDoCo: monitoring depth of anaesthesia during general anaesthesia; DECS: dexamethasone administration versus placebo during cardiac surgery; OCTOPUS: on-pump versus off-pump methods for cardiac surgery) on POCD risk, and included repeat neuropsychological testing with several post-surgery follow-up assessments of which we analysed the respective longest follow-up period (OCTOPUS: 12 months; DECS: 12 months; SuDoCo: 3 months).

Participants

A total of 1,849 patients were enrolled in the 3 studies between 1998 and 2011. Recruitment procedures and inclusion and exclusion criteria have been described in detail previously [18, 20, 21]. In brief, any patients with pre-existing neurological deficits were excluded in all 3 studies; in SuDoCo, MMSE <24 was also an exclusion criterion, and in DECS, patients with diagnosed mental illness were additionally excluded. Follow-up assessments were completed by 1,034 patients (Fig. 1). Patient dropout between baseline and follow-up was mainly due to lack of interest and withdrawal of consent. Cognitive deficit after surgery was evaluated as either primary or secondary outcome in each of the 3 studies. Surgical procedures included cardiac (OCTOPUS; DECS) and non-cardiac surgery types (SuDoCo), and interventions compared different surgical techniques (on-pump vs. off-pump CABG in OCTOPUS), preoperative administration of intravenous dexamethasone in cardiac surgery (DECS), or intraoperative neuromonitoring (SuDoCo).

Physical Examination

Diabetes and a history of hypertension were routinely ascertained during pre-surgery interview and from medical records. Though we were unable to distinguish between type 1 and type 2 diabetes based on the data, we assume that a majority of patients with diabetes will have suffered from type 2 diabetes based on sample age. Baseline blood pressure, height, and weight were measured at pre-surgery assessment, and height and weight were used to derive body mass index (BMI). In accordance with convention [22], we

defined obesity as BMI ≥30 kg/m^2. A conservative cut-point of BMI <20 kg/m^2 identified underweight patients.

Cognitive Examination and Definition of POCD

Trained staff administered several age-sensitive neuropsychological tests tapping various cognitive domains (OCTOPUS: *n* = 11 tests; DECS: *n* = 5 tests; SuDoCo: *n* = 6 tests; online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000492962) to the respective patient samples and additionally to non-surgical control samples for normative data. For the purpose of this analysis, we used POCD as dichotomous outcome as it was defined in the respective original studies. This varied between studies. For DECS and SuDoCo, POCD was defined through comparison of the cognitive change of patients with the average cognitive change of the respective control group; for OCTOPUS, POCD was determined from raw change in cognitive test scores (online suppl. Table 1).

Statistical Methods

Exposures of interest were the presence versus absence of diabetes, hypertension, and obesity, respectively. In addition, we also analysed BMI and systolic and diastolic baseline blood pressure. Outcome was POCD at the longest follow-up assessment in each cohort. A two-step approach was used to analyse exposure-outcome relationships [23, 24]. Initially, risk of POCD according to exposure to diabetes, hypertension, obesity, BMI, systolic blood pressure, and diastolic blood pressure was assessed separately for each of the 3 studies. We used logistic regression analyses with hierarchical model building: model 0 includes unadjusted associations, model 1 includes age and sex as covariates, model 2 additionally includes type of surgery and RCT treatment group, and model 3 additionally includes all of the respective remaining predictor variables (of diabetes, obesity, hypertension) to analyse potential mutual confounding. Baseline blood pressure and BMI were not included as covariates in model 3 to avoid collinearity as these variables contributed to the definition of "hypertension" and "obesity," respectively. For OCTOPUS and DECS, we also adjusted for education in models 2 and 3 but present data without that adjustment to allow cross-study comparison, as in SuDoCo, information on education was not available. Odds ratios (OR) are provided for 1-point increments in BMI and 10-point increments in baseline blood pressure values to aid interpretability of risk estimates.

In a second step, risk estimates were pooled across all 3 studies (total patients *n* = 1,034) for each exposure variable and for each of the statistical modelling steps using fixed-effects inverse variance analyses. This approach to combining data was selected on the basis that one true underlying effect was assumed to underlie all 3 studies [25] and weighs studies according to the standard error of their estimates (i.e., studies with lower standard error are given greater weight). The respective final models (Model 3) were repeated post hoc using random-effects models to show the mean distribution of effects [25]. The results of these analyses are shown as Supplemental Data (online suppl. Table 2). Statistical heterogeneity between studies was assessed using the I^2 index [26].

Analyses were repeated post hoc with exclusion of underweight patients to ensure that findings were not driven by underweight which is a well-established risk factor for age-related cognitive impairment [27] and may also be associated with POCD. Analyses were performed with IBM© SPSS© Statistics (version 23) and Review Manager (version 5.3). The statistical analysis plan was approved by an internal committee before any of the analyses were performed.

Results

Study Characteristics

Characteristics of the patient samples completing follow-up of the 3 studies are shown in Table 1. Mean BMI was 26.6 kg/m^2 (SD = 3.2) in OCTOPUS, 26.9 kg/m^2 (SD = 4.5) in DECS, and 27.3 kg/m^2 (SD = 4.9) in SuDoCo, and thus in the "overweight" category (BMI 25–30 kg/m^2) in all 3 studies. Underweight (BMI <20 kg/m^2) was rare. Mean BMI in the underweight groups was 19.2 kg/m^2 (SD = 1.3) in OCTOPUS (*n* = 5 underweight patients), 18.9 kg/m^2 (SD = 0.9) in DECS (*n* = 10 underweight patients), and 19.0 kg/m^2 (SD = 0.9) in SuDoCo (*n* = 17 underweight patients). In OCTOPUS, mean BMI was 31.6 kg/m^2 (SD = 1.1) in obese patients (BMI ≥30 kg/m^2). In DECS and SuDoCo, obese groups had mean BMIs of 33.8 kg/m^2 (SD = 3.1) and

Table 1. Sample characteristics of the 3 studies

	OCTOPUS	DECS	SuDoCo
Country	The Netherlands	The Netherlands	Germany
Enrollment period	March 1998 to August 2000	August 2010 to October 2011	March 2009 to May 2010
Subjects enrolled, *n*	281	291	1,277
Follow-up periods for POCD assessment	Discharge 3 months 12 months	1 month 12 months	1 week 3 months
Completed last follow-up, *n* (% enrolled)	252 (89.7%)	229 (78.7%)	553 (43.3%)
Type of surgery	All CABG	CABG *n* = 68 (29.7%) Valve *n* = 89 (38.9%) Combination valve/ CABG *n* = 36 (15.7%) Other *n* = 20 (8.7%) Missing *n* = 16 (7.0%)	General surgery *n* = 241 (43.6%) Orthopedics *n* = 187 (33.8%) Gynecology *n* = 62 (11.2%) Urology *n* = 44 (8.0%) Other *n* = 19 (3.4%)
Type of intervention	On-pump vs. off-pump CABG	Placebo vs. dexamethasone	BIS guided vs. BIS blinded anaesthesia
Type of anaesthesia[a]	–	Propofol-based *n* = 77 (33.6%) Volatile-based *n* = 152 (66.4%)	Propofol-based *n* = 177 (32%) Volatile-based *n* = 376 (68%)
Duration of surgery, min[a]	–	215±68	159±97
Age, years	61.0±9.1	64.7±11.6	69.5±6.3
Male	180 (71.4%)	172 (75.1%)	303 (54.8%)
Education[a], years	9.5±2.6	Primary education *n* = 101 (44.1%) Secondary education *n* = 62 (27.1%) Further/higher education *n* = 66 (28.8%)	–
Baseline SBP[a], mmHg	139±20	–	136±19
Baseline DBP[a], mmHg	80±10	–	74±12
Diabetes	36 (14.3%)	37 (16.2%)	119 (21.5%)
Hypertension	118 (46.8%)	123 (53.7%)	374 (67.6%)
BMI, kg/m^2	26.6±3.2	26.9±4.5	27.3±4.9
Underweight (BMI <20 kg/m^2)	5 (2.0%)	10 (4.4%)	17 (3.1%)
Obesity (BMI ≥30 kg/m^2)	39 (15.5%)	44 (19.2%)	131 (23.7%)

Data are presented as mean ± SD or *n* (%). BIS, bispectral index; SBP, systolic blood pressure; DBP, diastolic blood pressure. All data measured before surgery and shown for respective follow-up sample. For each study, loss to follow-up mainly due to non-response or change in intention of patients. Data on diabetes missing for 1 patient and on obesity for 2 patients in DECS. [a] Data not available for all cohorts.

34.1 kg/m^2 (SD = 4.1), respectively. Systolic and diastolic blood pressure correlated positively with one another in the 2 studies that measured blood pressure (r = 0.49–0.57; both $p < 0.001$), whereas neither was associated with BMI in those studies (all $p > 0.10$).

Associations of Diabetes, Hypertension, and Obesity with Risk of POCD

POCD occurred in 12 patients (5.2%) at 12-month follow-up in DECS. Of these, 4 had diabetes (33.3%), 4 were obese (33.3%), and 8 had hypertension (66.7%). In SuDoCo, POCD occurred in 52 patients (9.4%) at 3 months. Sixteen (30.8%) of those 52 patients had diabetes, 12 (23.1%) were obese and 38 (73.1%) had hypertension. Eighty-one patients (32.1%) in OCTOPUS had POCD at 12 months, of whom 15 (18.5%) had diabetes, 13 (16.0%) were obese, and 40 (49.4%) had hypertension. In the pooled analysis, after adjustment for age, sex, type of surgery and randomisation, diabetes was associated with a 1.97-fold (95% CI 1.24–2.97) higher risk of POCD, while hypertension was associated with a 1.50-fold (95% CI 1.01–2.24) higher risk (Table 2; Fig. 2). In contrast, obesity was not significantly associated with risk of POCD (OR 1.22; 95% CI 0.76–1.96). Risk estimates were similar when random-effects models were used (online suppl. Table 2), when underweight patients were excluded from analysis (data not shown) and also remained unchanged after additional adjustment for education in the 2 studies with education data (OCTOPUS; DECS; data not shown). After additional adjustment for hypertension and obesity, diabetes remained significantly associated with a higher risk of POCD, with a pooled OR of 1.84 (95% CI 1.14–2.97; Model 3 in Table 2 calculated from OCTOPUS, OR 1.90, 95% CI 0.86–4.21; DECS, OR 2.94, 95% CI 0.69–12.52; SuDoCo, OR 1.62, 95% CI 0.84–3.15) and no evidence of statistical heterogeneity between studies (χ^2 = 0.55; p = 0.76; I^2 = 0%). In contrast, hypertension was not significantly associated with risk of POCD after additional adjustment for diabetes and obesity (OR 1.37; 95% CI 0.91–2.07). Similar to the results reported above, obesity was not significantly associated with POCD in these fully adjusted models.

Associations of BMI and Systolic and Diastolic Baseline Blood Pressure with POCD

BMI was not significantly associated with risk of POCD (online suppl. Table 3; Fig. 3) in the analysis pooled across the 3 studies. Again, these results were not substantially different when random-effects models were used (online suppl. Table 2) or when underweight patients were excluded from the analysis (data not shown). Neither systolic nor diastolic baseline blood pressure was significantly associated with POCD risk, although this analysis was restricted to 2 studies (online suppl. Table 3).

Discussion

Across 3 studies, we found evidence that diabetes was associated with a 1.84-fold higher risk of POCD. Importantly, the association was independent of age, sex, type of surgery, and intervention, as well as obesity and hypertension. Hypertension and obesity were not independently associated with risk of POCD. These findings extend our previous meta-analyses which, largely based on unadjusted results of exploratory studies, had found significant associations for diabetes but not for obesity or hypertension with POCD risk [7, 8, 10].

The pathophysiology of developing POCD is poorly understood. Neuroinflammation with subsequent microglial overactivation and disruption of the blood brain barrier is assumed to play a role in the development of short-term postoperative cognitive impairment [28]. Other theories on causes of POCD include impaired cerebral perfusion during surgery [29], lasting neurotoxic effects of anaesthetics, as well as detrimental effects of perioperative opioid use on brain function [30, 31]. Environmental factors such as hospital environments and sleep

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Table 2. Association of diabetes, hypertension, and obesity with risk of POCD in each study, and pooled estimates

	OCTOPUS			DECS			SuDoCo			Pooled estimates	
	OR (95% CI)	*p*	weight	OR (95% CI)	*p*	weight	OR (95% CI)	*p*	weight	OR (95% CI)	*p*
Diabetes and risk of POCD											
Model 0: no adjustment	2.20 (1.03, 4.71)	0.04	35.2%	2.77 (0.79, 9.74)	0.11	12.9%	1.72 (0.92, 3.22)	0.09	51.8%	*1.99 (1.27, 3.13)*	*0.003*
Model 1: age, sex	2.11 (0.98, 4.55)	0.06	35.2%	2.54 (0.71, 9.01)	0.15	13.0%	1.68 (0.89, 3.18)	0.11	51.8%	*1.92 (1.22, 3.03)*	*0.005*
Model 2: +type of surgery, randomisation	2.08 (0.96, 4.50)	0.06	36.0%	3.77 (0.94, 15.16)	0.06	11.1%	1.66 (0.88, 3.13)	0.12	53.0%	*1.97 (1.24, 3.13)*	*0.004*
Model 3: +hypertension, obesity	1.90 (0.86, 4.21)	0.11	36.7%	2.94 (0.69, 12.52)	0.15	11.0%	1.62 (0.84, 3.15)	0.15	52.3%	*1.84 (1.14, 2.97)*	*0.01*
Hypertension and risk of POCD											
Model 0: no adjustment	1.76 (1.03, 3.00)	0.04	53.0%	1.77 (0.52, 6.07)	0.36	10.0%	1.33 (0.70, 2.53)	0.38	37.0%	*1.59 (1.08, 2.34)*	*0.02*
Model 1: age, sex	1.72 (0.99, 2.96)	0.05	52.7%	1.54 (0.44, 5.35)	0.50	10.1%	1.22 (0.64, 2.33)	0.55	37.2%	*1.49 (1.00, 2.22)*	*0.047*
Model 2: +type of surgery, randomisation	1.71 (0.99, 2.95)	0.06	53.1%	1.52 (0.42, 5.51)	0.53	9.5%	1.25 (0.65, 2.40)	0.51	37.3%	*1.50 (1.01, 2.24)*	*0.045*
Model 3: +diabetes, obesity	1.61 (0.92, 2.81)	0.10	54.4%	1.17 (0.31, 4.49)	0.82	9.4%	1.13 (0.57, 2.23)	0.73	36.3%	*1.37 (0.91, 2.07)*	*0.13*
Obesity and risk of POCD											
Model 0: no adjustment	1.07 (0.52, 2.20)	0.86	40.3%	2.19 (0.63, 7.62)	0.22	13.6%	0.98 (0.50, 1.94)	0.96	46.1%	*1.13 (0.71, 1.79)*	*0.60*
Model 1: age, sex	1.07 (0.51, 2.22)	0.86	40.5%	2.17 (0.60, 7.76)	0.24	13.4%	1.07 (0.54, 2.13)	0.84	46.1%	*1.18 (0.74, 1.87)*	*0.50*
Model 2: +type of surgery, randomisation	1.06 (0.51, 2.21)	0.88	41.6%	2.93 (0.74, 11.60)	0.13	11.8%	1.11 (0.55, 2.21)	0.77	46.7%	*1.22 (0.76, 1.96)*	*0.41*
Model 3: +diabetes, hypertension	0.92 (0.43, 1.95)	0.82	41.8%	2.26 (0.53, 9.61)	0.27	11.4%	0.96 (0.47, 1.96)	0.91	46.8%	*1.04 (0.64, 1.69)*	*0.88*

POCD determined at 12 months in OCTOPUS/DECS and at 3 months in SuDoCo. POCD occurred in 12 patients (5.2%) at 12-month follow-up in DECS, in 52 patients (9.4%) at 3 months in SuDoCo, and in 81 patients (32.1%) at 12 months in OCTOPUS. For each study, Model 3 is based on a single model.

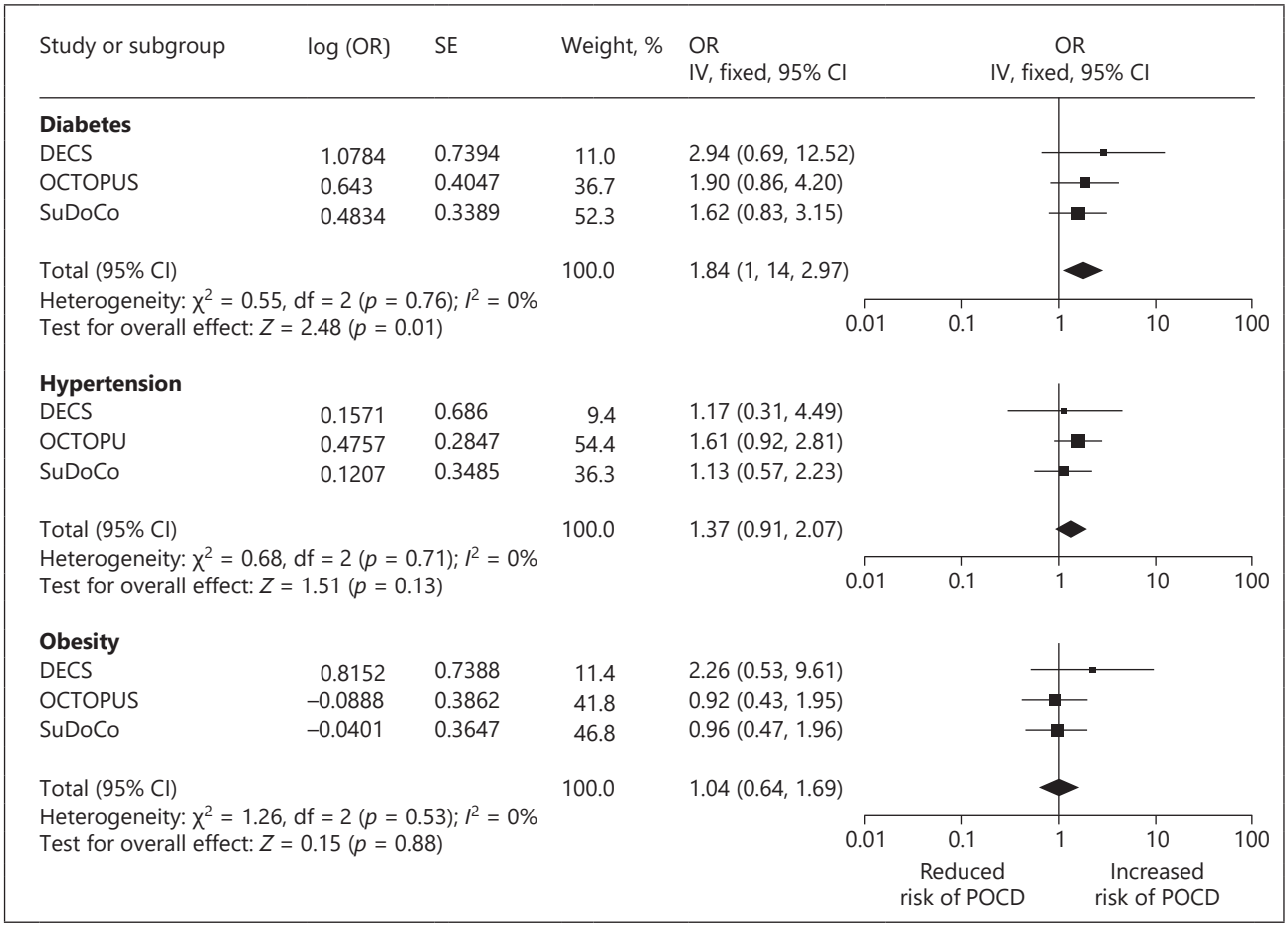

Fig. 2. Pooled effects of diabetes, hypertension, and obesity on risk of POCD (Model 3).

disturbances, too, may play a role [31]. However, these theories cannot easily explain the higher POCD risk in patients with diabetes. Patients with diabetes generally show greater cerebral and hippocampal atrophy [32–34], cerebral microvascular [35, 36] and macrovascular damage [37], and are also at increased risk of cognitive impairment [15, 38, 39] compared with non-diabetics. Similar observations have been made for hyperglycaemia short of diabetes diagnosis [40, 41] and poorer glycaemic control in patients with diabetes [42], which indicates fundamental influences of impaired glucose metabolism on the brain. It appears that the negative impact of hyperglycaemia on brain function may be accelerated due to surgery as it was observed for patients with diabetes during relatively short follow-up periods of 3–12 months in the present analysis. Further, our findings suggest somewhat higher odds of POCD in the 2 studies with cardiac patients (DECS; OCTOPUS) compared with the study of non-cardiac patients (SuDoCo), which reiterates a statistically non-significant trend in the same direction in our meta-analysis [8]. This warrants further evaluation. It may be that negative impacts of diabetes on the vasculature increase POCD risk following vascular interventions. Though we cannot determine causality on the basis of the present epidemiological findings, our results may reflect neurotoxic effects of persistently high blood glucose that ultimately impairs neurons with subsequent loss of function [43]. Surgery-associated high grade systemic inflammation [44] may have affected previously damaged neurons in patients with diabetes resulting in POCD. Further studies are thus needed to add to our understanding of

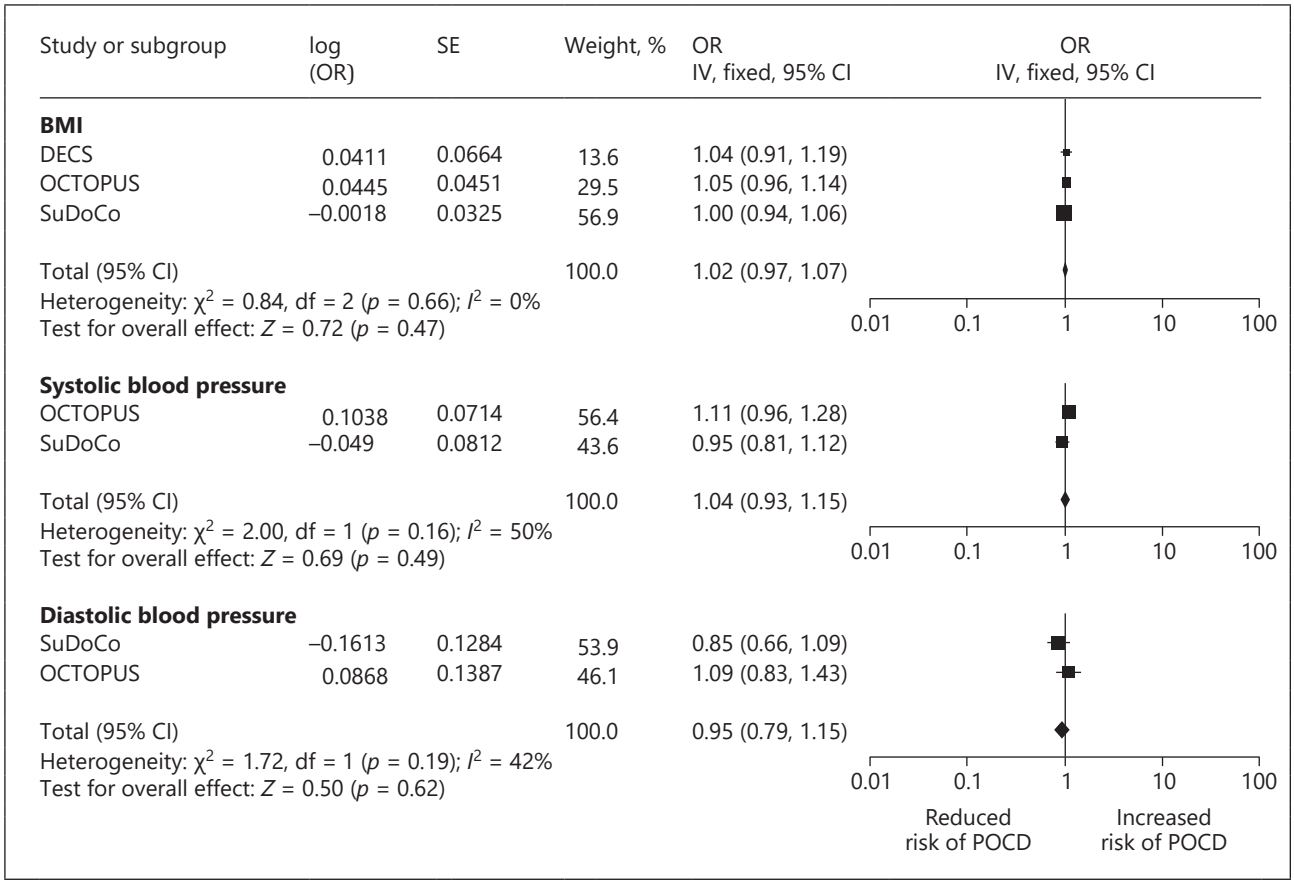

Fig. 3. Pooled effects of BMI and systolic and diastolic baseline blood pressure on risk of POCD (Model 3). Odds ratios correspond to 1 kg/m^2 increment in BMI and 10 mmHg increment in blood pressure.

the pathophysiology of surgical brain damage in the context of hyperglycaemia and diabetes. An influence of type of anti-diabetic treatment and glycaemic control including prior history of hypoglycaemia which itself seems to increase cognitive risk [45, 46] should additionally be considered in further observational studies that collect more detailed data, for instance on HbA1c levels, duration of diabetes, and treatment type, of their patients with diabetes, and trial studies may also be possible. An influence of improved glycaemic control during the weeks before surgery on POCD risk could be assessed in a sample of people with type 2 diabetes, for example.

Hypertension is a major influencing factor for cardiovascular events such as stroke and myocardial infarction due to vascular damage [47]. However, we did not see any significant influence of a prior history of hypertension on risk of POCD that was independent of its link to diabetes. The null finding suggests that vascular damage as a consequence of hypertension may only play a minor role in POCD development and replicates results of our meta-analysis of hypertension as a candidate risk factor for POCD [10]. Though we did not assess severity of hypertension which may be important in cognitive risk prediction [48], our finding warrants further enquiry particularly in view of established associations of this risk factor with cognitive impairment per se [15, 49, 50]. A beneficial effect of anti-hypertensive treatment on cognitive risk as an explanation of the null finding appears unlikely as the balance of evidence from RCTs speaks against such effects [51, 52].

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Obesity is a pro-inflammatory state characterised by raised circulating inflammatory markers [53, 54], which itself appears to promote cognitive dysfunction after surgery [55]. We therefore hypothesised that obesity may be a risk factor for POCD. The results of the present analysis and of our previous meta-analysis [7] do not appear to support this hypothesis. Indeed, when looking to age-related cognitive impairment, increasing evidence suggests that while midlife obesity appears to increase risk of later impairment, obesity in later life does not. For instance, a recent analysis of the Whitehall II study of >10,000 individuals in the UK found obesity at age 50 but not at age 60 or 70 predicted dementia risk [56]. Some studies even corroborate an "obesity paradox" with beneficial effects of obesity on cognitive function in later life [57] which may reflect effects of prodromal stages of dementia on body weight [56, 58]. We have no information on body weight status at midlife or weight trajectories of participants but suspect that similar processes may underlie the lack of an association of obesity and POCD risk in the present analysis. We also cannot rule out potential harmful effects of obesity that we may have missed due to lack of statistical power.

Strengths of our study include the use of primary data from 3 studies on POCD that allowed adjustment for a range of potential confounders. By entering all 3 exposures of interest into the same statistical models, our approach further allowed determination of the relative contribution of diabetes, obesity, and hypertension to POCD risk. Sensitivity analyses were able to show that the absence of an association of obesity or BMI with POCD risk was not driven by inclusion of underweight patients in the main analyses.

A number of limitations must be considered. We followed a two-step approach to data analysis and pooling of estimates rather than individual-patient meta-analysis. Readers should also be aware that we assessed 3 exposures for associations with POCD, which may have increased type I statistical error. However, findings on diabetes and POCD risk remained unchanged with Bonferroni correction of the critical *p* value indicative of statistical significance. Importantly, different psychological batteries for determining POCD were used in each of the 3 studies. This could have influenced POCD incidence, which was particularly low for DECS and thus may have limited our statistical modelling that included a number of covariates. Prevalence of diabetes and hypertension varied between the 3 studies, and likely reflected a difference in health status between samples. Generalisability of our findings is therefore unclear. As cognitive deficits often appear to resolve over time [3, 4, 59], the pooling of effects across studies with 3- to 12-month follow-up periods was suboptimal and will have led to incidence of POCD ranging from 5.2 to 32.1%. Cohort effects were introduced by recruitment periods spanning from 1998 to 2011, and our findings may not necessarily apply to patients undergoing surgery today. Further, the studies had not set out to investigate the present exposures of interest and risk of POCD. Thus, assessment of diabetes, hypertension, and obesity may not have been consistently rigorous, and we were not able to discriminate between type 1 and type 2 diabetes. An influence of other well-established risk factors for POCD, such as previous cerebrovascular event known to be associated with diabetes [60] as well as POCD [1], on our findings is also plausible. We deem an influence of pre-existing cognitive impairment which, too, is associated both with diabetes [14] and POCD [8] unlikely as SuDoCo, which was weighted most heavily in the combined analyses, excluded patients with baseline cognitive impairment. Between-study differences in assessment of other factors such as blood loss during surgery meant that adjustment was not possible for all potential confounders. Residual confounding is therefore possible. Various definitions of POCD were used. In DECS and SuDoCo, POCD was defined relative to cognitive change of non-surgical control groups, and neither had information available on prevalence of diabetes, hypertension and obesity in the control subjects. Thus, we cannot determine whether the present findings reflect associations of diabetes with POCD versus associations with cognitive decline per se. This also applies to the OCTOPUS study which defined POCD from raw cognitive

change. Here, patients with diabetes (even if not exposed to surgery) may have simply declined at steeper rates during follow-up compared with non-diabetics. OCTOPUS also reported an incidence rate of POCD of around one-third of patients at 12-month follow-up, which is high relative to previous studies [61]. Post-surgery stroke was considered as "POCD" in OCTOPUS and DECS, which complicates the interpretation of findings on POCD as a form of impairment as opposed to overt cerebrovascular disease. Further, any non-linear associations of BMI with POCD risk were presumably not well captured by a single cut-off at BMI ≥30 kg/m^2 for definition of obesity. However, when we excluded underweight patients and those with postoperative stroke from analyses, findings remained unchanged.

In conclusion, our results suggest that people with diabetes are at increased risk of POCD and independently of co-morbid obesity or hypertension. Consideration of diabetes status may thus be helpful for assessment of POCD risk to help clinicians and patients alike to make informed decisions when electing surgery. Enhanced post-surgery care for patients with diabetes that includes screening for POCD may also be indicated.

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Statement of Ethics

Participants gave written informed consent, and assessments complied with the Declaration of Helsinki. Though no new data were collected, ethical approval for the present analysis (EA1/242/08) was provided by the institutional review board (Ethikkommission der Charité – Universitätsmedizin Berlin, Berlin, Germany, Chairperson Prof. R. Uebelhack) on January 31, 2017.

Disclosure Statement

All authors declare no conflicts of interest related to this article.

Author Contributions

D.D. conceived and designed OCTOPUS. T.H.O. conceived and designed DECS. F.M.R. conceived and designed SuDoCo. G.L. and I.F. conceived the present study and performed the statistical analyses. G.L., I.F., and F.B. drafted the manuscript. G.L., I.F., F.B., C.S., and T.P. were involved in the interpretation of findings and preparation of the final manuscript. All authors commented on the final draft.

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Obesity, diabetes and hypertension as well as BMI, systolic and diastolic blood pressure were evaluated as potential risk factors for POCD using prospective data from the 3 RCTs (OCTOPUS; DECS; SuDoCo). Each study had several post-surgery follow-up sessions of which the respective longest follow-up period was selected for the purpose of this analysis (OCTOPUS 12 months; DECS 12 months; SuDoCo 3 months after surgery). Unlike in the cross-sectional analyses described in Section 2.1.1, on this occasion, we also adjusted for surgery type and randomization given that surgery- and intervention-related variables could well influence POCD risk and could also be related to the metabolic exposure. For instance, patients undergoing a more extensive surgical procedure could be more likely to have metabolic dysfunction and could also be exposed to increased risk of POCD. This adjustment avoided this possibility. POCD was defined by comparing a change in cognitive scores to the respective non-surgical control group in SuDoCo and DECS, and from raw change in scores in OCTOPUS (≥20% decline on ≥3 tests, or incident stroke).

14.0% of patients developed POCD. Pooled across the 3 studies, diabetes and hypertension, but not obesity, BMI or systolic and diastolic blood pressure, were associated with increased risk of POCD with age, sex, surgery type and RCT randomization controlled for. For diabetes, but not for hypertension, the finding remained statistically significant when all 3 categorical exposures (diabetes, hypertension, obesity) were entered into a single statistical model. Here, we have demonstrated for the first time that an association of diabetes with POCD risk may be independent of several other parameters of metabolic dysfunction. Thus, diabetes may in fact underlie associations of other parameters of metabolic dysfunction with POCD reported in previous studies.

2.3 Plasma Aβ as a diagnostic biomarker of AD

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Plasma Amyloid Concentration in Alzheimer's Disease: Performance of a High-Throughput Amyloid Assay in Distinguishing Alzheimer's Disease Cases from Controls

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Abstract.
Background: Collection of cerebrospinal fluid (CSF) for measurement of amyloid-β (Aβ) species is a gold standard in Alzheimer's disease (AD) diagnosis, but has risks. Thus, establishing a low-risk blood Aβ test with high AD sensitivity and specificity is of outmost interest.
Objective: We evaluated the ability of a commercially available plasma Aβ assay to distinguish AD patients from biomarker-healthy controls.
Method: In a case-control design, we examined plasma samples from 44 AD patients (A + N+) and 49 controls (A–N–) from a memory clinic. AD was diagnosed using a combination of neuropsychological examination, CSF biomarker analysis and brain imaging. Total $A\beta_{40}$ and total $A\beta_{42}$ in plasma were measured through enzyme-linked immunosorbent assay (ELISA) technology using ABtest40 and ABtest42 test kits (Araclon Biotech Ltd.). Receiver operating characteristic (ROC) analyses with outcome AD were performed, and sensitivity and specificity were calculated.

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Results: Plasma $A\beta_{42/40}$ was weakly positively correlated with CSF $A\beta_{42/40}$ (Spearman's rho 0.22; $p = 0.037$). Plasma $A\beta_{42/40}$ alone was not able to statistically significantly distinguish between AD patients and controls (AUC 0.58; 95% CI 0.46, 0.70). At a cut-point of 0.076 maximizing sensitivity and specificity, plasma $A\beta_{42/40}$ had a sensitivity of 61.2% and a specificity of 63.6%.

Conclusion: In this sample, the high-throughput blood Aβ assay was not able to distinguish well between AD patients and controls. Whether or not the assay may be useful in large-scale epidemiological settings remains to be seen.

Keywords: Alzheimer's disease, amyloid, diagnosis, high-throughput assay, plasma

INTRODUCTION

Alzheimer's disease (AD) is threatening global healthcare systems [1] and generates immense economic, medical, and societal costs [2]. As its neuropathological hallmark, AD is characterized by an accumulation of amyloid-β (Aβ) peptides in the brain and AD diagnosis largely depends on an estimation of brain Aβ burden. Aβ is derived through cleavage of the amyloid-β protein precursor (AβPP), a transmembrane protein, and aggregates as neurotoxic amyloid plaques ultimately impairing synaptic function [3], though whether or not Aβ causes AD or functions as a 'bystander' of AD pathogenesis is yet to be determined [4, 5].

Brain Aβ antemortem is quantifiable via radioactive labelling on positron emission tomography (PET) [6] and can also be estimated from Aβ concentrations in cerebrospinal fluid (CSF) as a molecular biomarker [7]. Amyloid PET and CSF Aβ can be used interchangeably for clinical diagnosis [7, 8] and are increasingly relied upon in diagnostic frameworks [9, 10]. Both have also been shown to predict future cognitive decline [11–13]. Nonetheless, amyloid PET and CSF Aβ are used infrequently in clinical practice [14]. Amyloid PET is cost-intensive and dependent on radioactive tracers; lumbar punctures to obtain CSF can cause minor complications such as back pain as well as more severe complications such as spinal hematoma [15], and can lead to psychological distress [16]. In contrast, blood collection is well-tolerated, making measurement of blood Aβ for estimation of brain Aβ burden suitable for large-scale application in routine diagnostics. For instance, with sufficient sensitivity and specificity, analysis of blood Aβ could serve as a first-step screening tool for selection of patients for more cost-intensive and high-risk diagnostic measures. Ultimately, blood Aβ analysis might have a comparable impact on diagnostic procedures as amyloid PET [6, 17] and CSF Aβ analysis [18, 19], and even more so due to a projected wider uptake.

However, measuring Aβ in blood is inherently difficult [20, 21]. Plasma concentrations of Aβ are around 10-fold lower than in CSF, whereas the total protein content is 10-fold higher [22], causing technical difficulties. Sophisticated methods for Aβ analysis have been developed in recent years, but results from the first diagnostic and epidemiological applications of these methods have been inconsistent. A number of studies have found an association of lower plasma Aβ concentrations (thought to reflect a greater brain Aβ burden) with more severe neuropsychological deficits [23, 24], with an increased risk of developing AD [25, 26], and with amyloid-positive PET [8, 27, 28] or amyloid-abnormal CSF [29, 30] as current gold standards for AD diagnosis. Others report results in the opposite direction [31–34] and null findings, too, are frequent [35–37]. It has been suggested that one reason for this inconsistency may lie in between-study differences in the cognitive profiles of study samples given that plasma Aβ levels follow a complex temporal trajectory: concentrations increase with age but, potentially due to brain Aβ aggregation, reduce in symptomatic stages of AD [22, 32, 38]. The inconsistent research findings may additionally stem from variations in Aβ measurement methods. Of note, in-house methods with limited feasibility for upscaling are frequent [27] but hinder clinical application which is dependent on high-throughput methods.

Here, we determined the ability of plasma Aβ concentration to discriminate between AD patients and biomarker-healthy, non-diseased controls. We used a recently established, commercially available and high-throughput plasma Aβ assay that to our knowledge has never been evaluated independently of the manufacturer. We hypothesized that Aβ concentration was lower in the plasma of AD patients than in controls. The ratio of plasma $A\beta_{42/40}$ served as the main biomarker of interest as it reflects the more pathological of the amyloid species ($A\beta_{42}$) [39] with individual differences in overall Aβ production ($A\beta_{40}$) accounted for.

MATERIALS AND METHOD

Study design and sample size calculation

In a case-control study design, Aβ was measured in plasma samples previously stored at a biobank for AD patients and biomarker-healthy, non-diseased controls. With a two-tailed analysis and a power of 80%, 47 observations were required per group (total N = 94) to detect statistically significant group differences in plasma Aβ (expected effect size $d = 0.6$). To account for occasional technical difficulty in biomarker measurement, we arrived at a target sample size of N = 100. The study complied with the Declaration of Helsinki.

Study sample

Cases in our study included patients with AD, who were diagnosed during a visit to a memory clinic in Berlin, Germany, between 2014 and 2018. Controls were selected among individuals who presented to the clinic with memory concerns during the same time period, but who were otherwise neurobiologically healthy and consequently did not receive a diagnosis of AD or other forms of dementia. The memory clinic is part of the German Dementia Competence Network (DCN). AD patients and controls were not matched.

Clinical examinations

All participants underwent a thorough and identical clinical examination that included lumbar puncture for CSF collection and collection of blood. Participants were not required to fast. Plasma samples were stored at a biobank for future analysis. CSF was collected into polypropylene tubes and frozen at –80°C according to standard operating procedures detailed elsewhere [40]. Total tau (t-tau), $A\beta_{40}$, and $A\beta_{42}$ in CSF were measured in Mesoscale System (MSD) immunoassays (Mesoscale Discovery, Gaithersburg, MD, USA) at a laboratory adjacent to the clinic site. For t-tau, the MSD MS6000 Phospho-, Total Tau Kit was used; for $A\beta_{40}$ and $A\beta_{42}$, the MSD MS6000 Human (6E10) Aβ3-Plex Kit was used [41]. The ratio $A\beta_{42/40}$ was calculated. Consenting participants were genotyped for apolipoprotein (*APOE*) status. '*APOE* ε4' was defined as presence of at least one ε4 allele. Participants additionally underwent computed tomography (CT) and/or magnetic resonance imaging (MRI) on a separate visit. Neuropsychological testing was mainly based on the CERAD (Consortium to Establish a Registry for Alzheimer's Disease) recommendations. Tests included the Mini-Mental State Examination (MMSE) [42], Boston Naming, verbal fluency (category), figure copying, and word list recall. The battery was supplemented by the Clock Drawing test as a screening tool for dementia and Trail-Making Tests A and B (TMT-A; TMT-B) as measures of processing speed and executive function. The Logical Memory subtest of the Wechsler Memory Scale 4th edition assessed verbal memory and included immediate and delayed recall.

Clinical diagnosis of cases and controls

AD was diagnosed according to DSM-V criteria in a consensus conference involving psychiatrists, physicians and neuropsychologists from a combination of results from the neuropsychological examination, CSF biomarker analysis and brain imaging data. Diagnostic confidence was exceptionally high compared with non-specialized centers, as AD patients were selected for enrollment into clinical trials at the memory clinic. AD patients were thus considered both clinically and neurobiologically diseased, whereas the control group was considered biomarker-healthy. Plasma Aβ concentration was unknown at the time of diagnosis.

Aβ in plasma

Plasma samples were extracted from the biobank in 2018 and shipped to an analysis laboratory (Araclon Biotech Ltd., Zaragoza, Spain) for measurement of total $A\beta_{40}$ (referred to as $A\beta_{40}$ hereafter) and total $A\beta_{42}$ (referred to as $A\beta_{42}$ hereafter) through enzyme-linked immunosorbent assay (ELISA) technology using the ABtest40 and ABtest42 test kits (Araclon Biotech Ltd., Zaragoza, Spain) [43]. The laboratory was blinded to our research question and to patient characteristics. Of N = 100, the analysis produced data on $A\beta_{40}$ for $n = 97$ ($n = 50$ controls; $n = 47$ patients) and on $A\beta_{42}$ for $n = 93$ participants ($n = 49$ controls; $n = 44$ patients). Intra-assay coefficient of variation (CV) was 4.5% for $A\beta_{40}$ and 15.8% for $A\beta_{42}$. Inter-assay CV was 3.7% for $A\beta_{40}$ and 5.0% for $A\beta_{42}$. The ratio $A\beta_{42/40}$ was calculated for $n = 49$ controls and $n = 44$ patients, and served as the main plasma biomarker of interest.

Table 1
Sociodemographic, clinical, and cognitive characteristics in controls and AD patients

	Controls ($n = 50$)	AD ($n = 50$)	p
Age, years, mean ± SD	65.82 ± 8.96	71.30 ± 7.42	0.001
Female sex, n (%)	26 (52.0%)	25 (50.0%)	0.841
Years of education*, mean ± SD	14.27 ± 2.98	13.46 ± 2.96	0.187
≥1 *APOE* ε4 allele**, n (%)	11 (26.8%)	33 (71.7%)	<0.001

Results from t-tests, Mann-Whitney tests or χ^2 tests. *total $n = 94$. **total $n = 87$.

Table 2
Correlations of plasma Aβ with CSF Aβ

	CSF $A\beta_{40}$	CSF $A\beta_{42}$	CSF $A\beta_{42/40}$
Total sample			
Plasma $A\beta_{40}$	0.10 (0.350)	–0.05 (0.637)	–0.14 (0.171)
Plasma $A\beta_{42}$	0.24 (0.023)	0.26 (0.012)	0.13 (0.220)
Plasma $A\beta_{42/40}$	0.23 (0.029)	0.33 (0.001)	0.22 (0.037)
Controls			
Plasma $A\beta_{40}$	–0.05 (0.741)	–0.07 (0.636)	–0.11 (0.482)
Plasma $A\beta_{42}$	0.15 (0.332)	0.31 (0.043)	0.24 (0.112)
Plasma $A\beta_{42/40}$	0.15 (0.334)	0.34 (0.026)	0.29 (0.052)
AD			
Plasma $A\beta_{40}$	0.22 (0.131)	–0.01 (0.953)	–0.32 (0.025)
Plasma $A\beta_{42}$	0.27 (0.057)	0.23 (0.116)	–0.04 (0.761)
Plasma $A\beta_{42/40}$	0.26 (0.071)	0.28 (0.053)	0.07 (0.636)

Spearman's rho (p-value). CSF; cerebrospinal fluid. $n = 44$ to 97.

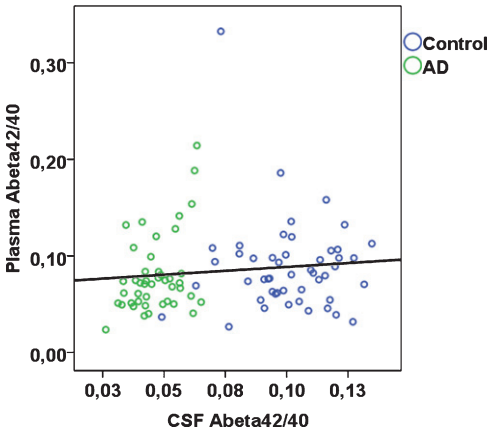

Fig. 1. Plasma $A\beta_{42/40}$ plotted against CSF $A\beta_{42/40}$ according to diagnostic group (rho = 0.22; $p = 0.037$ across total sample).

Statistical analysis

Differences between AD patients and controls in terms of sociodemographics, frequency of the *APOE* ε4 allele and CSF biomarkers were compared using independent samples t-tests, Mann-Whitney tests or χ^2 tests. In the total sample, associations of plasma $A\beta_{42}$, $A\beta_{40}$, and $A\beta_{42/40}$ with CSF $A\beta_{42}$, $A\beta_{40}$, and $A\beta_{42/40}$ were determined using univariate Spearman correlation analyses.

Plasma $A\beta_{42}$, $A\beta_{40}$, and $A\beta_{42/40}$ were compared between AD patients and controls, and between carriers of the *APOE* ε4 allele (≥1 allele) and non-carriers using Mann-Whitney tests.

The diagnostic accuracy of plasma $A\beta_{40}$, plasma $A\beta_{42}$, and plasma $A\beta_{42/40}$ was determined in receiver operating characteristic (ROC) analyses to calculate areas under the curve (AUCs) with the outcome AD patients versus controls. ROC analyses were performed separately for age, *APOE* ε4, plasma $A\beta_{40}$, plasma $A\beta_{42}$, and plasma $A\beta_{42/40}$, and for selected combinations of these predictors. For plasma $A\beta_{42/40}$ as the main biomarker of interest, the optimal cut-off and associated sensitivity, specificity and Youden's index [44], as well as positive predictive value (PPV) and negative predictive value (NPV) were calculated. Analyses were performed in SPSS (Version 18, IBM SPSS, Chicago, Illinois) and R.

RESULTS

Sample characteristics

AD patients were statistically significantly older and were more likely to have at least one *APOE* ε4 allele compared with controls (Table 1). CSF $A\beta_{42}$, CSF $A\beta_{42/40}$, CSF t-tau, and neuropsychological test results were in line according to diagnostic group (data not shown).

Associations of plasma Aβ with CSF biomarkers

In the total sample, plasma $A\beta_{40}$ was significantly positively correlated with plasma $A\beta_{42}$ (Spearman's rho 0.46; $p < 0.001$). Plasma $A\beta_{42}$ and plasma $A\beta_{42/40}$ were each significantly, albeit weakly, positively correlated with CSF $A\beta_{40}$, $A\beta_{42}$; plasma $A\beta_{42/40}$ was additionally positively associated with CSF $A\beta_{42/40}$ (Table 2, Fig. 1). Plasma $A\beta_{40}$ was not significantly correlated with CSF $A\beta_{40}$, $A\beta_{42}$, or $A\beta_{42/40}$. When stratified by case-control status, in controls, plasma $A\beta_{42}$ and $A\beta_{42/40}$ were significantly correlated with CSF $A\beta_{42}$, whereas none of the remaining correlations were statistically significant (Table 2). In AD patients, plasma $A\beta_{40}$ was signif-

Table 3
Plasma Aβ concentration in controls and AD patients

	Controls			AD			Mann-Whitney
	Min	Max	Median (interquartile range)	Min	Max	Median (interquartile range)	*p*
Plasma $A\beta_{40}$ (pg/mL)	129	415	237 (212 – 264)	109	376	237 (216 – 267)	0.809
Plasma $A\beta_{42}$ (pg/mL)	5.8	88.2	19.9 (13.2 – 26.4)	4.8	53.3	17.4 (12.1 – 27.1)	0.404
Plasma $A\beta_{42/40}$	0.03	0.33	0.08 (0.06 – 0.10)	0.02	0.21	0.07 (0.05 – 0.08)	0.173

$n = 93$ to 97.

icantly inversely correlated with CSF $A\beta_{42}/_{40}$, but none of the remaining correlations were statistically significant. $A\beta_{40}$ and $A\beta_{42}$ concentrations were overall around 30-fold and 26-fold higher in CSF than in plasma respectively (CSF $A\beta_{40}$, median 6,727 pg/mL in controls and 7,345 pg/mL in AD patients; CSF $A\beta_{42}$, median 677 pg/mL in controls and 310 pg/mL in AD patients; plasma $A\beta_{40}$, median 237 pg/mL in controls and 237 pg/mL in AD patients; plasma $A\beta_{42}$, median 20 pg/mL in controls and 17 pg/mL in AD patients).

Plasma Aβ in AD patients and controls

Plasma $A\beta_{40}$, plasma $A\beta_{42}$, and plasma $A\beta_{42/40}$ were not significantly different between AD patients and controls (Table 3; Supplementary Figure 1).

In ROC analyses, the area under the curve (AUC) was 0.51 (95% CI 0.40, 0.63; $p = 0.809$) for plasma $A\beta_{40}$, 0.55 (95% CI 0.43, 0.67; $p = 0.404$) for plasma $A\beta_{42}$, and 0.58 (95% CI 0.46, 0.70; $p = 0.173$) for plasma $A\beta_{42/40}$, indicating that the ability to discriminate between AD patients and controls based solely on these plasma markers is poor. In comparison, the AUCs based on age only or based on *APOE* ε4 only were 0.70 (95% CI 0.59, 0.80; $p = 0.001$) and 0.73 (95% CI 0.62, 0.83; $p < 0.001$) respectively. When plasma $A\beta_{42/40}$ as the main biomarker of interest was added to these models, the AUCs did not change (age and $A\beta_{42/40}$, AUC, 0.70; 95% CI 0.59, 0.80; $p = 0.001$; p for difference 0.999; *APOE* ε4 and $A\beta_{42/40}$, AUC, 0.76; 95% CI 0.65, 0.87; $p < 0.001$; p for difference 0.429). The AUC for a model that included age and *APOE* ε4 was 0.79 (95% CI 0.69, 0.89; $p < 0.001$). When plasma $A\beta_{42/40}$ was added to this model, the AUC was 0.80 (95% CI 0.70, 0.91; $p < 0.001$; p for difference 0.879 see Fig. 2 for selected biomarker combinations). Taken together, these data show that plasma $A\beta_{42/40}$ did not contribute to the ability to discriminate between AD patients and controls.

Based on the ROC analysis, we determined a cut-point of 0.076 for a plasma $A\beta_{42/40}$ concentration

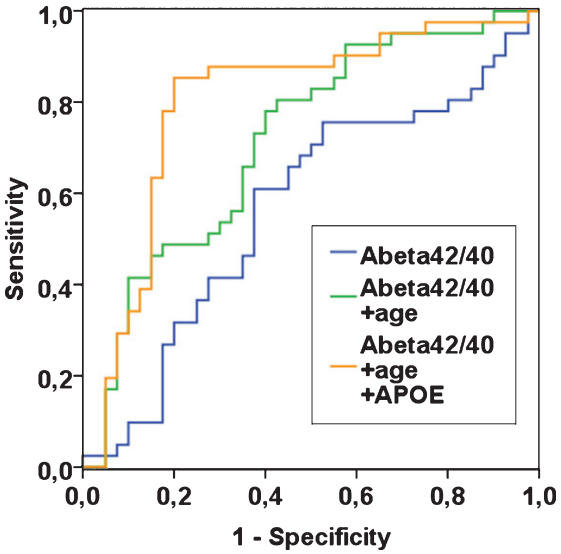

Fig. 2. ROC curves for plasma $A\beta_{42/40}$ alone, plasma $A\beta_{42/40}$ with age, and plasma $A\beta_{42/40}$ with age and *APOE* ε4, in $n = 81$ patients with complete data. Outcome is "AD" with reference "controls". To create a ROC curve *above* the reference line, $A\beta_{42/40}$ was transformed to "1- $A\beta_{42/40}$" (blue line).

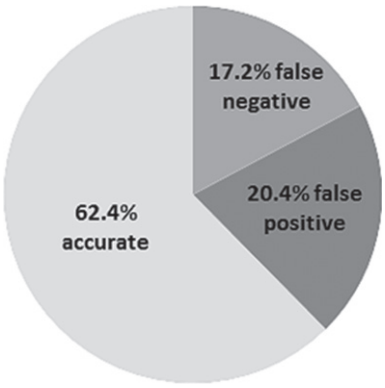

Fig. 3. Diagnostic accuracy of plasma $A\beta_{42/40}$ at optimal cut-point (total $n = 93$).

with a maximum in both sensitivity and specificity. However, at this cut-point, plasma $A\beta_{42/40}$ had low sensitivity (61.2%) and specificity (63.6%; Youden's

index 0.25) and correctly identified 28 of the 44 AD patients and 30 of the 49 controls. Sixteen AD patients were misclassified as controls (false negatives) and 19 controls were misclassified as AD cases (false positives). Plasma $A\beta_{42/40}$ at this cut-point had a positive predictive value (PPV) of 59.6% and a negative predictive value (NPV) of 65.2%. We applied further experimental cut-points to plasma $A\beta_{42/40}$ in *post-hoc* analyses to reduce the number of false positives, but all resulted in low diagnostic accuracy (Supplementary Table 1).

Plasma Aβ in non-carriers and carriers of APOE ε4

Across the full study sample, plasma $A\beta_{40}$ (median 238.1 pg/mL versus 228.9 pg/mL; $p = 0.466$), plasma $A\beta_{42}$ (median 21.3 pg/mL versus 16.7 pg/mL; $p = 0.251$), and plasma $A\beta_{42/40}$ (median 0.08 versus 0.07; $p = 0.212$) were each not statistically different in non-carriers and in carriers of the *APOE ε4* allele, respectively.

DISCUSSION

Blood-based biomarkers of AD have the potential to revolutionize AD diagnostic procedures. Here, in a unique case-control study with exceptionally detailed assessments that included a neuropsychological examination, CSF biomarker analysis and brain imaging as gold standards in AD diagnosis, we found that plasma Aβ was not able to distinguish AD patients well from biomarker-healthy, non-diseased controls. Sensitivity and specificity based on plasma $A\beta_{42/40}$ levels alone were low and not indicative of a diagnostic test with scope for clinical application. Only 64% of AD patients were correctly detected based on plasma $A\beta_{42/40}$.

Plasma $A\beta_{42/40}$ was only weakly but significantly correlated with CSF $A\beta_{42/40}$. This finding is in agreement with several previous investigations [27, 30, 45] though the strength of this correlation was markedly smaller in our sample. CSF Aβ itself comes with measurement difficulties [12, 41], but based on its established function as a gold-standard in AD diagnosis [7], combined with the fact that CSF Aβ was measured using the Mesoscale System (MSD) [41], our finding suggests that plasma Aβ reflected brain Aβ burden only to some limited extent. In contrast to several previous studies comparing AD patients and controls [22, 30], we did not find evidence of reduced plasma Aβ in AD patients. Several reasons may underlie this null result. Firstly, plasma Aβ may in fact be unrelated to AD status. Secondly, due to the 'noise' associated with peripheral production and clearance of Aβ [46], effect sizes may have been too small to detect differences in plasma Aβ between AD cases and controls. Thirdly, measurement error from varying time lapse before freezing, from varying storage time of plasma samples, uncontrolled fasting status and time of day, and/or plasma Aβ analysis itself may have affected results. To our knowledge, we provide the first application of a novel, high-throughput technique for plasma Aβ analysis [43] to a research study that was run independently of the manufacturer. The assay had previously been used in four studies [28, 45, 47, 48] of which one [47] used a subsample of an earlier investigation [45]. In sum, the studies found correlations of plasma $A\beta_{42/40}$ with CSF $A\beta_{42/40}$ [45], as well as associations of low plasma Aβ with presence of [28, 45, 47, 48] and an increased 3-year accumulation of Aβ burden on PET [28]. Further, a lower plasma $A\beta_{42/40}$ was reported in patients with mild cognitive impairment (MCI) compared with cognitively normal individuals; additionally MCI patients with lower plasma $A\beta_{42/40}$ were at increased risk of 2-year conversion to AD [45]. In two of the four studies sensitivity, specificity and AUC of plasma $A\beta_{42/40}$ for Aβ-positive PET were more promising [28, 47] compared with our own analysis comparing AD patients with controls. Yet, in one of these studies, when the full cohort was analyzed rather than a subsample, plasma $A\beta_{42/40}$ performed poorly in discriminating MCI from cognitively normal individuals [47], mirroring our own results. A cross-sectional analysis of people with subjective cognitive decline, too, found low AUC and low specificity of the compound alone for Aβ-positive PET [48]. The final, prospective study on conversion from MCI to AD only reported a fully adjusted model that included plasma Aβ as well as age, *APOE*, and education [45] so that the added benefit of plasma Aβ is difficult to evaluate.

The discrepancy of our results from many of the manufacturer-funded results remains unclear. AD diagnosis in our study was based on neuropsychological test scores, CSF biomarker analysis and brain imaging results, and so we are confident that we have been successful in selecting neurobiologically diseased AD patients and neurobiologically healthy controls. That, combined with recent reports of acceptable diagnostic performance of plasma Aβ when measured using different high-throughput tech-

niques [8, 30], leads us to suggest that the assay may have failed to produce accurate plasma Aβ data. Technical issues in our study were also indicated by the fact that plasma Aβ relative to CSF Aβ was far lower than the expected 10-fold difference [22] our >20-fold difference mirrored that of another investigation which also found no association of plasma Aβ with cognitive status [36].

Aβ metabolism is strongly influenced by the *APOE* protein. *APOE* is involved in cholesterol transport in the brain as well as in Aβ production and clearance, and binds to Aβ in CSF [49]. The *APOE* gene occurs in three polymorphisms (ε2; ε3; ε4) of which the *APOE* ε4 allele is a strong predictor of late-onset AD [49]. Carriers of *APOE* ε4 have greater brain Aβ burden imaged on PET [50, 51] and lower CSF Aβ compared with non-carriers [51–53]. Several population-based cohort studies also point to lower plasma Aβ in carriers [8, 54], but we and others that have used the same assay [48] found no such evidence. Effect sizes speak against low statistical power as the root cause, corroborating plasma Aβ—at least when measured using the present assay—as a peripheral biomarker with little scope for capturing AD-type neuropathological burden.

Detailed characterization of participants using genetic, CSF biomarker, and brain imaging data is a strength of our study, but some limitations must be considered. Due to small sample size, our analyses were underpowered to detect more subtle group differences in plasma Aβ. For instance, we only had a two-tailed power of around 30% to detect a small group difference. Nonetheless, the anticipated large effect had been reasonable given that we had selected distinct groups of neurobiologically confirmed AD patients and biomarker-healthy controls. A large group difference is also a prerequisite for implementation of a diagnostic test in clinical settings, which is at the core of plasma Aβ research. Time interval between plasma collection and freezing, fasting status, and time of day had not been fully standardized and this may have contributed to measurement error. However, recent evidence suggests that plasma Aβ concentration is relatively immune to these factors [55, 56]. Plasma samples had been stored for between 7 months and 4 years prior to extraction from the biobank for Aβ analysis. Though we are not aware of studies that have assessed an influence of storage time on plasma Aβ, we have no reason to believe it may be less stable compared with Aβ in frozen CSF for which we have previously demonstrated long-term stability [41]. Finally, we did not consider AD staging and included both early-onset and late-onset AD in our sample (6 AD patients were <65 years old). All of these factors may have played a role in generating a large range of plasma Aβ measurements thus may have contributed to our null findings. At the same time, with exception of storage time, they are all part of a real-world setting which any diagnostic test for AD must be able to withstand for implementation in the clinic.

In a recent analysis of a mostly cognitively unimpaired older cohort, baseline plasma Aβ measured with immunoprecipitation and liquid chromatography-mass spectrometry assay predicted conversion from amyloid-negative to amyloid-positive PET during a 4-year follow-up. Results indicated that implementing the plasma Aβ test in clinical practice would reduce PET scans by 62% [8]. Further studies in this direction are needed in spite of the present null findings to fully determine the diagnostic value of plasma Aβ and for head-to-head comparison with other biomarkers of brain Aβ burden. For instance, plasma t-tau [57] and plasma neurofilament light (NFL) [58] have recently been reported as predictive of AD in three independent cohorts. Serum NFL has also been shown to be elevated in patients with familial AD [59] and to predict their rate of cognitive decline [60]. A substantial proportion of patients with MCI or dementia with potential AD etiology appears to be misdiagnosed once followed up with amyloid PET [17], and plasma biomarkers could be evaluated as follow-up diagnostic tools. For Aβ in particular, different methods for measuring plasma concentration of the protein should be compared with one another and with a recently developed structure-based approach that measures misfolded Aβ [61]. The goal should be to standardize analysis methods across labs. Here, we did not create CSF/plasma Aβ ratios, because AD diagnosis was based in part on CSF Aβ so that such ratios would have led to circular arguments, but future studies could explore their usefulness (e.g., [36]) as well as ratios combining several plasma biomarkers (e.g., [62]).

Any biomarker of AD needs to offer scope for large-scale application. Here, we used a recently established, commercially available, high-throughput technique and found that plasma Aβ correlated weakly with CSF Aβ and was unable to distinguish between AD patients and biomarker-healthy, non-diseased controls. Plasma Aβ at the cut-point with maximum sensitivity and specificity identified 38% of our sample incorrectly as false pos-

itive or false negative. We thus deem its performance inacceptable. Diagnostic confidence for clinical AD diagnosis can be considered exceptionally high in our study because AD diagnosis was based on a combination of detailed diagnostic procedures that are not routinely applied in clinical practice outside of specialized memory clinics. Plasma Aβ measured with the present assay can therefore be expected to be even less adequate in more diverse, 'real-world' samples that include 'gray zones' and prodromal stages of AD. Nonetheless, plasma Aβ may well be a useful biomarker of age-related cognitive impairment in population-based epidemiological research studies aimed at risk stratification and elucidation of pathophysiological mechanisms underlying impairment. The utility of the blood Aβ assay presented here is yet to be determined in that context.

Overall, we conclude that as the evidence currently stands, the plasma Aβ concentration assay may have limited ability to distinguish AD cases from biomarker-healthy, non-diseased controls. Its evaluation in larger samples and, potentially, a shift of focus toward other blood-based biomarkers and/or efforts for technological advancement of plasma Aβ measurement, which has recently gained momentum [30], are warranted.

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SUPPLEMENTARY MATERIAL

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Dementia as the most severe form of ACI is difficult to diagnose in clinical practice. Diagnostic procedures for AD as its most common form of dementia can be costly (brain imaging) and invasive (lumbar puncture) and are infrequently used. Discovery of a blood-based biomarker of AD thus would alleviate the current burden of diagnostic procedures. Any well-established blood-based biomarker of AD could additionally be evaluated in future research studies to determine its ability to predict future AD or potentially even milder forms of ACI. As reviewed in Section 1.2, despite intensive research in this direction, there is currently no method for a blood-based biomarker for AD available with potential for upscaling. A novel, commercially available assay for plasma Aβ [16] had recently been developed and in studies affiliated with the manufacturer had been found to distinguish well between adults with ACI and cognitively healthy older adults [142-144]. Here, we aimed to contribute to the research field by providing an independent, strategic evaluation of that assay. We used data and biomaterial of 100 patients who had attended a memory clinic in Berlin between 2014 and 2018 were included. 50 were patients with confirmed AD and 50 were cognitively normal. Diagnostic confidence was exceptionally high given that neuropsychological assessment and CSF biomarker measurement had been performed in all patients and brain imaging data were available for most. The AD group in this analysis can therefore be considered a "gold standard" for evaluation of a novel potential diagnostic marker such as plasma Aβ. For the 100 selected patients, total plasma Aβ40 and total plasma Aβ42 – the more detrimental Aβ species compared with Aβ40 [145] – were measured and the ratio of Aβ42/40 was derived.

Plasma Aβ correlated only weakly and not statistically significantly with CSF Aβ. This applied to Aβ40, Aβ42 as well as their ratio. Receiver operating characteristics (ROC) analyses determined that Aβ42/40 as the main plasma amyloid marker of interest was not able to distinguish well between AD patients and controls. Addition of plasma Aβ42/40 also did not improve the diagnostic accuracy of a model including age and the apolipoprotein E e4 allele, which is among the most well-established risk factors for AD [146]. Sensitivity and specificity of Aβ42/40 at its optimal cut-point were low. No data on metabolic function of participants were available and so that this part of our research question could not be addressed in this study.

3. Discussion

3.1 Metabolic dysfunction and cognitive impairment in the perioperative setting

3.1.1 Overview

Knowledge of risk factors for cognitive impairment before and after surgery is vital for understanding pathophysiological mechanisms underlying the conditions, for appropriate patient care and risk stratification and, potentially, for prevention. In the analyses described here, the association of metabolic dysfunction with age-related cognitive impairment (ACI) and risk of post-operative cognitive dysfunction (POCD) after surgery was assessed. We found in a series of cross-sectional analyses that obesity defined by BMI was associated with ACI in the 3 RCTs [147] but not in BioCog [148,149]. A higher plasma leptin [149] and a lower HDL cholesterol concentration [150] were also each associated with ACI. MetS, hyperglycemia, hypertension and adiponectin concentration were not associated with ACI throughout [147,149,150].

In the prospective analyses, patients with diabetes undergoing surgery were at an unadjusted 99% increased risk of developing POCD compared with those without diabetes [148] supporting findings from our meta-analysis of 14 previously published studies [119]. Considering that POCD is a relatively common occurrence in older patients during the first few months after surgery, this implies a substantial absolute risk for patients with diabetes. Obesity and hypertension were each not associated with POCD risk [148]. Findings are summarized in Figure 3.

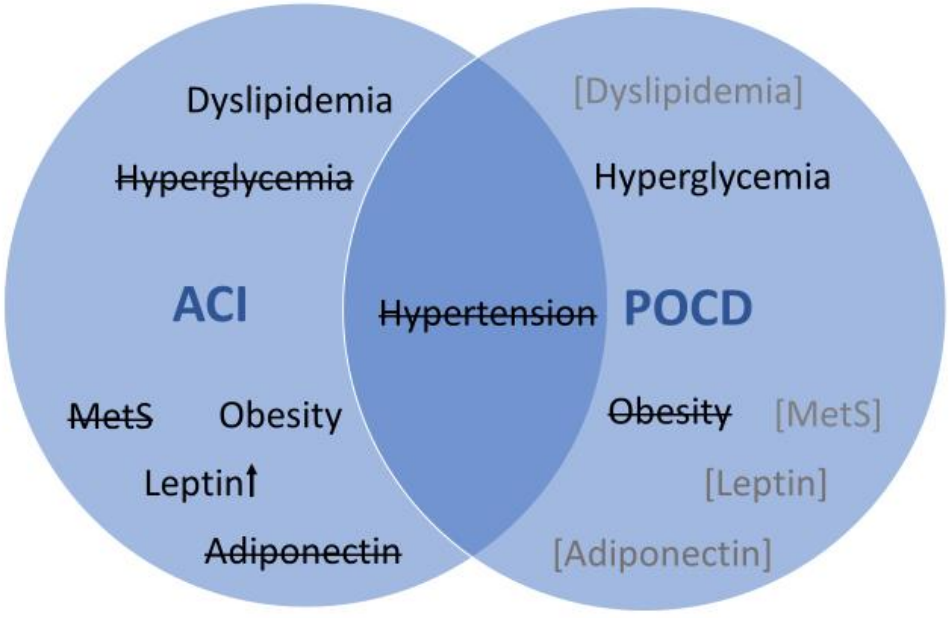

Figure 3: Summary of findings in this work (black font, identified as an independent risk factor for ACI/POCD in the respective fully adjusted model; strike through, not identified as independent risk factor; factors in brackets were not assessed). *for adjustment variables, see Sections 2.1 to 2.2*

3.1.2 Metabolic dysfunction is a potent risk factor for ACI

Previous research suggests that the association of metabolic dysfunction and ACI is complex and time-dependent (see Section 1.5.4). Whereas midlife metabolic dysfunction appears to increase later cognitive risk, once older age has been reached, this relationship appears to even out so that non-significant findings become more frequent. Metabolic dysfunction may even be associated with a reduced cognitive risk at this time. Here, in a series of cross-sectional analyses of metabolic dysfunction and ACI, we made a substantial contribution to the research field. We used 4 large cohorts of middle-aged to older adults. each with extensive anthropometric, clinical (and for BioCog, molecular) phenotyping as well as detailed cognitive testing procedures. Epidemiological studies of metabolic dysfunction and ACI thus far had frequently investigated isolated components, i.e. had focused exclusively on hyperglycemia for instance. Here, we ran hierarchical multivariate adjustment and within each study entered the individual parameters of metabolic dysfunction into a single statistical model to determine the potential independence of associations. This allowed preliminary conclusions as to the potential metabolic parameters statistically driving previous reports of associations of metabolic dysfunction with ACI and may provide a first insight into a potential causal relationship underlying any univariate associations. Additionally, for the first time, metabolic dysfunction and ACI were assessed in the perioperative setting, in patients who are scheduled to undergo surgery during the next few days. Results were mostly consistent with one another and with the research literature on ACI in non-surgical samples to some extent, but – mirroring the inconsistencies and often conflicting results of the literature itself – not entirely as further discussed below.

In the 3 RCTs, a higher BMI was identified as an independent risk factor for the presence of ACI [147]. This finding supports numerous previous studies, often of middle-aged to older age groups, that too had found cross-sectional associations of obesity with ACI [151-153], but it contrasts with other studies, often of older age groups, that had implicated obesity as associated with a reduced risk of ACI [96,97,100,101,154] or had reported null findings [94,99,155]. Relatively low sample age in the 3 RCTs (mean 61 years in OCTOPUS; mean 64 years in DESC; mean 70 years in SuDoCo) which in sum could be considered as "young-old" (e.g., [156]) may be a contributing factor here. Participants may simply not yet have been at an age where associations of obesity with increased risk of ACI begin to inverse, initially moving towards null before leading to associations of obesity with a reduced ACI risk in older age. We can only speculate as to the reason for the absence of an association of obesity with ACI in BioCog. Inspection of effect sizes and direction of associations suggests that a low statistical power was not the issue here. The marginally higher mean sample age of 72 years in the BioCog study may have contributed: BMI may have been a less accurate measure of obesity in BioCog as has been described previously for older age groups [97]; in the 3 RCTs BMI may have performed better as measure of obesity due to somewhat lower sample age. The null findings in BioCog may also reflect survival bias of "healthier" obese individuals to older age, or an influence of frailty, prodromal dementia or other

health conditions on metabolism, which overall may have evened out any associations of BMI with ACI in this cohort (see Section 1.5.4.3).

Albeit correlating relatively strongly with BMI, which itself was not associated with ACI, a higher plasma leptin concentration was associated with increased odds of having ACI in BioCog [149], as was also found for a higher HDL cholesterol concentration [150]. This work therefore adds to the limited epidemiological research literature on adipokines and ACI that had previously reported a higher leptin concentration as a risk factor for ACI [114] but also as associated with a lower risk of ACI [116]. It further adds to the literature on late-life lipids and ACI, which too had produced mixed results [85,98] and again had occasionally implicated dyslipidemia as associated with a reduced risk of ACI in older age [157,158] (see Section 1.5.4).

Crucially, BMI in the 3 RCTs [147], HDL cholesterol [150] and leptin in BioCog [149] each remained statistically significantly associated with ACI following adjustment for other metabolic parameters. Our data thus suggest that the link of obesity (3 RCTs), HDL cholesterol (BioCog) and leptin (BioCog) with ACI did not simply reflect their potential function as correlates of diabetes, hypertension and (for HDL cholesterol and leptin) BMI. Previous studies, too, had found that associations of leptin with ACI were independent of BMI (e.g., [114,159]) so that clearly the role of leptin goes beyond its function as a correlate of obesity, at least when measured using BMI. Leptin levels in the circulation are derived mainly from SAT [160], whereas adiponectin is derived from VAT [161]. Combined with the fact that BMI and adiponectin were each not associated with ACI in this cohort, the observed association of leptin with ACI may indicate that SAT, rather than total body obesity or VAT, may be a risk factor for ACI. However, again an inappropriateness of BMI as a measure of obesity in older age groups [97] and a possibility that the adiponectin assay did not produce accurate adiponectin data (which may be indicated by the observation that adiponectin did not correlate with leptin) are also strong possible explanations for the absence of statistically significant findings on these parameters. We did not have any data on other measures of obesity, such as % body fat, or on waist circumference which could have provided further insight into the role of fat mass and type of body fat in ACI risk.

Our results also show that the associations of BMI (3 RCTs) and leptin (BioCog) were not confounded by a low pre-morbid IQ indexed by education predisposing both poor lifestyle (leading to obesity [96,135,136]) and to low late-life cognition owed to the fact that people who start off with low IQ have a high probability of having a low IQ in later stages of life. As we did not adjust for pre-morbid IQ to preserve analysis N in the analysis of HDL cholesterol, its contribution to the observed association with ACI remains unknown. We cannot rule out that a lower pre-morbid IQ led both to dyslipidemia in older age as well as to ACI.

Throughout the analyses reported here, MetS and hypertension each appeared to play only a minor role as correlates of ACI even in analyses with minimal adjustment. This contrasts with many previous

research studies associating these risk factors with ACI [80,81,88,162,163] that too had occasionally included studies with brief follow-up periods (e.g., [86]) and cross-sectional design [164,165]. For instance, ACI was associated with hypertension in the Framingham Study of older adults with mean age 67 years [166] and with MetS in the Singapore Longitudinal Ageing Study with mean age 65 years. In the latter study, sensitivity analyses determined that the finding was driven by <75 year olds [81], again suggesting that the relationship of MetS with ACI may change across the lifespan. Of note, both in BioCog and the 3 RCTs, metabolic dysfunction was not a central part of the studies' primary research question. This may have affected ascertainment of metabolic dysfunction parameters. In BioCog for instance, MetS was defined from BMI rather than waist circumference as required per consensus statement [52]; hypertension was defined only from self-report and use of anti-hypertensive treatment rather than any blood pressure measurement. Of course, it is also possible that our binary operationalization of ACI may have "missed" important information on the spectrum of impairment that may have become apparent had we used ACI as a continuous variable (e.g., scores on a global ability factor).

The absence of an association with ACI in our studies was particularly surprising for hyperglycemia as it contradicts current understanding. Among the metabolic dysfunction parameters, hyperglycemia is the most consistently found and well-established risk factors for ACI in middle-age (e.g., [93,167]) as well as in older age (e.g., [109,168,169]) (see Section 1.5.4). Null findings on diabetes and ACI even when both are measured in older age are rare (e.g., [103]). Reported associations also typically remain statistically significant even after multivariate adjustment for potential confounding factors in these studies (e.g., [166]), whereas here, even minimally adjusted models did not reveal any associations of hyperglycemia with ACI across cohorts. Hyperglycemia indeed takes on a role as a risk factor in epidemiological research that is a strong candidate for causal effects on brain function: Observational evidence suggests an association of some forms of anti-hyperglycemic treatment with a lower risk of ACI [170] and a positive dose-response relationship between duration of diabetes and ACI risk (e.g., [93]). Additionally, the fact that type 1 diabetes too is a risk factor for ACI [171] offers striking evidence for detrimental causal effects of hyperglycemia per se on brain function. After all, type 1 diabetes is caused by factors unrelated to lifestyle [172] and does not cluster with obesity, dyslipidemia and hypertension. An influence of further, unmeasured factors is also possible. For instance, a recent meta-analysis suggests that the cognitive risk associated with hyperglycemia may be moderated by apolipoprotein E (APOE) genetic status such that the increased risk may only be found in carriers of the high-risk e4 allele [173]. APOEe4 may have been rare by chance in the analysis of only N=202 individuals in BioCog leading to null findings on hyperglycemia and ACI, though in the 3 RCTs with more than 1500 participants this explanation again is less likely to apply.

The surgical nature of our study samples could also be a contributing factor for our null results. We could simply observe the fact that MetS, hyperglycemia, hypertension, as well as adiponectin

concentration, play a different, less central role in ACI within this specific patient population as compared with the general older population that had produced previous epidemiological research of ACI.

Taken together, our results support metabolic dysfunction, and particularly obesity, elevated leptin and reduced HDL cholesterol concentrations as correlates of ACI. Independence from a range of potential confounders including pre-morbid IQ as well as (in some of the analyses presented here) one another may indicate a possible causality as underlying the associations which are further described below (see Section 3.1.4). Based on the totality of evidence from previous research, we can continue to consider hyperglycemia a firm risk factor for ACI at any age despite the present null results for this parameter across our samples of middle-aged to older adults. However, as this part of our results contradicts current understanding, further studies are needed in this direction.

3.1.3 First robust evidence for diabetes as an independent risk factor for POCD

The role of metabolic dysfunction in the development of POCD was almost entirely unknown prior to this work. Across several meta-analyses of previous epidemiological research, we determined that diabetes appeared to increase POCD risk [119]. Since almost all previous studies had reported unadjusted results, conclusions on any potential confounding factors versus potentially underlying causal relationships were rendered impossible based on the research literature, however. The analysis of metabolic dysfunction and POCD risk using original data from the 3 RCTs was an important next step as it allowed statistical adjustment for potential confounders. The conclusion of the meta-analysis was corroborated and extended by our results: diabetes was associated with an increased risk of POCD [148]. Thus, the well-established role of hyperglycemia as a risk factor for cognitive impairment appears to extend from ageing populations in general [82,174] to those that have been exposed to surgery. The association was of considerable effect size and was independent of age, sex, surgery-related factors, hypertension and obesity. The results extend findings from a previous small study of 75 patients undergoing carotid endarterectomy reporting that associations of diabetes with increased POCD risk at 1-month follow-up were independent of age, APOEe4 genotype and obesity (BMI>30kg/m^2) [175]. In our analysis, the association of diabetes with POCD was also independent of hypertension and of pre-morbid IQ indexed by educational level. This is a novel contribution to the field and indicates that the findings were not simply due to low-IQ individuals being predisposed to developing diabetes (e.g., [137]) as well as POCD [24]. Of note, our meta-analysis had determined no association of dyslipidemia with POCD across an analysis of 12 studies mainly reporting unadjusted results [121]. Thus, although we could not control for dyslipidemia due to a lack of data on cholesterol and triglyceride concentrations, we can assume that the diabetes-POCD association was unlikely statistically driven by dyslipidemia. Obesity and hypertension were each not independently associated with POCD in our analysis. It follows that the statistically non-significant trend for an association of obesity with increased POCD risk across 6 studies included in our meta-analysis that had mainly reported unadjusted results [20] may have been

(partly or fully) explained by obesity associations with diabetes. The absence of an association of hypertension partly defined from use of anti-hypertensive treatment with POCD is consistent with our meta-analysis of 24 previous studies [120]. Of note, analyses of hypertension when defined from anti-hypertensive treatment is hindered by the fact that patients receiving treatment may have normal blood pressure, often over the course of the previous decades, evening out any potential detrimental effects of hypertension itself on systemic vascular function. However, in support of this null finding, in our analysis, we also found no association with POCD for measured systolic and diastolic blood pressure.

In sum, the results presented here provide strong evidence for metabolic dysfunction, and particularly hyperglycemia, as an independent risk factor for POCD.

3.1.4 Potential mechanisms linking metabolic dysfunction to cognitive risk

A number of candidate mechanisms could explain observations of metabolic dysfunction associations with cognitive impairment. Psychosocial factors could mediate the relationship. For instance, metabolic dysfunction has a bidirectional relationship with depression [176]; depression in turn can impact on cognitive risk [177]. Further, highly correlated, mediating factors could include metabolic dysfunction-induced systemic endothelial dysfunction and atherosclerosis [178,179] affecting the entire body including the brain, as well as a systemic inflammatory response extending to the brain in form of neuroinflammation [180]. Consistent with such mechanisms, metabolic dysfunction has frequently been associated with cerebrovascular disease and damage, including stroke, altered white matter structure and function [181-183], as well as with a reduced cerebral blood flow (e.g., [184]) and deposition of Aβ in the brain (e.g., [185]). Of note, at least for our findings on HDL cholesterol and leptin, we found no evidence for mediation by cerebrovascular disease. Their associations with ACI remained statistically significant following adjustment for stroke and TIA, although a possibility for mediation by asymptomatic, subclinical cerebrovascular damage remains. Direct neurotoxic effects of glucose in particular are also well-described [186] and could contribute to any associations of metabolic dysfunction parameters with cognitive risk. Of course, these various potential mediators are also highly inter-related: inflammation promotes deposition of Aβ for instance [180]; atherosclerosis is linked to a reduced cerebral blood flow [187]. All may contribute to an increased cognitive risk in individuals with metabolic dysfunction.

In addition to its function as an indicator of metabolic dysfunction and particularly SAT mass, following transport across the BBB, leptin in particular may additionally exert causal negative effects on the brain [65], involving for instance an impact on vascular function and an increased inflammatory response [68]. In our analysis, leptin associations with ACI were found to be independent from concentrations of inflammatory markers [149], but these compounds were measured in the circulation and at a single time point. Thus, they may not be accurate markers of long-term exposure to neuroinflammatory processes, which may well have mediated the link of leptin with ACI in our study. A potential for a causal effect

of leptin on the brain is corroborated by our observation that leptin was associated with ACI only in non-obese (BMI<30 kg/m^2, i.e. presumably not leptin-resistant) but not in obese (BMI≥30 kg/m^2 i.e., presumably leptin resistant) individuals [149]. This type of pattern has been described previously in a study reporting that associations of leptin with ACI were restricted to participants without central obesity (albeit in that study a higher leptin associated with lower ACI risk in that subgroup) [116]. Leptin concentration was not measured in the 3 RCTs, but considering that the associations of BMI with ACI were driven by the obese (i.e., presumably leptin-resistant) subgroup speaks against mediation of the BMI-ACI relationship by leptin in that analysis.

In the cross-sectional analyses presented here, the possibility of reverse causality, with ACI leading to metabolic dysfunction, can presumably be neglected. Whereas beginning ACI can be accompanied by a reduced food intake for instance due to sensory impairment or a loss of appetite, an effect of beginning ACI on increased food intake leading to obesity, dyslipidemia and elevated leptin levels appears unlikely. Reverse causality is also unlikely to explain the results from our prospective analyses showing that diabetes is associated with an increased POCD risk.

Potential confounding factors need to be considered. Each of our findings were independent of a range of potential confounders (see Section 3.1.2), but as in all epidemiological research, other, unmeasured factors may have contributed. Based on the present observational data, we are unable to determine which (if any) of these processes underlay our data.

3.2 Low diagnostic accuracy for AD of novel plasma Aβ assay

Although there is currently no effective treatment for dementia, people living with dementia are reliant on diagnostics for appropriate care and awareness among families, physicians and employers. AD diagnosis using currently available diagnostic tools (brain imaging; measurement of CSF biomarkers) is costly and distressing to patients. In a methodological study, we therefore aimed to determine whether the diagnostic procedure for AD can be improved by a novel, commercially available assay for measurement of Aβ concentration in plasma. In the study of 100 patients attending a memory clinic, of whom 50 had AD and 50 were dementia-free, we found that the assay was unable to distinguish well between confirmed AD cases and controls [188]. In contrast, age and presence of the APOEe4 allele performed well as expected based on their roles as the most prominent predictors of AD [146]. Thus, we can conclude that measurement of plasma Aβ – at least when measured using the present assay – is not useful as an additional diagnostic step over and above the established biomarkers for AD let alone milder forms of ACI within the spectrum of impairment between normative decline and dementia. This finding contradicts previous studies affiliated with the manufacturer [142] including some published after our analysis [189] and necessitates further evaluation, because small sample size was a major limitation.

4. Implications

Epidemiological research provides information on potential underlying mechanisms, i.e., pathophysiology, on at-risk individuals and on potential targets for intervention. Even if non-causal mechanisms are found for a specific risk factor, then this risk factor offers important information on at-risk individuals. Thus, our results support metabolic dysfunction as a correlate of and a risk factor for cognitive impairment that could be used for risk stratification and risk prediction. For instance, a physician could gauge the individual risk of a patient based on their metabolic profile and initiate regular cognitive monitoring. With respect to POCD in particular, the information on cognitive risk could be used for decision-making on whether or not to suggest elective surgery at all. Patients themselves could also be empowered in this decision-making process. Our findings suggest that careful consideration of whether or not to perform surgery could be indicated particularly for patients with diabetes who appear to be at a substantially increased risk of developing POCD.

Metabolic dysfunction is a modifiable risk factor. Thus, if associations of metabolic dysfunction with cognitive impairment in the present and previous studies indeed reflect causality, for instance through the mechanisms described in Section 3.1.4, then this implies a potential for intervention. While prevention of metabolic dysfunction is a priority to avoid a range of complications such as diabetic neuropathy and cardiovascular disease, the present results underline that cognitive impairment should be added to this list of potentially avoidable complications.

This work has contributed to epidemiological research that to date had focused primarily on ACI rather than POCD by showing that metabolic dysfunction not only increases ACI risk but also POCD risk. This shared risk factor may support POCD as a condition that mirrors cognitive ageing processes and may share pathophysiology with ACI. Nonetheless, among the parameters of metabolic dysfunction, results were not entirely consistent across ACI and POCD with evidence of obesity, elevated leptin concentration and reduced HDL concentration (at least in some of the analyses presented here) as risk factors for ACI and hyperglycemia as a risk factor for POCD. The topic requires further research ideally in a single sample with data on ACI as well as POCD to refute or confirm the results presented here.

Finally, our evaluation of the diagnostic accuracy of a novel plasma Aβ assay has advanced the research field of AD diagnostics. A wave of research papers has been published on blood-based biomarkers of AD in recent years. By showing that the assay presented here did not perform well, we have been able to steer the research community towards more promising directions. Research can now focus on other measurement techniques for plasma Aβ (e.g., [14,190]) or other blood-based biomarkers altogether (e.g., [191,192]). Based on recent advances in the field, we are hopeful that imaging and CSF biomarker analysis for AD diagnosis can eventually be replaced by simple blood collection for biomarker analysis.

5. Outlook

Further research is needed to determine the replicability and generalizability of the findings presented in this work with the aim to fully elucidate the association of metabolic dysfunction and cognitive impairment in the perioperative setting. The prospective analysis of the BioCog cohort will provide an important next step and will allow an in-depth analysis of associations of conventional metabolic dysfunction parameters as well as adipokine concentration with POCD.

Based on the present results, researchers investigating metabolic dysfunction and cognitive impairment are advised to run sensitivity analyses comparing findings for instance for obese versus non-obese subgroups throughout. Future epidemiological studies on metabolic dysfunction and cognitive impairment should also consider not only measuring parameters of metabolic dysfunction at a single time point, but also assessing within-person variability in metabolic parameters over time. Such variability has recently been identified as a potential additional risk factor for ACI [193,194] and has never been investigated in the context of POCD. Whereas here, we used ACI as encompassing any type of impairment, a comparison of metabolic dysfunction associations with ACI stemming from vascular damage (vascular dementia, VaD) versus AD-type pathology could prove useful. Based on pro-inflammatory effects of leptin compromising vascular health combined with evidence from mouse models for a potential of leptin to reduce brain Aβ burden [195] and resultant cognitive impairment [196], one could expect that higher leptin concentration is associated particularly with VaD rather than AD, for instance.

Observational studies could be supplemented by trial studies to determine causality in associations that could potentially result in preventive measures. For instance, an RCT could evaluate whether the various forms of anti-diabetic treatment and their intensity (i.e., glycemic treatment targets) differently affect patients' POCD risk in analyses akin to existing studies of ACI [197].

The prospective data available for BioCog can now also be used to further evaluate the plasma Aβ assay. Although based on the evidence presented here an ability of the plasma Aβ assay to add to the epidemiological characterization of POCD or to add to a potential future diagnostic procedure for POCD is doubtful, further exploration in this direction using available BioCog data will help further advance the field.

6. Conclusion

ACI and POCD share symptomology but whether or not they share epidemiology to date had not been determined. We used a total of 4 cohorts of middle-aged to older surgical patients and found evidence for metabolic dysfunction as a risk factor for ACI before surgery as well as for POCD although the specific metabolic parameters predictive of the conditions differed for ACI and POCD. Combined with findings from previous research, our results indicate a – in part – shared epidemiology which may potentially suggest shared underlying pathophysiological mechanisms. Our findings imply metabolic dysfunction as a key parameter that allows for risk stratification, cognitive monitoring and (potentially) intervention with the aim to reduce cognitive risk in older people in general and after surgery. Further studies in this direction should be made a priority. A novel assay for measurement of Aβ in plasma did not perform well as a diagnostic tool for AD and cannot be recommended for future use based on our data.

7. References

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9. Declaration

Erklärung

§ 4 Abs. 3 (k) der HabOMed der Charité

Hiermit erkläre ich, dass ich

- weder früher noch gleichzeitig ein Habilitationsverfahren durchgeführt oder angemeldet wurde,

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- mir die geltende Habilitationsordnung bekannt ist.

Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

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