Metabolic Syndrome, Insulin Resistance, and Cognitive Dysfunction: Does Your Metabolic Profile Affect Your Brain?

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Dementia and type 2 diabetes are both characterized by long prodromal phases, challenging the study of potential risk factors and their temporal relation. The progressive relation among metabolic syndrome, insulin resistance (IR), and dementia has recently been questioned, wherefore the aim of this study was to assess the potential association among these precursors of type 2 diabetes and cognitive dysfunction. Using data from the Prospective Epidemiological Risk Factor (PERF) Study (*n* = 2,103), a prospective study of elderly women in Denmark, we found that impaired fasting plasma glucose concentration was associated with 44% (9–91%) larger probability of cognitive dysfunction. In addition, subjects above the HOMA-IR threshold (HOMA-IR >2.6) had 47% (9–99%) larger odds of cognitive dysfunction. The associations could indicate that a significant proportion of dementia cases in women is likely to be preventable by effective prevention and control of the insulin homeostasis.

The sedentary Western lifestyle has led to an epidemic-like increase in the prevalence of obesity that is closely linked to the occurrence of type 2 diabetes (1,2). Also the prevalence of cognitive dysfunction and dementia is increasing, and epidemiological studies suggest an association between type 2 diabetes and increased risk of dementia and cognitive dysfunction (3). With metabolic syndrome (MetS) considered to be a precursor of type 2 diabetes (4) and central obesity and insulin resistance (IR) recognized as important causative factors in the pathogenesis of MetS (5), a precursor state for dementia may be developed over several years.

The long prodromal phases characterizing dementia and type 2 diabetes challenge the study of potential risk factors and their temporal relation (6,7), and in studies with short follow-up periods putative relationships may be unreliable. Thus, reported associations among type 2 diabetes, MetS, and cognitive dysfunction are somewhat contrary. Until recently, the brain was considered an insulin-insensitive organ; it has, however, now been accepted that insulin, partly of peripheral origin, acts through its own receptors in the brain controlling cognition and memory (8). Thus, it may be that IR is a condition affecting both peripheral and central insulin receptors with cerebral IR being part of a preclinical state of Alzheimer disease (AD) (9). Importantly, the temporal relation among MetS, IR, and cognitive dysfunction/dementia has recently been questioned (10,11). This prompted us to conduct the current study in which data obtained as part of The Prospective Epidemiological Risk Factor (PERF) Study, a prospective study of Danish postmenopausal women (12), underwent an evaluation with the aim to study the hypothesis that there is a temporal relation between MetS and IR and cognitive dysfunction. Data from the PERF study were used to evaluate whether there is an association between the MetS or IR and cognitive impairment at a follow-up 15 years later including only subjects without signs of cognitive dysfunction at the baseline examination (*n* = 1,759).

RESEARCH DESIGN AND METHODS

The PERF Study

The PERF Study, an observational, prospective cohort study of Danish postmenopausal women, was designed with the purpose of obtaining knowledge of age-related diseases in postmenopausal women. The baseline examination (PERF I) took place between 1999 and 2001 (*n* = 5,855), and over

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14 months (from September 2013) 2,103 participants were included in a follow-up (PERF II) as described previously (12). The studies were performed in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use-Good Clinical Practice with study protocol approval from The Research Ethics Committee of Copenhagen County. Written informed consent was obtained from all subjects prior to any study-related procedures.

Study Populations

This study was based on all subjects who completed the follow-up examination PERF II (n = 2,103), and from this population we identified the analytical sample as outlined in Fig. 1.

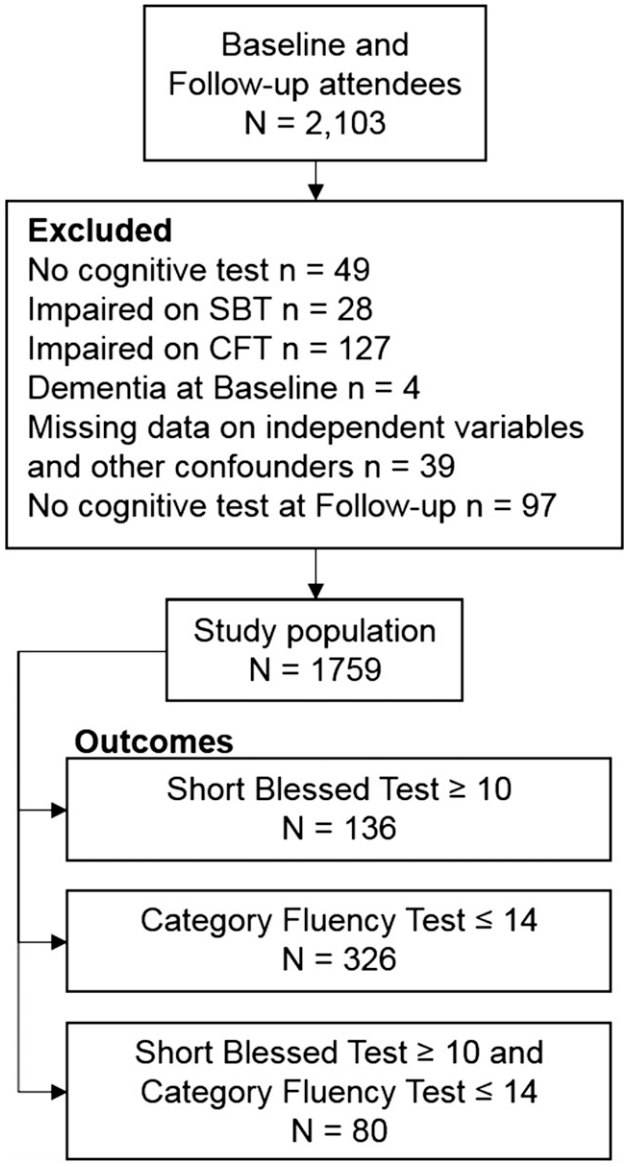

Figure 1—Flowchart for the identification of the analytical sample. Each outcome was determined independent of the other outcomes.

The study population included all subjects who had undergone valid cognitive tests at baseline and follow-up. Exclusion criteria were cognitive dysfunction at baseline and missing data on any of the confounders included in the analysis. This qualified 1,759 subjects for the analysis.

Cognitive Dysfunction

Two short cognitive screening tests were applied to assess cognitive function at baseline and follow-up. The Short Blessed Test (SBT) is a six-item test assessing orientation, concentration, and memory. The score ranges from 0 to 28, with lower scores indicating better performance. A threshold of ≥10 was previously identified as cognitive impairment consistent with dementia (13). The category fluency test (CFT) with animal naming is a measure of verbal fluency where the subjects should name as many animals as possible in 60 s. Higher scores indicate better performance and the recommended threshold for dementia is ≤14 (14).

MetS at Baseline

MetS was defined using a modified version of the definition recommended by the International Diabetes Federation (15). In addition to the entrance criteria of central obesity, subjects should present two or more of the following risk factors: increased triglyceride levels (>1.7 mmol/L), lowered level of HDL cholesterol (<1.29 mmol/L), an increase in fasting plasma glucose level (>5.6 mmol/L) or previously diagnosed type 2 diabetes and hypertension (systolic pressure >130 mmHg or diastolic pressure >85 mmHg or existing treatment of hypertension) to qualify for MetS. A direct measure of waist circumference was not obtained at baseline; therefore, the entrance criteria of central obesity was only defined by a BMI >30 kg/m^2, and because specific hyperlipidemia treatment was not part of the baseline questionnaire we were unable to determine whether participants were receiving specific lipid-lowering medication.

Subjects without MetS were divided into the following three groups: *1*) subjects having a BMI >30 kg/m^2 and only one additional risk factor, *2*) subjects presenting with a BMI <30 kg/m^2 but with one to four risk factors for MetS, and *3*) subjects without any risk factors for MetS. This latter group was used as the reference group in the regression analysis.

The HOMA Index

The HOMA-IR index was used to assess the degree of IR (16). The HOMA-IR index was calculated by multiplying fasting levels of plasma glucose by the concentration of insulin divided by the constant 22.5. Fasting plasma glucose was measured directly after collection in both PERF I and II, using a Vitros 250 slide cartridge with no reagent system (Ortho Clinical) in PERF I and an enzymatic measurement method using the Avida 1800 (Siemens) in PERF II. Insulin levels at PERF I and PERF II were measured in thawed samples from the PERF biobank (stored at −80°C) on a Cobas e411 analyzer (Roche). Blood samples were collected after fasting in the morning.

Statistical Analysis

Statistical analysis was conducted using R version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria). Spearman rank correlation was used to measure the association between scores of the two cognitive tests. By use of the *glm* function, logistic regression assessed the association between risk factors for the MetS, metabolic profiles and cognitive dysfunction. Three separate multivariable analyses were completed. In all analyses, baseline age and baseline cognitive performance were included as continuous variables, and education level (primary school/high school/university), smoking history (never/former/current), alcohol consumption (none, <10.5 alcohol units/week, 10.5–21 alcohol units/week, >21 alcohol units/week), physical activity (inactive/one time per week/two times per week/three or more times per week), and current use of hormone replacement therapy (yes/no) were used as categorical covariates.

We first tested each of the single risk factors comprising the MetS. The variables were dichotomized as described in the subsection METS AT BASELINE above. Using the dichotomized variables, we then studied how metabolic profiles at baseline were associated with cognitive dysfunction. First, we used the modified definition of MetS followed by the cumulative sum of MetS risk factors, ranging from zero to five, then we assessed the association between IR and the risk of cognitive dysfunction. The baseline HOMA-IR index was used as a continuous variable and was further dichotomized at 2.6, where subjects above the threshold were considered to be insulin resistant. The outcome variables used were *1*) cognitive dysfunction shown on the SBT (SBT ≥10), *2*) cognitive dysfunction shown on the CFT (CFT ≤14), and *3*) cognitive dysfunction shown on both the SBT and CFT (SBT ≥10 and CFT ≤14).

The Hosmer-Lemeshow test was used to test the goodness of fit for the logistic regression models.

RESULTS

Of the 1,759 subjects included in the analysis, 136 had cognitive dysfunction according to the SBT, whereas 326 were classified with cognitive dysfunction when it was determined by CFT. A total of 80 subjects showed signs of cognitive dysfunction on both tests.

Characteristics of the Study Population

The baseline characteristics of the study population are shown in Table 1. All subjects were on average 68 years old at baseline, with the nonimpaired group being the youngest and the group of subjects with impaired cognition on both tests being the oldest.

There was a negative correlation between scores in the SBT and the CFT ($\rho = -0.294$ [95% CI -0.336 to -0.250]; $P < 0.0001$).

Association Between MetS and IR and Cognitive Dysfunction

Table 2 shows the association among metabolic risk factors, MetS, IR, and cognitive dysfunction at follow-up. Fasting plasma glucose level was associated with impairment in CFT results, suggesting that hyperglycemia increases the risk for the development of cognitive dysfunction by 44% (odds ratio [OR] 1.44; 95% CI 1.09–1.91). Having from one to four metabolic risk factors did not significantly alter the risk of cognitive dysfunction at follow-up when compared with subjects with no risk factors. In subjects with the worst metabolic profile, holding all five risk factors for MetS, the risk for cognitive dysfunction on verbal fluency was three times higher (OR 3.09; 95% CI 1.09–8.69) compared with subjects who did not present any of the MetS risk factors. MetS was, however, not associated with an increased risk of cognitive dysfunction at follow-up.

IR was associated with an increased risk of cognitive dysfunction, calculated both as CFT results and a combination of the SBT and the CFT results (Table 2). The risk of cognitive dysfunction increased between 8% and 10% for every unit increase on the HOMA-IR index scale, and, when dichotomized, subjects above the threshold of 2.6 had a 47% higher risk of cognitive dysfunction on verbal fluency (OR 1.47; 95% CI 1.09–1.99) compared with subjects below the HOMA-IR threshold.

DISCUSSION

In the current study, we assessed the temporal relation between biomarkers and precursors of type 2 diabetes and cognitive dysfunction; specifically, we evaluated whether MetS and IR are associated with the development of cognitive dysfunction. Based on data with a follow-up period of up to 15 years, it is demonstrated that *1*) subjects with impaired fasting plasma glucose have larger odds of the development of cognitive dysfunction and *2*) subjects with IR as determined by the HOMA-IR index have a higher probability of the development of cognitive dysfunction. Although fasting plasma glucose levels were specifically associated with dysfunction on the verbal fluency test, IR seemed to result in more global cognitive dysfunction as determined by a combination of two short cognitive screening tests. The third important finding is that subjects with a poor metabolic profile, reflected by the presence of several metabolic and cardiovascular risk factors, have threefold to fourfold larger odds of the development of cognitive dysfunction than subjects with an ideal metabolic profile. Overall, the data suggest that IR is a cause rather than a consequence of cognitive dysfunction.

Fasting plasma glucose level was the single metabolic risk factor that was most strongly associated with cognitive dysfunction. With cognitive function assessed by the CFT, subjects with impaired fasting plasma glucose levels had 44% (9–91%) larger odds of cognitive dysfunction compared with normoglycemic subjects. Although the presence of MetS in itself does not seem to provoke an elevated risk of cognitive dysfunction, subjects with a poor metabolic profile have three to four times larger odds of the development of cognitive dysfunction when compared with subjects with an ideal metabolic profile. The Framingham cohort has recently shown that subjects with ideal cardiovascular

Table 1—Baseline characteristics of the study population

	Nonimpaired (n = 1,377)	SBT ≥10 (n = 136)	CFT ≤14 (n = 326)	SBT ≥10/CFT ≤14 (n = 80)
Demographics				
Age (years)	66.9 ± 5.6	70.6 ± 6.5	70.5 ± 5.8	72.4 ± 5.7
Education				
Primary school	903 (65.6)	96 (70.6)	225 (69.0)	56 (70.0)
High school	332 (24.1)	26 (19.1)	77 (23.6)	17 (21.2)
University	142 (10.3)	14 (8.1)	24 (7.4)	7 (8.8)
Lifestyle				
BMI (kg/m^2)	26.0 ± 4.0	26.3 ± 4.8	26.5 ± 4.4	26.3 ± 4.3
<18.5	19 (1.2)	1 (0.7)	2 (0.6)	0
18.5–24.9	686 (42.3)	63 (46.3)	133 (40.8)	36 (45.0)
25.0–29.9	653 (40.2)	46 (33.8)	127 (39.0)	28 (35.0)
≥30.0	265 (16.3)	26 (19.1)	64 (19.6)	16 (20.0)
Smoking history				
Never	723 (52.5)	68 (50.0)	167 (51.2)	45 (56.2)
Former	403 (29.3)	41 (30.1)	89 (27.3)	23 (28.7)
Current	251 (18.2)	27 (19.9)	70 (21.5)	12 (15.0)
Alcohol use				
None	512 (37.2)	66 (48.5)	148 (45.4)	36 (45.0)
<10.5 alcohol units/week	312 (22.7)	22 (16.2)	61 (18.7)	15 (18.8)
10.5–21 alcohol units/week	423 (30.7)	38 (27.9)	89 (27.3)	22 (27.5)
>21 alcohol units/week	130 (9.4)	10 (7.4)	28 (8.6)	7 (8.8)
Physical activity				
Inactive	306 (22.2)	40 (29.4)	103 (31.6)	22 (27.5)
1 time/week	310 (22.5)	29 (21.3)	54 (16.6)	17 (21.2)
2 times/week	204 (14.8)	18 (13.2)	48 (14.7)	11 (13.8)
≥3 times/week	557 (40.5)	49 (36.0)	697 (37.1)	30 (37.5)
Metabolic and vascular factors				
Systolic blood pressure (mmHg)	145.5 ± 23.1	148.9 ± 23.7	148.8 ± 23.2	150.2 ± 23.9
Diastolic blood pressure (mmHg)	81.9 ± 10.5	82.0 ± 10.5	82.0 ± 11.0	81.5 ± 10.8
Fasting plasma glucose (mmol/L)	5.4 ± 1.0	5.6 ± 1.5	5.6 ± 1.1	5.8 ± 1.8
Insulin (mmol/L)	54.9 ± 34.6	58.7 ± 44.5	60.9 ± 38.8	61.5 ± 42.1
HOMA-IR	2.0 ± 1.5	2.4 ± 3.6	2.3 ± 2.6	2.6 ± 4.3
HDL (mmol/L)	1.7 ± 0.4	1.7 ± 0.4	1.8 ± 0.5	1.8 ± 0.4
Triglycerides (mmol/L)	1.3 ± 0.6	1.4 ± 0.7	1.4 ± 0.7	1.4 ± 0.7
Cognitive performance				
SBT	1.3 ± 1.9	2.4 ± 2.4	1.7 ± 2.1	2.4 ± 2.3
CFT	24.3 ± 5.2	21.5 ± 4.5	20.6 ± 4.2	20.8 ± 4.4

Data are shown as absolute numbers (%) for categorical variables and as mean ± SD for numerical variables.

health, determined from a 7-point scale proposed by the American Heart Association, are at lower risk of dementia, cognitive decline, and brain atrophy (17). Of the seven risk factors defining an ideal cardiovascular health profile, four are identical to or at least very similar to those defining the MetS, suggesting that cardiovascular and metabolic health are closely linked to brain health.

Peripheral IR has been shown to alter the transport of insulin through the blood-brain barrier. The insulin transport is reduced by peripheral hyperinsulinemia (18), which can directly contribute to cognitive impairment and promote AD pathology (19,20). It has also recently been shown that IR predicts worse memory performance through a reduction in regional cerebral glucose metabolism (21), supporting IR as being a causal risk factor for the development of cognitive dysfunction. Although the study design does not allow for causal conclusions, the data presented here can be taken to indicate a temporal relation between IR and cognitive dysfunction. However, we cannot rule out the possibility that dementia or cognitive dysfunction may lead to a diabetic phenotype and that a disturbance in insulin homeostasis, as a secondary process, may accelerate certain dementia pathologies (22). IR may be a shared underlying pathological mechanism, since it is part of the prodromal phase of both type 2 diabetes and dementia. Interestingly, amyloid formation is a pathological hallmark of both type 2 diabetes and AD: islet amyloid polypeptide is found in the pancreata of subjects with type 2 diabetes, and β-amyloid is found in the brains of subjects with AD (23). A recent study (24) has even suggested that pancreas-derived amyloid may enter the brain and exacerbate the disposition of β-amyloid through cross-seeding.

There are previous studies indicating an association between sleep disturbances and dementia (25). There are many mechanisms underlying this association, and IR is speculated to play an important role; however, the causal link has not been elucidated. The menopausal transition is associated with sleep disturbances, which are also found to

Table 2—Association between MetS and IR and cognitive dysfunction

	Cognitive status at follow-up					
	SBT ≥10		CFT ≤14		SBT ≥10/CFT ≤14	
Predictor variables	OR*	95% CI	OR*	95% CI	OR*	95% CI
Individual components of MetS						
BMI (>30 kg/m^2)	1.22	0.76–1.94	1.24	0.88–1.74	1.26	0.70–2.30
Elevated blood pressure	0.88	0.56–1.38	1.07	0.76–1.50	0.68	0.38–1.23
Impaired fasting plasma glucose	1.12	0.76–1.64	1.44	1.09–1.91	1.56	0.96–2.52
Low HDL	1.01	0.59–1.74	1.19	0.81–1.74	0.99	0.47–2.09
Elevated triglycerides	1.25	0.81–1.91	0.98	0.71–1.36	1.09	0.61–1.95
Cumulative sum of risk factors for MetS						
0				Reference		
1	0.72	0.40–1.27	1.02	0.65–1.59	0.72	0.34–1.56
2	0.64	0.35–1.19	1.06	0.66–1.69	0.60	0.27–1.38
3	1.18	0.61–2.27	1.19	0.70–2.03	1.02	0.41–2.52
4	0.59	0.22–1.60	1.39	0.71–2.71	0.66	0.19–2.33
5	2.56	0.75–8.79	3.07	1.09–8.69	4.35	1.02–18.6
MetS						
No MetS				Reference		
Risk factors for MetS with BMI <30 kg/m^2	0.98	0.65–1.49	1.08	0.80–1.46	0.94	0.55–1.61
BMI >30 kg/m^2 and <2 risk factors	1.11	0.53–2.33	1.30	0.77–2.19	1.61	0.69–3.77
MetS	1.28	0.71–2.29	1.30	0.82–1.94	1.18	0.55–2.55
IR (HOMA-IR)						
Dichotomized (HOMA-IR >2.6)	0.98	0.64–1.52	1.47	1.09–1.99	1.33	0.77–2.27
Continuous (per unit increase)	1.05	0.98–1.13	1.08	1.01–1.16	1.10	1.01–1.19

*ORs were adjusted for age at baseline, smoking history, alcohol consumption, physical activity, education, and hormone replacement therapy.

increase the risk of type 2 diabetes (26,27). We observed a link between IR and cognitive dysfunction, and this could indicate that IR is an intermediate mechanism for the causal association between sleep disturbances and cognitive dysfunction. We can, however, not address this in the current study as we did not collect information on sleep disturbances and sleep patterns at baseline.

The small, albeit significant, correlation between the two tests was expected and indicates that the two tests are not equivalent. This was reflected in the observed domain-specific effect of fasting plasma glucose level and IR on cognition specifically related to verbal fluency. A similar domain-specific effect on verbal fluency has previously been found in two cross-sectional studies (28,29). One of the studies found that the effect of IR on cognition was modulated by sex, indicating that IR was associated with poor performance on verbal fluency only in women. Verbal fluency performance is functionally linked to the frontal and temporal lobe areas. These brain areas rich in insulin receptors are found to be associated with memory function (28,30). There are several neuropathological conditions that affect memory-related areas in the brain, and AD is one of them. A structural alteration of semantic networks located in the frontal and temporal lobe areas has been found to be characteristic for AD even in the early stages of AD (31,32).

The concept of precision medicine is emerging in relation to the prevention and treatment of AD (33), and the abundant evidence of various AD phenotypes, of which the metabolic phenotype is one, suggests that it is extremely relevant in this field. A recent meta-analysis (34) indicated that insulin-sensitizer drugs, like metformin and thiazolidinediones, might be useful in the prevention of dementia in patients with diabetes. Whether there is a direct mechanistic link is still controversial, but evidence from rat studies has shown that the glucagon-like peptide 1 analog liraglutide, another insulin sensitizer, interacts directly with processes leading to amyloid plaques and neurofibrillary tangles, which are the two pathological hallmarks of AD (35,36). Moreover, clinical trials have shown promising effects of intranasal insulin in subjects with AD and its prodrome mild cognitive impairment (37,38) and also on spatial memory in young men (39).

Limitations

The analysis was restricted to subjects attending the follow-up examination; therefore, selection bias may affect the internal validity and question the generalizability of our results because it is well known that cognitive dysfunction and dementia affect attrition. We have previously assessed the similarities between follow-up participants and follow-up nonparticipants on a cohort level and found that the two populations are very similar (12). This should strengthen the internal validity. Further, we based our determination of cognitive dysfunction on results from two short cognitive screening tools at the follow-up visit; therefore, we cannot rule out the possibility that cognitive dysfunction in the current study may be caused by reversible conditions and thereby potentially may have resulted in misclassification.

The diagnostic accuracy of the two tests in relation to dementia is excellent (40–43). They have even been shown to outperform more comprehensive tests like the Mini-Mental State Examination in the identification of milder levels of impairment (44,45). In the absence of a comprehensive diagnostic workup with a complete neuropsychological test battery, this evidence supports the use of these simple tests.

Another limitation of the study is the lack of repeated measurements of glucose, insulin, and cognition throughout the follow-up period because it would allow for a better assessment of the mutual trajectories and also result in a more accurate determination of the onset of cognitive dysfunction. Given the previously reported interconnection between genetic and metabolic risk factors, the lack of genetic risk factors in our studies is a limitation that could result in unmeasured confounding. For example, it has been suggested that the insulin metabolism may differ between apolipoprotein E ε4 allele carriers and noncarriers (46).

Conclusions

The precursors of type 2 diabetes, impaired fasting plasma glucose levels and IR, are associated with an increased risk of the development of cognitive dysfunction in elderly women. Moreover, cognitive dysfunction is more likely to develop in subjects with a poor metabolic profile than in subjects with an ideal metabolic profile. If the observed association between metabolic risk factors and cognitive dysfunction is truly causal, it could suggest that a significant proportion of cases of dementia in women may be preventable by effective control of insulin homeostasis.

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