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Metabolic syndrome and the risk of postoperative delirium and postoperative cognitive dysfunction: a multi-centre cohort study

Insa Feinkohl[1,2,*], Jürgen Janke[2,3], Arjen J. C. Slooter[4,5,6], Georg Winterer[7], Claudia Spies[7], Tobias Pischon[2,3,7,8], the BioCog Consortium

[1]Witten/Herdecke University, Medical Biometry and Epidemiology Group, Witten, Germany, [2]Max-Delbrueck-Center for Molecular Medicine in the Helmholtz Association (MDC), Molecular Epidemiology Research Group, Berlin, Germany, [3]Max-Delbrueck-Center for Molecular Medicine in the Helmholtz Association (MDC), Biobank Technology Platform, Berlin, Germany, [4]Department of Intensive Care Medicine, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands, [5]Department of Psychiatry and UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands, [6]Department of Neurology, UZ Brussel and Vrije Universiteit Brussel, Brussels, Belgium, [7]Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany and [8]Berlin Institute of Health at Charité - Universitätsmedizin Berlin, Core Facility Biobank, Berlin, Germany

*Corresponding author. E-mails: insa.feinkohl@uni-wh.de, insa.feinkohl@mdc-berlin.de

Abstract

Background: Metabolic syndrome and its components are risk factors for cognitive impairment, but their contribution to perioperative neurocognitive disorders is unknown. We examined their associations with the risk of postoperative delirium (POD) and postoperative cognitive dysfunction (POCD) in older patients.

Methods: In 765 male and female participants aged ≥65 years, we measured preoperative metabolic parameters and screened for POD for 7 days or until discharge. POCD was defined through comparison of cognitive change on six neuropsychological tests with non-surgical controls. Multiple logistic regression analyses examined the association of metabolic parameters with risk of POD and POCD with adjustment for age, sex, and surgery type.

Results: A total of 149 patients (19.5% of 765) developed POD and 53 (10.1% of 520 attendees) had POCD at 3 months. Patients with metabolic syndrome were at 1.85-fold higher risk of POD (95% confidence interval [CI] 1.26–2.70). Each 1 mM higher high-density lipoprotein cholesterol (HDL-C) was associated with a 0.47-fold lower POD risk (95% CI 0.30–0.74). Each 1 kg m^{-2} higher body mass index (BMI) was associated with a 1.09-fold higher POCD risk (95% CI 1.02–1.16).

Conclusions: Older surgical patients with metabolic syndrome were at increased risk of POD. Only reduced HDL-C was significantly associated with POD. For POCD, a higher preoperative BMI was identified as a risk factor. These findings add to mounting evidence of a distinct epidemiology of POD and POCD. Screening programmes taking advantage of HDL-C and BMI measurements and of metabolic interventions in reducing perioperative neurocognitive disorders should be evaluated.

Clinical trial registration: NCT02265263.

Keywords: cholesterol; epidemiology; metabolic syndrome; obesity; postoperative cognitive dysfunction; postoperative delirium

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Editor's key points

- Metabolic syndrome characterized by a cluster of metabolic abnormalities has been associated with age-related cognitive impairment, whereas its role in perioperative neurocognitive disorders is unclear.
- Among a large cohort of 765 older surgical patients, we found that those with metabolic syndrome were at increased risk of developing postoperative delirium during the immediate postoperative phase.
- Obesity defined by body mass index was identified as a risk factor for postoperative cognitive dysfunction at 3 months.
- Our results support postoperative delirium and postoperative cognitive dysfunction as distinct conditions with distinct risk factor profiles.
- Patients' preoperative metabolic state could be used for risk assessment and potentially function as a target for intervention in future trials.

Neurocognitive disorders are common complications of surgery. Postoperative delirium (POD) is characterised by acute cognitive disturbances, such as agitation or confusion, during the days after surgery. Postoperative cognitive dysfunction (POCD) describes a decline in cognitive test performance compared with presurgical performance. More than 20% of surgical patients can be affected by POD[1] and 10–25% develop POCD during the 3–6 months after surgery.[2] In view of an estimated 313 million surgical procedures performed each year,[3] the resulting high absolute numbers of affected patients burden health systems globally. Nonetheless, research into POD and POCD has only recently gained in momentum.[2] Knowledge of POD and POCD risk factors is crucial to gaining insight into their aetiologies, which are unclear as yet,[1] and to initiate preventive measures.

Metabolic dysfunction was traditionally a 'Western world' problem but is gaining in relevance in developing countries.[4] Metabolic syndrome (MetS) is a cluster of abnormalities that tend to coexist, including abdominal obesity, elevated blood pressure, elevated blood glucose levels, low high-density lipoprotein cholesterol (HDL-C) levels, and elevated triglyceride levels. Although the concept of MetS has been a matter of debate, it is now frequently used for assessment of cardiovascular and mortality risk.[5] Prospective cohort studies have shown that MetS or its components are also related to age-related cognitive impairment. Hyperglycaemia,[6] dyslipidaemia,[7] obesity,[8] hypertension,[9] and MetS[10,11] each have been associated with accelerated cognitive ageing. However, whether or not MetS and its components are relevant risk factors in the perioperative setting is uncertain. Recent systematic reviews and meta-analyses in this context[12–16] are limited by the fact that included studies had small sample sizes, used heterogeneous definitions of POD/POCD, often used coarse cognitive screening instruments for POCD, and infrequently applied statistical adjustment for confounding factors.

We therefore aimed to evaluate the associations of preoperative metabolic syndrome and its components with the risk of POD and POCD in a large cohort of older surgical patients.

Methods

Study design

The Biomarker Development for Postoperative Cognitive Impairment in the Elderly (BioCog) study was a cohort study with recruitment of surgical patients in hospitals in Berlin, Germany and Utrecht, the Netherlands.[17] Patients were at least ≥65 yr old and had Mini-Mental State Examination scores ≥24 (full inclusion criteria[18]).

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, Ref 14/469).

Baseline sociodemographic, clinical, and mood assessments

Sociodemographic information was self-reported. Medical history (hypertension, coronary heart disease, transient ischaemic attack, stroke, diabetes) was determined from a combination of self-report and local hospital records. The Geriatric Depression Scale assessed depressive symptoms. A vocabulary-based test estimated pre-morbid intelligence quotient (IQ) before any age-related or disease-related declines. Blood was collected in the supine position after an overnight fast immediately before surgery and was sent to a laboratory adjacent to the respective hospital site. Blood was stored in a central biobank at −80°C for future analysis. Surgery type and anaesthesia duration were recorded.

Preoperative metabolic dysfunction

Height and weight were measured for calculation of body mass index (BMI). Haemoglobin A1c (HbA1c) was measured from ethylenediaminetetraacetic acid (EDTA) whole blood samples at laboratories adjacent to the hospital sites. Glucose, triglyceride, and HDL-C were measured from serum at adjacent laboratories for a subset of patients (513 of 765 patients). For logistical reasons, for another subset (252 of 765 patients), they were measured from biobank serum. Statistical analyses controlled for this factor. We defined MetS[10] (see Feinkohl and colleagues[7]; Supplementary Table S1) as ≥3 of 5 criteria: (1) obesity, (2) elevated fasting triglyceride, (3) reduced HDL-C, (4) elevated blood pressure, and (5) elevated glucose.

Postoperative delirium

Patients were monitored for POD by trained staff daily after surgery at 8 am and 7 pm (plus or minus 1 h). POD was identified if patients were positive at least once between surgery and postoperative day 7 or discharge, on one or more of: (1) ≥2 cumulative points on the Nursing Delirium Screening Scale; (2) positive Confusion Assessment Method or Confusion Assessment Method-Intensive Care Unit score; (3) patient chart review that showed descriptions of delirium (e.g., agitated, drowsy).

Postoperative cognitive dysfunction

Preoperatively and at the 3-month follow-up, patients performed six age-sensitive neuropsychological tests. Four were from the CANTAB® battery (Verbal Recognition Memory; Paired Associates Learning; Spatial Span; Simple Reaction

Time) and two were conventional tests (Trail-Making Test; Grooved Pegboard). POCD was defined using International Study of Postoperative Cognitive Dysfunction criteria which rely on comparison of a patient's change in performance with the mean change in a non-surgical control group. The control group consisted of volunteers aged >65 yr and based in Berlin or Utrecht, who were recruited from outpatient clinics, primary care facilities, care homes, and public talks, but who had not been exposed to surgery during the previous 6 months or the next 3 months.[19]

Dataset for analysis and missing data

Any missing data on adjustment variables were imputed. Data on surgery type were missing for nine patients. These patients were assigned the most frequently observed type (peripheral surgery; e.g., knee surgery). Missing data on coronary heart disease (n=20), transient ischaemic attack (n=21), and stroke (n=16) were assigned as 'absent'. Data on anaesthesia duration were missing for 10 patients. As a result of late introduction of assessment of pre-morbid IQ and depression, data on these parameters were missing for 124 patients. For each of these latter continuous variables, patients were assigned the medians. For exposure (metabolic parameters) or outcome (POD, POCD) variables, only cases with complete data were used. This applied also to analyses of POCD at 3 months which were affected by loss to follow-up.

Statistical analysis

Each metabolic parameter was used as a continuous exposure and as quartiles. MetS and each of the five MetS components were used as categorical exposures. We created a numeric variable based on the number of MetS components present in a patient (range 0–5). Baseline patient characteristics were compared between groups using t-test, Mann–Whitney U-test, and χ^2 test. The χ^2 tests determined the associations among the five MetS components, and the association of POD with POCD.

Multiple logistic regression analyses examined the associations of exposure to each metabolic parameter with the outcomes POD and POCD. Model 1 adjusted for the potential confounding factors age, sex, analysis laboratory, analysis batch, and surgery type. Models 2 and 3 additionally adjusted for the potential preoperative mediators coronary heart disease, transient ischaemic attack, stroke, and depression. Model 3 additionally adjusted for anaesthesia duration as a potential intraoperative mediator (Supplementary Figs S1–S3).

Associations that were statistically significant in model 3 were: (1) adjusted for pre-morbid IQ to determine a confounding role of a low cognitive reserve (possibly leading to metabolic dysfunction and to POCD[20] and POD[1,12]; (2) repeated with exclusion of underweight patients (BMI <18.5 kg m^{-2}); and (3) (for POCD only) adjusted for POD to evaluate a mediating role of POD. In a final step, all metabolic parameters were entered concurrently into model 3 to determine their relative independence.

In *post hoc* analyses, we repeated model 3 with exclusion of patients with C-reactive protein (CRP) ≥10 mg L^{-1} to assess whether any patients affected by inflammatory diseases (e.g., infections) had potentially skewed our results. We also split up the 'elevated glucose' exposure into its components 'diabetes' and 'glucose ≥5.5 mM, to further explore the surprising null findings found for this exposure.

Results

Sample characteristics

A total of 765 patients had complete metabolic and POD data and provided the analysis sample for the outcome of POD. Of those, 423 patients (55.3%) underwent peripheral surgery, 331 (43.3%) had abdominal, thoracic, or pelvic surgery, and 10 (1.3%) had intracranial surgery. 520 patients (68.0%) attended the 3-month follow-up. These patients were more likely to be male and had a better metabolic profile (Supplementary Table S2). Reasons for non-attendance included lack of interest and death (33 patients died by 3 months).

Preoperative metabolic dysfunction

Prevalence of MetS was 37.1%. Baseline characteristics of the entire study population, and stratified by MetS, are shown in Table 1. All five MetS components were strongly associated with one another (see Supplementary Table S3). MetS was not associated with surgery type (P=0.25), but was associated with a longer anaesthesia duration (MetS, median 220 min; no MetS 185 min; P<0.001).

Postoperative delirium and postoperative cognitive dysfunction

Of 765 patients, 149 (19.5%) developed POD between surgery and postoperative day 7 or discharge. Of 520 attendees of the 3-month follow-up (68.0% of the 765 patients), 72 (13.8%) had experienced POD and 53 (10.1%) had developed POCD. Of the latter 53, five (9.4% of 53) had experienced POD previously. POD was not significantly associated with POCD (P=0.33).

Preoperative metabolic dysfunction and postoperative delirium risk

Results on metabolic parameters are shown in Table 2. Each 1 mM higher HDL-C was associated with a 0.47-fold lower POD risk (model 1, 95% confidence interval [CI] 0.30–0.74). For triglyceride, some degree of non-linearity was observed, given that patients in quartile 4 of triglyceride were at 2.34-fold higher risk of POD (95% CI 1.35–4.06) whereas triglyceride as a continuous measure was not associated with POD. HbA1c, glucose, and BMI were not associated with POD throughout.

Reduced HDL-C was associated with a 2.11-fold higher POD risk (model 1, 95% CI 1.43–3.12; Table 3). The remaining four components were each associated with modestly higher POD risk, but none of these associations were statistically significant. Patients with MetS were at a 1.85-fold increased risk of POD (95% CI 1.26–2.70). Each additional MetS component present within a patient was associated with a 1.24-fold higher POD risk (95% CI 1.08–1.42; Table 3, Supplementary Table S4).

Results in model 1 survived adjustment for coronary heart disease, transient ischaemic attack, stroke, and depression (model 2). A longer anaesthesia duration was associated with an increased POD risk (odds ratio [OR] per 1 h increment 1.17, 95% CI 1.11–2.24) and its addition into model 3 reduced the strengths of associations throughout.

When BMI, triglyceride, HDL-C, and glucose were entered into a single model 3, the association of a higher HDL-C with reduced POD risk persisted (OR mM increment 0.54, 95% CI

Table 1 Baseline characteristics according to metabolic syndrome (MetS) status. Data on any variables with missing data shown before imputation. *t-test, Mann–Whitney or χ^2 test comparing groups with *vs* without MetS. ‡Data for *n*=695. ¶For definitions, see Supplementary Table S1. BP, blood pressure; CHD, coronary heart disease; HbA1c, haemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; IQ, intelligence quotient; IQR, inter-quartile range; MetS, metabolic syndrome; MMSE, Mini Mental State Examination; SD, standard deviation; TG, triglycerides; TIA, transient ischaemic attack..

	Patients with data until 7-days/hospital discharge					Attendees of 3-month follow-up		
	All (*n*=765)		Patients without MetS (*n*=481)	Patients with MetS (*n*=284)	P-value*	Patients without MetS (*n*=345)	Patients with MetS (*n*=175)	P-value*
	Missing *n* (%)	Mean (SD), median (IQR), or *n* (%)	Mean (SD), median (IQR), or *n* (%)	Mean (SD), median (IQR), or *n* (%)		Mean (SD), median (IQR), or *n* (%)	Mean (SD), median (IQR), or *n* (%)	
Age, yr, mean (SD)	—	72.4 (5.0)	72.5 (5.1)	72.3 (4.8)	0.59	72.4 (5.2)	71.8 (4.4)	0.21
Male sex, *n* (%)	—	439 (57.4)	297 (61.7)	142 (50.0)	0.002	217 (62.9)	99 (56.6)	0.16
CHD, *n* (%)	20 (2.6)	145 (19.5)	79 (17.0)	66 (23.7)	0.03	53 (15.9)	43 (24.7)	0.02
TIA, *n* (%)	21 (2.7)	28 (3.8)	12 (2.6)	16 (5.7)	0.03	9 (2.7)	11 (6.4)	0.05
Stroke, *n* (%)	16 (2.1)	43 (5.7)	25 (5.4)	18 (6.4)	0.57	16 (4.6)	11 (6.3)	0.42
MMSE, median (IQR)	—	29 (28–30)	29 (28–30)	29 (27–30)	0.03	29 (28–30)	29 (28–30)	0.29
Pre-morbid IQ, mean (SD)	124 (16.2)	112 (13)	114 (14)	110 (15)	<0.001	115 (14)	109 (15)	<0.001
Depression score, median (IQR)	124 (16.2)	1 (1–2)	1 (0–2)	2 (1–3)	<0.001	1 (0–2)	2 (1–3)	0.001
Glucose, mM, median (IQR)	—	5.5 (4.8–6.4)	5.1 (4.5–5.7)	6.4 (5.7–7.7)		5.2 (4.6–5.8)	6.4 (5.7–7.6)	
HbA1c‡, mM, median (IQR)	70 (9.2)	35 (32–39)	34 (31–37)	38 (34–46)		34 (32–37)	38 (34–47)	
HDL-C, mM, mean (SD)	—	1.3 (0.4)	1.5 (0.4)	1.1 (0.4)		1.5 (0.4)	1.1 (0.4)	
TG, mM, median (IQR)	—	1.5 (1.1–1.9)	1.3 (1.0–1.6)	2.0 (1.5–2.6)		1.2 (0.9–1.6)	1.9 (1.5–2.6)	
BMI, kg m^{-2}, mean (SD)	—	27.2 (4.7)	25.6 (3.6)	29.9 (5.1)		25.7 (3.4)	30.0 (4.5)	
Underweight (BMI<18.5 kg m^{-2}), *n* (%)	—	10 (1.3)	9 (1.9)	1 (0.4)		4 (1.2)	0 (0)	
Normal weight (18.5–24.9 kg m^{-2}), *n* (%)	—	238 (31.1)	198 (41.2)	40 (14.1)		139 (40.3)	18 (10.3)	
Overweight (25–29.9 kg/m^2), *n* (%)	—	339 (23.3)	234 (48.6)	105 (37.0)		174 (50.4)	68 (38.9)	
Obesity (≥30 kg m^{-2}), *n* (%)	—	178 (23.3)	40 (8.3)	138 (48.6)		28 (8.1)	89 (50.9)	
Elevated TG¶, *n* (%)	—	291 (38.0)	96 (20.0)	195 (68.7)		65 (18.8)	112 (64.0)	
Reduced HDL-C¶, *n* (%)	—	240 (31.4)	58 (12.1)	182 (64.1)		38 (11.0)	102 (58.3)	
Elevated BP¶, *n* (%)	—	490 (64.1)	241 (50.1)	249 (87.7)		162 (47.0)	156 (89.1)	
Elevated fasting glucose¶, *n* (%)	—	408 (54.0)	162 (33.4)	243 (85.6)		126 (36.5)	150 (85.7)	
Number of MetS components	—							
0	—	95 (12.4)	95 (19.8)			77 (22.3)		
1	—	176 (23.0)	176 (36.6)			117 (33.9)		
2	—	210 (27.5)	210 (43.7)			151 (43.8)		
3	—	166 (21.7)	—	166 (58.5)		—	106 (60.6)	
4	—	81 (10.6)	—	81 (28.5)		—	54 (30.9)	
5	—	37 (4.8)	—	37 (13.0)		—	15 (8.6)	

Table 2 Risk of postoperative delirium (POD) according to metabolic parameters. Results shown for logistic regression analyses with outcome cognitive impairment. Model 1: adjusted for age, sex, analysis laboratory, analysis batch, surgery type. Model 2: + coronary heart disease, transient ischaemic attack, stroke, depression score. Model 3: + anaesthesia duration. *Data for n=695. †Results of model 3 with BMI, triglyceride (TG), HDL-C, and glucose entered into single model: BMI, OR 1.00, 95% CI 0.96–1.05; TG, OR 0.92, 95% CI 0.76–1.11; HDL-C, OR 0.54, 95% CI 0.33–0.89; glucose, OR 1.02, 95% CI 0.90–1.16. ‡Results of single model with BMI, TG, HDL-C, and HbA1c: HbA1c, OR 1.01, 95% CI 0.98–1.03. CI, confidence interval; HbA1c, haemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; OR, odds ratio.

	Quartiles				P_{trend}	Continuous parameters	
	1	2	3	4		OR (95% CI) per unit increment	P-value
Body mass index							
Cut-point	14.7–24.1	24.1–26.7	26.7–29.4	29.5–46.8			
n with POD/*N* total	45/193	31/190	34/192	39/190			
Model 1	Ref	0.68 (0.40–1.15)	0.79 (0.47–1.33)	0.91 (0.55–1.51)	0.51	1.01 (0.97–1.05)	0.65
Model 2	Ref	0.69 (0.41–1.18)	0.81 (0.48–1.37)	0.84 (0.50–1.41)	0.61	1.00 (0.96–1.04)	0.91
Model 3	Ref	0.80 (0.46–1.40)	0.89 (0.51–1.55)	0.91 (0.53–1.56)	0.90	1.01 (0.97–1.05)†	0.67†
Triglycerides							
Cut-point (mM)	0.3–1.1	1.1–1.5	1.5–1.9	1.9–28.9			
n with POD/*N* total	28/196	42/188	27/191	52/190			
Model 1	Ref	1.92 (1.10–3.34)	0.92 (0.51–1.68)	2.34 (1.35–4.06)	0.001	1.07 (0.95–1.20)	0.27
Model 2	Ref	1.91 (1.09–3.35)	0.94 (0.51–1.72)	2.31 (1.32–4.02)	0.001	1.07 (0.95–1.19)	0.28
Model 3	Ref	1.69 (0.94–3.03)	0.90 (0.48–1.69)	1.84 (1.04–3.29)	0.03	0.99 (0.86–1.15)†	0.94†
HDL-C							
Cut-point (mM)	0.1–1.0	1.1–1.3	1.3–1.6	1.6–3.1			
n with POD/*N* total	55/193	39/196	24/185	31/191			
Model 1	Ref	0.64 (0.39–1.05)	0.64 (0.39–1.05)	0.49 (0.29–0.83)	0.005	0.47 (0.30–0.74)	0.001
Model 2	Ref	0.66 (0.40–1.08)	0.44 (0.25–0.77)	0.53 (0.31–0.90)	0.02	0.50 (0.32–0.79)	0.003
Model 3	Ref	0.68 (0.40–1.14)	0.49 (0.27–0.88)	0.57 (0.32–0.99)	0.08	0.57 (0.36–0.19)†	0.02†
Glucose							
Cut-point (mM)	1.6–4.8	4.8–5.5	5.5–6.4	6.4–16.0			
n with POD/*N* total	33/203	37/188	35/186	44/188			
Model 1	Ref	1.30 (0.75–2.24)	1.51 (0.86–2.67)	1.71 (1.00–2.91)	0.25	1.10 (0.99–1.21)	0.08
Model 2	Ref	1.27 (0.73–2.20)	1.46 (0.83–2.58)	1.56 (0.91–2.68)	0.42	1.08 (0.97–1.20)	0.15
Model 3	Ref	1.33 (0.76–2.33)	1.26 (0.70–2.28)	1.31 (0.74–2.30)	0.74	1.04 (0.92–1.16)†	0.54†
HbA1c*							
Cut-point (mM)	15–32	32–35	35–39	39–88			
n with POD/*N* total	47/211	29/162	31/157	33/165			
Model 1	Ref	0.89 (0.52–1.53)	1.01 (0.58–1.74)	1.01 (0.60–1.72)	0.97	1.01 (0.99–1.03)	0.56
Model 2	Ref	0.92 (0.53–1.58)	0.97 (0.56–1.58)	0.91 (0.53–1.58)	0.99	1.00 (0.98–1.03)	0.76
Model 3	Ref	1.02 (0.58–1.78)	0.90 (0.50–1.60)	0.89 (0.50–1.57)	0.96	1.01 (0.98–1.03)‡	0.68‡

Table 3 Metabolic syndrome each of the five metabolic syndrome components, and postoperative delirium risk. *N*=765. Model 1: adjusted for age, sex, analysis laboratory, analysis batch, surgery type. Model 2: + coronary heart disease, transient ischaemic attack, stroke, depression score. Model 3: + anaesthesia duration. *For definitions, see Supplementary Table S1. Each row represents a separate analysis. ‡Results of model 3 with 'obesity', 'elevated TG', 'reduced HDL-C', 'elevated BP', and 'elevated glucose' entered concurrently into single model: 'obesity', OR 1.09, 95% CI 0.67–1.76; 'elevated TG', OR 1.00, 95% CI 0.65–1.54; 'reduced HDL-C', OR 1.87, 95% CI 1.21–2.91; 'elevated BP', OR 0.98, 95% CI 0.62–1.55; 'elevated glucose', OR 0.90, 95% CI 0.58–1.40. BP, blood pressure; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; OR, odds ratio; TG, triglycerides.

	Model 1		Model 2		Model 3	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Metabolic syndrome*	1.85 (1.26–2.70)	0.002	1.70 (1.15–2.50)	0.008	1.58 (1.06–2.38)	0.03
Obesity*	1.22 (0.79–1.89)	0.37	1.12 (0.72–1.75)	0.62	1.13 (0.71–1.80)‡	0.60‡
Elevated TG*	1.38 (0.94–2.02)	0.10	1.37 (0.93–2.01)	0.12	1.16 (0.77–1.74)‡	0.49‡
Reduced HDL-C*	2.11 (1.43–3.12)	<0.001	2.01 (1.35–2.98)	0.001	1.84 (1.21–2.78)‡	0.004‡
Elevated BP*	1.18 (0.79–1.77)	0.42	1.05 (0.69–1.59)	0.83	1.02 (0.66–1.59)‡	0.92‡
Elevated glucose*	1.35 (0.92–1.99)	0.13	1.27 (0.86–1.88)	0.24	1.06 (0.70–1.60)‡	0.77‡
Number of metabolic syndrome components (continuous)	1.24 (1.08–1.42)	0.003	1.19 (1.04–1.38)	0.02	1.13 (0.97–1.31)	0.18

Table 4 Risk of postoperative cognitive dysfunction (POCD) according to metabolic parameters. Results shown for logistic regression analyses with outcome POCD. Model 1: adjusted for age, sex, analysis laboratory, analysis batch, surgery type. Model 2: + coronary heart disease, transient ischaemic attack, stroke, depression score. Model 3: + anaesthesia duration. *Data for *n*=462. †Results of model 3 with BMI, TG, HDL-C, and glucose entered into single model: BMI, OR 1.08, 95% CI 1.01–1.18; TG, OR 0.86, 95% CI 0.58–1.29; HDL-C, OR 0.70, 95% CI 0.32–1.54; glucose, OR 1.00, 95% CI 0.82–1.23. ‡Results of single model with BMI, TG, HDL-C, and HbA1c: HbA1c, OR 0.99, 95% CI 0.95–1.03. CI, confidence interval; HbA1c, haemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; OR, odds ratio. Bold signifies statistically significant at p<0.05.

	Quartiles				P_{trend}	Continuous parameters	
	1	2	3	4		OR (95% CI) per unit increment	P-value
Body mass index							
Cut-point	14.7–21.1	24.1–26.7	26.7–29.4	29.5–41.8			
n with POCD/*N* total	19/122	17/140	16/132	20/126			
Model 1	Ref	1.32 (0.54–3.23)	1.44 (0.57–3.65)	2.55 (1.09–5.97)	0.14	1.09 (1.02–1.16)	0.009
Model 2	Ref	1.33 (0.54–3.27)	1.42 (0.56–3.61)	2.47 (1.05–5.84)	0.18	1.09 (1.02–1.16)	0.01
Model 3	Ref	1.34 (0.55–3.30)	1.42 (0.56–3.60)	2.47 (1.05–5.83)	0.18	1.09 (1.02–1.16)†	0.01†
Triglycerides							
Cut-point (mM)	0.3–1.1	1.1–1.5	1.5–1.9	1.9–28.9			
n with POCD/*N* total	16/151	25/132	11/126	20/111			
Model 1	Ref	1.74 (0.78–3.88)	1.46 (0.62–3.40)	1.47 (0.60–3.60)	0.60	0.96 (0.77–1.19)	0.70
Model 2	Ref	1.72 (0.76–3.87)	1.45 (0.62–3.43)	1.45 (0.59–3.57)	0.63	0.96 (0.77–1.20)	0.70
Model 3	Ref	1.70 (0.75–3.85)	1.45 (0.61–3.43)	1.43 (0.58–3.55)	0.64	0.95 (0.76–1.20)†	0.68†
HDL-C							
Cut-point (mM)	0.1–1.0	1.1–1.3	1.3–1.6	1.6–3.1			
n with POCD/*N* total	23/115	21/130	12/131	16/144			
Model 1	Ref	1.40 (0.59–3.31)	1.38 (0.57–3.34)	0.71 (0.27–1.87)	0.36	0.62 (0.30–1.26)	0.19
Model 2	Ref	1.41 (0.59–3.37)	1.50 (0.61–3.69)	0.76 (0.29–2.00)	0.36	0.64 (0.31–1.32)	0.23
Model 3	Ref	1.42 (0.59–3.38)	1.53 (0.62–3.76)	0.76 (0.29–2.00)	0.35	0.65 (0.31–1.34)†	0.24
Glucose							
Cut-point (mM)	1.6–4.8	4.8–5.5	5.5–6.4	6.4–16.4			
n with POCD/*N* total	18/132	18/133	19/131	17/124			
Model 1	Ref	0.44 (0.17–1.14)	1.10 (0.47–2.59)	1.60 (0.72–3.54)	0.06	1.09 (0.91–1.30)	0.37
Model 2	Ref	0.43 (0.17–1.10)	1.13 (0.48–2.65)	1.57 (0.71–3.48)	0.06	1.08 (0.90–1.30)	0.39
Model 3	Ref	0.43 (0.17–1.10)	1.13 (0.48–2.66)	1.57 (0.71–3.49)	0.06	1.08 (0.90–1.30)†	0.41†
HbA1c*							
Cut-point (mM)	16.4–31.7	32.0–35.0	35.0–39.0	39.3–88.0			
n with POCD/*N* total	23/130	15/111	15/114	11/107			
Model 1	Ref	0.15 (0.04–0.53)	0.42 (0.17–1.07)	0.94 (0.42–2.09)	**0.01**	1.00 (0.96–1.04)	0.99
Model 2	Ref	0.15 (0.04–0.54)	0.43 (0.17–1.09)	0.91 (0.40–2.08)	**0.01**	1.00 (0.96–1.04)	0.96
Model 3	Ref	0.15 (0.04–0.54)	0.43 (0.17–1.09)	0.91 (0.40–2.07)	**0.01**	1.00 (0.96–1.04)†	0.98‡

Table 5 Metabolic syndrome each of the five metabolic syndrome components, and postoperative cognitive dysfunction (POCD) risk. N=520. Model 1: adjusted for age, sex, analysis laboratory, analysis batch, surgery type. Model 2: + coronary heart disease, transient ischaemic attack, stroke, depression score. Model 3: + anaesthesia duration. *For definitions, see Supplementary Table S1. Each row represents a separate analysis. †Results of model 3 with 'obesity', 'elevated TG', 'reduced HDL-C', 'elevated BP' and 'elevated glucose' entered concurrently into single model: 'obesity', OR 2.12, 95% CI 1.07, 4.19; 'elevated TG', OR 0.69, 95% CI 0.35, 1.38; 'reduced HDL-C', OR 1.23, 95% CI 0.63, 2.43; 'elevated BP', OR .0.92, 95% CI 0.46, 1.83; 'elevated glucose', OR 1.50, 95% CI 0.76, 2.93. CI, confidence interval; BP, blood pressure; HDL, high-density lipoprotein; OR, odds ratio; TG, triglycerides.

	Model 1		Model 2		Model 3	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Metabolic syndrome*	1.18 (0.63–2.19)	0.61	1.14 (0.61–2.13)	0.69	1.13 (0.60–2.12)	0.71
Obesity*	2.27 (1.22–4.33)	0.01	2.20 (1.15–4.22)	0.02	2.20 (1.15–4.21)†	0.02†
Elevated TG*	0.84 (0.43–1.58)	0.60	0.82 (0.42–1.58)	0.55	0.81 (0.42–1.57)†	0.53†
Reduced HDL-C*	1.30 (0.69–2.47)	0.42	1.25 (0.66–2.39)	0.50	1.24 (0.65–2.38)†	0.52†
Elevated BP*	1.20 (0.65–2.24)	0.56	1.21 (0.64–2.30)	0.56	1.21 (0.63–2.29)†	0.57†
Elevated glucose*	1.58 (0.85–2.92)	0.15	1.59 (0.85–2.95)	0.14	1.58 (0.84–2.95)†	0.15†
Number of metabolic syndrome components (continuous)	1.21 (0.97–1.52)	0.10	1.20 (0.95–1.51)	0.12	1.20 (0.95–1.51)	0.13

0.33–0.89). Similarly, when all five MetS components were entered concurrently, the association of 'reduced HDL-C' with POD persisted (OR 1.87; 95% CI 1.21–2.91). Inclusion of 'reduced HDL-C' in model 3 led to a null association of MetS with POD (*P*=0.37).

Preoperative metabolic dysfunction and postoperative cognitive dysfunction risk

Each 1 kg m^{-2} higher BMI was associated with a 1.09-fold higher POCD risk (model 1, 95% CI 1.02–1.16; Table 4). Adjustment in model 2 and addition of anaesthesia duration (itself not associated with POCD; *P*=0.51) in model 3 did not change this result. Triglyceride, HDL-C, glucose, and HbA1c each were not associated with POCD, though some degree of non-linearity was observed for HbA1c with a lower POCD risk in quartile 2 compared with quartile 1 (OR 0.15; 95% CI 0.04–0.53) but no associations with HbA1c as a continuous exposure.

Patients with 'obesity' were at a 2.27-fold higher POCD risk (model 1, 95% CI 1.22–4.33; Table 5). Adjustment in models 2 and 3 did not change this result. The remaining four MetS components were not associated with POCD (Table 5, Supplementary Table S5).

When BMI, triglyceride, HDL-C, and glucose were entered into a single model 3, the association of BMI with POCD persisted (OR per kg m^{-2} increment 1.08; 95% CI 1.01–1.18), as did the finding on 'obesity' when all five MetS components were entered concurrently (OR 2.12, 95% CI 1.07–4.19).

Pre-planned additional analyses

Adjustment for pre-morbid IQ did not substantially alter any of the results on POD or POCD in terms of estimates and CI, though statistical significance was lost for the association of MetS with POD (model 3; Supplementary Table S6). *Post hoc* analyses revealed that the association in model 1 (accounting only for potential confounding factors) was independent of pre-morbid IQ (OR 1.68, 95% CI 1.14–2.48), however, showing that only once potential mediators were entered, the association became statistically non-significant. Adjustment of findings on POCD for POD, or exclusion of 10 underweight patients, also did not substantially change results (Supplementary Table S6). An exploratory *post hoc* exclusion of 151 patients with CRP ≥10 mg L^{-1} also did not affect the results (Supplementary Tables S7 and S8). 'Glucose ≥5.5 mM' was unrelated to POD (*P*=0.08) but was associated with a 1.91-fold higher POCD risk (model 1, OR 1.91, 95% CI 1.04–3.60). Diabetes (present in 20.2% of 520 patients) was not associated with POD (*P*=0.31) or POCD (*P*=0.46).

Discussion

Principal findings

We found that patients with MetS were at increased risk of POD during hospital stay. Furthermore, an increment in the number of metabolic abnormalities was associated with an incrementally increased POD risk, suggestive of a dose-response function. Among the five MetS components, low HDL-C was the strongest risk factor for POD. For POCD at 3 months, obesity was associated with a higher risk, whereas MetS and the remaining individual metabolic abnormalities played a lesser role. Associations were of considerable effect size throughout, though CIs were large. Findings were independent of age, sex, surgery type, and pre-morbid IQ. Findings on reduced HDL-C and POD, and on obesity and POCD, were also independent of remaining metabolic parameters.

With MetS and its components as vascular risk factors, underlying mechanisms (assuming that causality underlies our findings) could include a (potentially decades-long) build-up of endothelial dysfunction, cerebral hypoperfusion, cerebrovascular disease, neuroinflammation, blood–brain barrier leakiness[1] or depression.[21] Each or interactions thereof could increase patients' vulnerability to the acute stressor of surgery that involves raised inflammatory molecules[1] and stress-induced hyperglycaemia.[22] We found no evidence for a confounding role of pre-morbid IQ, indicating that it was not generally the case that patients with a lower IQ during adulthood (before the onset of ageing or disease) were at increased metabolic risk in later life and cognitive risk, in absence of a true relationship between the latter two. This is despite the fact that prior research indeed frequently indicated such a confounding role of pre-morbid IQ,[23] and could certainly be attributable to our reliance on an estimate of pre-morbid IQ that was also affected by a substantial proportion of missing data. Interestingly, in our analysis, when we adjusted for cerebral/coronary macrovascular disease, depression, and

anaesthesia duration, the associations were not substantively attenuated, suggesting that these potentially intermediary factors also did not account for the relationships seen.

Comparison with other studies

In this study to evaluate HDL-C and MetS in the context of POD, we have shown that patients with reduced HDL-C and those with MetS (partly because of its HDL-C component) are at a substantially increased POD risk, independently of potential confounders. Three previous studies had reported univariate associations of hypercholesterolaemia or hyperlipidaemia with a reduced POD risk[24,25] or had reported null findings,[26] but they used relatively broad definitions of these exposures and did not differentiate LDL-C and HDL-C.

Prior evidence points to an association between hypertension and increased POD risk.[12,27] Reliance on self-report/hospital records may have contributed to our null results. With obesity and hyperglycaemia each not associated with POD, we have added to mixed evidence on their roles in POD[26,28–32] that extends to disparate conclusions of systematic reviews.[12,27,33] Interestingly, exclusion of patients with CRP $\geq$10 mg L^{-1} led to a statistically significant association of 'elevated glucose' with an increased POD risk. We speculate that inflammatory conditions blurred the associations for elevated glucose with POD in the total sample.

The increased POCD risk in patients with obesity is in line with a trend observed in our 2016 meta-analysis.[13] We are aware of only four more recent studies, with mixed results.[34–37] Here, we provide the evidence that the association of obesity with POCD at 3 months may be independent of the remaining metabolic parameters, and of POD. MetS had previously been suggested as a risk factor for POCD in anecdotal evidence[38] and a rodent model.[39] A single epidemiological study including 60 noncardiac surgery patients reported, in an unadjusted analysis, that patients with MetS were at an increased POCD risk at 1 month.[40]

Hyperglycaemia, including diabetes mellitus, pre-diabetes, and higher glucose or HbA1c levels, has consistently been linked to age-related cognitive impairment.[41] There have also been reports of diabetes and (among people with diabetes) higher HbA1c as increasing POCD risk,[14,37,42] but no study to date had investigated glucose or HbA1c and POCD risk in the general population. In our study, results were somewhat conflicting. Glucose concentrations were not associated with POCD, whereas glucose $\geq$5.5 mM was associated with an increased POCD risk.

Finally, the negligible contribution of dyslipidaemia and hypertension to POCD, even in largely unadjusted analyses, was consistent with our meta-analyses[15,16] which had found that, when pooled across 17 studies and 24 studies, respectively, dyslipidaemia[16] and hypertension[15] were not risk factors for POCD.

Strengths and limitations

The investigation of both POD and POCD in a single large cohort is a strength of our study. We only recruited Caucasian individuals, so the relevance of our findings for other ethnicities is unclear. Our patients were of a high IQ as is common in studies on cognitive outcomes. Our study was affected by a substantial loss to follow-up of 32% by 3 months, which led a smaller analysis cohort for the outcome of POCD compared with the outcome of POD. We compared results on both outcomes despite the fact that the analyses of POCD included attendees of the 3-month follow-up who were healthier and were less likely to have metabolic dysfunction compared with non-attendees. The at-risk group of patients who had experienced POD was also underrepresented in the group of attendees, further supporting a limited possibility of comparing results on POD with those of POCD. However, when we repeated our analysis on HDL-C and POD, and on MetS and POD, in the 3-month attendee cohort, effect sizes were close to identical, although statistical significance was partly lost. We used single imputation to replace missing data on some of the covariates. When we repeated the main analyses in a complete-case approach, effect sizes were marginally reduced and statistical significance lost for some of our results. We had no data on chronicity of metabolic dysfunction (having measured metabolic status at a single time point), on POD/POCD severity, or on blood loss/transfusions during surgery which could have been additional relevant factors to consider. A large number of statistical analyses were performed; however, we deemed correction for multiple testing too conservative for our hypothesis-driven analysis. The risk of type I error should be considered in the interpretation of *P*-values from our analyses while additional consideration of effect estimates and CIs is advised.[43] The absence of an association of POD with POCD was unexpected[44] and may indicate measurement problems, though incidences of POD (19.5%) and POCD (10.1%) were as expected.[1,2] Finally, we interpreted OR as relative risks under the rare disease assumption. Our estimates for associations with POD were marginally overestimated, given that POD strictly cannot be considered a 'rare' outcome.[45]

Implications of this study

If supported, and potentially in combination with other established risk factors, our findings may prove useful for informed decision-making, risk stratification, and monitoring. Preoperative BMI or HDL-C are currently not typically measured in clinical practice. Here, we have provided evidence for the usefulness of their introduction into the preoperative schedule. With metabolism as a modifiable factor, if our results are found to reflect causality in the future, they could also pave the way for intervention studies and prevention programmes.

Conclusions

In the this assessment of metabolic syndrome in the context of perioperative neurocognitive disorder, we showed that patients with metabolic syndrome were at increased risk of postoperative delirium. Among the five metabolic syndrome components, a reduced HDL-C was the strongest contributor to this relationship. Obesity was a risk factor for postoperative cognitive dysfunction. We found no consistent evidence for an influence of confounders or mediators to our findings. Our results add to evidence of postoperative delirium and postoperative cognitive dysfunction as distinct conditions, with potentially distinct aetiology, and highlight the need to tease out their respective epidemiology within single sets of patients.

Authors' contributions

Study concept and design: AS, GW, CS, TP

Data collection: IF, JJ
Statistical analysis and interpretation: IF
Drafting of initial manuscript: IF, TP
Review of manuscript for critical intellectual content: IF, JJ, AS, CS, GW, TP
Read and approved the final manuscript: all authors
Fulfilled the International Committee of Medical Journal Editors (ICMJE) criteria for authorship: all authors

Declaration of 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 and TP are project leaders in BioCog. IF, JJ, AS, CS, and TP declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2023.04.031.

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