Metabolic Syndrome and Risk for Incident Alzheimer's Disease or Vascular Dementia

The Three-City Study

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OBJECTIVE — Associations between metabolic syndrome and its individual components with risk of incident dementia and its different subtypes are inconsistent.

RESEARCH DESIGN AND METHODS — The 7,087 community-dwelling subjects aged ≥65 years were recruited from the French Three-City (3C) cohort. Hazard ratios (over 4 years) of incident dementia and its subtypes (vascular dementia and Alzheimer's disease) and association with metabolic syndrome (defined according to the National Cholesterol Education Program Adult Treatment Panel III criteria) and its individual components (hypertension, large waist circumference, high triglycerides, low HDL cholesterol, and elevated fasting glycemia) were estimated in separate Cox proportional hazard models.

RESULTS — Metabolic syndrome was present in 15.8% of the study participants. The presence of metabolic syndrome increased the risk of incident vascular dementia but not Alzheimer's disease over 4 years, independent of sociodemographic characteristics and the apolipoprotein (apo) Eε4 allele. High triglyceride level was the only component of metabolic syndrome that was significantly associated with the incidence of all-cause (hazard ratio 1.45 [95% CI 1.05–2.00]; $P = 0.02$) and vascular (2.27 [1.16–4.42]; $P = 0.02$) dementia, even after adjustment of the apoE genotype. Diabetes, but not impaired fasting glycemia, was significantly associated with all-cause (1.58 [1.05–2.38]; $P = 0.03$) and vascular (2.53 [1.15–5.66]; $P = 0.03$) dementia.

CONCLUSIONS — The observed relation between high triglycerides, diabetes, and vascular dementia emphasizes the need for detection and treatment of vascular risk factors in older individuals in order to prevent the likelihood of clinical dementia.

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Dementia is the most severe form of pathological brain aging, defined by the coexistence of memory disorders and deficit in at least one other cognitive function (impairment of abstract thinking; impaired judgment; other disturbances of higher cortical function, such as aphasia, apraxia, agnosia, or constructional difficulty; or personality change), with a significant impact on activities of daily living (1). Eighteen percent of people aged >75 years have dementia. Its most frequent form is Alzheimer's disease (~50–60% of cases) ([1]), vascular dementia accounting for most of the other causes (1). The underlying pathophysiological mechanisms, and hence risk factors, of Alzheimer's disease and vascular dementia remain uncertain (2), and no etiologic treatment is available yet. Nevertheless, several potentially modifiable risk factors of dementia have been identified. Hypertension, especially in mid-life, increases the likelihood of developing dementia (3). Although less studied, obesity (4) and dyslipidemia (5) are also being recognized as possible modifiable risk factors of dementia. Some studies have shown that diabetes increases the risk of developing dementia (6). These factors usually coexist under the heading of metabolic syndrome, which is a cluster of five cardiovascular risk factors including hypertension, abdominal obesity, high triglycerides, low HDL cholesterol, and elevated fasting glycemia (impaired fasting glucose or diabetes) (7).

Metabolic syndrome is associated with increased risk of cardiovascular disease (8). If metabolic syndrome were also associated with increased risk of developing dementia, the screening and management of its components might offer avenues for prevention of cardiovascular disease and dementia as well. However, the association between metabolic syndrome, or its individual components, and dementia has received little attention (9–14). Three longitudinal studies (10–12) showed that metabolic syndrome as a whole is related to higher risk of cognitive decline, but they did not examine the association with the risk of dementia. While a cross-sectional study (13) found a higher prevalence of dementia in women with metabolic syndrome, the single published prospective study (14) showed no association between metabolic syndrome and incident dementia. On the other hand, only some components of the metabolic syndrome (and not the metabolic syndrome itself) might be associated with an increased risk of incident dementia. In particular, several prospective studies evidenced that the presence of diabetes was associated with increased incidence of Alzheimer's disease and vascular dementia (6,14). However, the role of hypergly-

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cemia in the absence of diabetes (impaired fasting glucose) needs to be well defined (15).

We therefore aimed to estimate the prospective association between metabolic syndrome, or its individual components, with the risk of incident dementia and the potential differences according to the subtype of dementia: Alzheimer's disease or vascular dementia, in a large prospective epidemiological study conducted in community-dwelling older subjects. We focused on the component "elevated fasting glycemia" to study the specific role of diabetes versus impaired fasting glucose.

RESEARCH DESIGN AND METHODS

The subjects included in the present study were a subsample of the Three-City (3C) Study, a large French multicenter prospective epidemiologic study of vascular risk factors for dementia. The study protocol has been described previously (16) and was approved by the Consultative Committee for the Protection of Persons Participating in Biomedical Research of the University Hospital of Kremlin-Bicêtre (Paris, France). All participants gave their written informed consent. Briefly, noninstitutionalized subjects aged ≥65 years were selected from electoral rolls of three cities and their suburbs (Bordeaux in the southwest, Dijon in the northeast, and Montpellier in the southeast of France) and then invited to participate in the study. Sample size was estimated to achieve a sufficient number of health events over 4 years. At baseline in 1999–2000, the sample included 9,294 subjects (3,718 men and 5,576 women; 2,104 in Bordeaux, 4,931 in Dijon, and 2,259 in Montpellier).

For the present study of incident dementia (screening procedure described below), we excluded 215 participants already demented at baseline (1999–2000). We also excluded 1,341 subjects because of incomplete data for defining metabolic syndrome (623 subjects with no blood samples and 971 with no waist circumference measurement). This gave a baseline sample of 7,738 subjects. At the second round of the study (2001–2002), 6,964 (90.0%) subjects were examined again, 134 were deceased, and 640 refused to participate or were lost to follow-up. At the third round (2003–2004), 6,262 subjects were examined (84.9% of the survivors after the second round), the cumulated number of deaths was 358, and 1,118 refused to participate or were lost to follow-up. Finally, 7,087 (91.6%) participants had at least one follow-up examination over 4 years and formed the sample of the present study.

Diagnosis of dementia

A three-step procedure was used to diagnose cases of dementia (16). First, screening was based on a thorough neuropsychological examination by trained psychologists. This examination included a battery of cognitive tests covering memory, attention, language, and visuo-spatial abilities. Data on activities of daily living, severity of cognitive disorders, and, where possible, magnetic resonance images or computed tomography scans were collected (16). Second, the participants who were suspected of having dementia on the basis of their neuropsychological performance (in particular the Mini Mental Status Examination, the Benton Visual Retention Test, and the Isaac's Set Test administered uniformly in all three study centers at each follow-up [16]) were examined by a neurologist in the three study centers (16). Finally, all suspected dementia cases were analyzed by a common independent committee of neurologists according to the criteria of the DSM-IV (16). This committee of neurologists reviewed by teleconference all potential cases of dementia of the three study centers to obtain a consensus on its diagnosis and etiology based on all existing information. With regard to the different subtypes of dementia, we considered the two most frequent causes of dementia as determined by committee (Alzheimer's disease according to National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria [16] and vascular dementia based on history of vascular disease, Hachinski score [16], and magnetic resonance imaging whenever possible).

Definition of metabolic syndrome

Baseline metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria, which requires the presence of three or more alterations among the following cardiometabolic parameters (being dichotomized as present or absent): *1*) elevated systolic (>130 mmHg) or diastolic blood pressure (>85 mmHg) or use of antihypertensive medication, *2*) large waist circumference (>88 cm in women and >102 cm in men), *3*) high triglycerides (≥150 mg/dl), *4*) low HDL cholesterol (men <40 and women <50 mg/dl), and *5*) elevated fasting glycemia (≥110 mg/dl) or nonfasting glycemia (≥200 mg/dl) or antidiabetes medication (17).

To better understand the specific role of diabetes versus impaired fasting glucose, we made further analyses distinguishing subjects with diabetes (fasting glycemia ≥126 mg/dl or nonfasting glycemia ≥200 mg/dl or antidiabetes medication) (1999 World Health Organization criteria) (18), subjects with impaired fasting glucose (fasting glycemia ≥110 mg/dl without diabetes), and those with normal fasting glycemia (<110 mg/dl) without diabetes (category of reference, subjects with no glucose regulation disorder).

Assessment of metabolic syndrome components

Blood pressure was measured twice in a sitting position using a digital electronic tensiometer, and the average was used in the statistical analyses. Height, weight, and waist circumference were measured in lightly dressed subjects. Waist circumference was measured between the lower rib margin and the iliac crest following a normal expiration. All pharmacological treatments taken during the month preceding the time of the interview were recorded. Medical prescriptions and, when feasible, the medications themselves were checked by the interviewer.

Blood samples were collected (EDTA plasma samples stored at −80°C), and centralized measurements of fasting blood glucose, HDL cholesterol, and triglycerides were performed. As we had to include only type 2 diabetic patients by virtue of the definition of the metabolic syndrome component (17), we excluded patients who were considered to have type 1 diabetes based on the definition of the World Health Organization 1999 criteria (18) and who were treated by insulin alone ($n = 26$).

Potential confounders and effect modifiers

Sociodemographic information recorded at baseline during a face-to-face interview included age, sex, and educational level (in two classes: subjects who received primary or no education versus the others [6 years of schooling or more] and 10 missing data). Determination of the apolipoprotein (apo) E genotype was carried out at the Lille Genopole, located in Lille, France (http://www.genopole-lille.fr/

Table 1—*Baseline characteristics according to the presence of metabolic syndrome and associations between the different components of the metabolic syndrome: the 3C Study, France, 1999–2004*

	Total cohort	Metabolic syndrome	No metabolic syndrome	*P*	Components of the metabolic syndrome: High blood pressure	High waist circumference	High triglycerides	Low HDL cholesterol	High glycemia
n	7,087	1,121	5,966		6,064	2,049	1,247	741	816
Age (years)	73.4 ± 4.9	73.8 ± 4.8	73.4 ± 4.9	0.05	73.7 ± 4.9	74.0 ± 4.9	73.3 ± 4.9	73.6 ± 4.9	73.2 ± 4.7
Men (%)	39.0	41.6	38.5	0.05	40.8	32.3	45.9	35.4	39.0
Education level (no or primary)	23.6	29.1	22.6	<0.0001	24.4	28.8	25.9	29.9	23.6
ApoE ε4*	20.4	21.0	20.3	0.60	20.3	19.6	20.4	23.5	20.4
High blood pressure†	85.6	98.2	83.2	<0.0001	NA	91.6	90.0	88.3	95.2
High waist circumference‡	28.9	78.5	19.6	<0.0001	31.0	NA	44.2	50.4	50.2
High triglycerides§	17.6	66.4	8.4	<0.0001	18.5	26.9	NA	50.5	32.0
Low HDL cholesterol‖	10.5	47.6	3.5	<0.0001	10.8	18.3	30.2	NA	22.8
High glycemia¶	11.5	47.6	4.7	<0.0001	12.9	20.0	20.9	25.0	NA
Impaired fasting glucose without diabetes**	3.9	15.3	1.8	<0.0001	4.3	6.9	6.1	7.0	34.2
Diabetes††	7.6	32.3	2.9	<0.0001	8.6	13.1	14.8	18.0	65.8

Data are means ± SD or percent. Metabolic syndrome was defined by the NCEP ATP III criteria.*ApoE ε4: presence of at least one allele ε4 in apoE genotype. †Systolic blood pressure >130 mmHg or diastolic blood pressure >85 mmHg or medication. ‡Waist circumference >88 cm in women or >102 cm in men. §Triglycerides ≥150 mg/dl. ‖HDL cholesterol <50 mg/dl in women or <40 mg/dl in men. ¶Fasting glycemia ≥110 mg/dl or nonfasting glycemia ≥200 mg/dl or antidiabetes medication. **Impaired fasting glucose ≥110 mg/dl without diabetes. ††Diabetes: fasting glycemia ≥126 mg/dl or nonfasting glycemia ≥200 mg/dl or antidiabetes medication. *P* value: Student and Pearson χ^2 tests used for continuous and categorical variables, respectively, to compare baseline characteristics between subjects with metabolic syndrome and those without. NA, nonapplicable.

spip/). All these characteristics are potential risk factors of dementia (1) and might be associated with some metabolic syndrome components, thus acting as potential confounders.

Statistical analysis

Baseline characteristics of the subjects were compared according to the presence of metabolic syndrome using Student's *t* and Pearson χ^2 tests for continuous and categorical variables, respectively. Associations between metabolic syndrome, or each of its components, with incident dementia over 4 years were estimated using separate proportional hazards models with delayed entry and age as time scale (9). This model allowed estimation of the strength of the association between metabolic syndrome and each of its components with age at onset of dementia, taking censoring by death or loss to follow-up into account, over the 4 years of follow-up. All metabolic syndrome components were then included in a single model to evaluate their own independent effect on the risk of dementia. Models tested associations with all-cause dementia and its different subtypes (Alzheimer's disease/vascular dementia). Models were adjusted for sociodemographic characteristics (age [already taken into account by the model], sex, education level, and study center). We tested the potential interactions between each component of the metabolic syndrome and apoE genotype (presence of at least one versus no ε4 allele) on the risk of incident dementia. If no significant interaction was detected, analysis was further adjusted on the apoE genotype. We also tested the interaction between age and waist circumference. All statistical tests were two sided, and a *P* value of <0.05 was considered statistically significant, except for the interaction terms, for which a level of significance of 0.10 was used in order to better identify biologically meaningful associations. Statistical analyses were performed with the SAS Statistical Package release 9.1 (SAS Institute, Cary, NC).

RESULTS

General baseline characteristics

The study sample consisted of 4,323 women and 2,764 men who had at least one reexamination over 4 years and for whom all metabolic syndrome components were measured at baseline. The 651 subjects with no follow-up did not differ significantly from the 7,087 subjects having at least one reexamination in terms of metabolic syndrome components ($P = 0.07$ for hypertension, $P = 0.12$ for high waist circumference, $P = 0.22$ for high triglycerides, $P = 0.10$ for elevated fasting glycemia; data not shown), except for low HDL cholesterol ($P = 0.001$), which was more frequent in subjects with no follow-up (data not shown).

The baseline characteristics of the whole cohort according to the presence of metabolic syndrome are reported in Table 1. Mean age was 73.4 (4.9) years. According to the NCEP ATP III criteria, metabolic syndrome was present in 15.8% of the study participants. Subjects with metabolic syndrome were more often men and slightly older and less educated than those without metabolic syndrome. There were no differences in the prevalence of the apoE ε4 allele between the two groups. High blood pressure was the most frequent metabolic syndrome component, followed by high waist circumference, high triglycerides, low HDL cholesterol, and elevated fasting glycemia. About two-thirds of participants with hyperglycemia so defined had diabetes.

Associations between metabolic syndrome at baseline, its components, and incident dementia during follow-up

During 4 years of follow-up, 208 incident cases of all-cause dementia were validated (i.e., 0.84 incident dementia cases per 100 person-years [95% CI 0.72–0.95]). This incidence was 1.13 (0.79–1.46) per 100 person-years in subjects with meta-

Table 2—*Association between the metabolic syndrome at baseline or each of its components (in separate models and then in a single model) and risk for incident dementia over 4 years: the 3C Study, France, 1999–2004*

	All-cause dementia	*P*	Alzheimer's disease	*P*	Vascular dementia	*P*
n	7,077		7,077		7,077	
Separate models						
Metabolic syndrome	1.28 (0.92–1.80)	0.15	0.81 (0.50–1.31)	0.39	2.42 (1.24–4.73)	0.01
High blood pressure*	1.07 (0.66–1.72)	0.79	1.06 (0.58–1.92)	0.86	3.82 (0.52–27.91)	0.19
High waist circumference†	0.86 (0.64–1.17)	0.34	0.63 (0.43–0.94)	0.02	0.82 (0.41–1.66)	0.58
High triglycerides‡	1.45 (1.05–2.00)	0.02	0.90 (0.57–1.43)	0.67	2.27 (1.16–4.42)	0.02
Low HDL cholesterol§	1.22 (0.82–1.81)	0.33	0.76 (0.42–1.35)	0.34	2.06 (0.94–4.53)	0.07
High glycemia‖	1.28 (0.88–1.88)	0.20	1.04 (0.62–1.74)	0.89	1.89 (0.89–4.02)	0.10
Variable high glycemia (split into two variables)						
Impaired fasting glucose¶	0.63 (0.26–1.53)	0.30	0.79 (0.29–2.16)	0.65	0.63 (0.09–4.60)	0.64
Diabetes**	1.58 (1.05–2.38)	0.03	1.15 (0.64–2.05)	0.64	2.53 (1.15–5.66)	0.02
Single model						
High blood pressure*	1.06 (0.65–1.70)	0.83	1.10 (0.60–2.01)	0.75	3.73 (0.51–27.4)	0.20
High waist circumference†	0.83 (0.61–1.12)	0.22	0.64 (0.43–0.95)	0.03	0.65 (0.31–1.33)	0.24
High triglycerides‡	1.42 (1.00–2.01)	0.05	1.00 (0.61–1.64)	0.998	1.98 (0.95–4.13)	0.07
Low HDL cholesterol§	1.05 (0.68–1.62)	0.81	0.80 (0.43–1.48)	0.47	1.52 (0.64–3.62)	0.34
High glycemia‖	1.21 (0.82–1.80)	0.34	1.13 (0.67–1.92)	0.65	1.61 (0.74–3.50)	0.23

Data are hazard ratio (95% CI). Models are adjusted by age, sex, educational level, and city center: $n = 7077$, without missing data. Regressions analyzed by proportional hazards models with delayed entry and age as time scale. *Systolic blood pressure >130 mmHg or diastolic blood pressure >85 mmHg or medication. †Waist circumference >88 cm in women or >102 cm in men. ‡Triglycerides ≥ 150 mg/dl. §HDL cholesterol <50 mg/dl in women or <40 mg/dl in men. ‖Fasting glycemia ≥110 mg/dl or nonfasting glycemia ≥200 mg/dl or antidiabetes medication. ¶Impaired fasting glucose: fasting glycemia ≥110 mg/dl without diabetes. **Diabetes: fasting glycemia ≥126 mg/dl or nonfasting glycemia ≥200 mg/dl or antidiabetes medication.

bolic syndrome (44 cases) and 0.78 (0.66–0.90) in the others (164 cases). The incidence of Alzheimer's disease (134 cases, 64% of dementia cases) was 0.54 (0.45–0.63) per 100 person-years in the whole cohort, 0.51 (0.29–0.74) in subjects with metabolic syndrome (20 cases), and 0.55 (0.45–0.65) in the others (114 cases). The incidence of vascular dementia (40 cases, 19.2% of dementia cases) was 0.16 (0.11–0.21) per 100 person-years in the whole cohort, 0.33 (0.15–0.51) in subjects with metabolic syndrome (13 cases), and 0.13 (0.08–0.18) in the others (27 cases).

Subjects with metabolic syndrome at baseline had a nonsignificant increased risk of all-cause dementia over 4 years (Table 2). Table 2 also reports the association between each component of metabolic syndrome and the risk of all-cause dementia over 4 years of follow-up in separate models. High triglyceride level at baseline was the only component significantly associated with all-cause dementia, the risk being increased by 45%. This association remained significant and virtually unchanged after additional adjustment on apoE genotype (hazard ratio 1.47 [95% CI 1.06–2.03]; $P = 0.02$).

Regarding the link between metabolic syndrome and the risk of dementia subtypes, no association was found between metabolic syndrome at baseline and the risk of Alzheimer's disease over 4 years (Table 2). None of the metabolic syndrome components was associated with a significantly increased risk of Alzheimer's disease. On the contrary, a high waist circumference was associated with a decreased risk of Alzheimer's disease (Table 2). This association remained unchanged after additional adjustment of apoE genotype (hazard ratio 0.62 [95% CI 0.41–0.92]; $P = 0.02$).

Subjects with metabolic syndrome at baseline had a significantly increased risk of vascular dementia over 4 years (Table 2), even after additional adjustment on apoE4 genotype (hazard ratio 2.44 [95% CI 1.25–4.77]; $P = 0.01$). High triglyceride level was the only component significantly associated with vascular dementia. This significant association persisted after additional adjustment of the apoE genotype (2.36 [1.21–4.61]; $P = 0.02$). Elevated fasting glycemia at baseline according to the NCEP ATP III criteria was not significantly associated with increased risk of incident dementia. However, when this variable was split into two dummy variables, the presence of diabetes was significantly associated with increased risk of all-cause and vascular dementia, not Alzheimer's disease, while impaired fasting glucose was not associated with any type of dementia (Table 2). There was no interaction between age and waist circumference. ($P = 0.44$ in the model with all-cause dementia, $P = 0.76$ in the model with Alzheimer's disease, and $P = 0.45$ in the model with vascular dementia). We also found no interaction between age and elevated fasting glycemia for the risk of all-cause dementia ($P = 0.78$), Alzheimer's disease ($P = 0.24$), or vascular dementia ($P = 0.23$) (data not shown).

The results remained unchanged when all five metabolic syndrome components were entered simultaneously as explanatory variables in a single model (Table 2, *bottom*, *single model*). In this analysis, the results for each metabolic syndrome component were similar to those obtained with separate regressions with each component. Hazard ratios and significance levels were only slightly attenuated because of some collinearity among metabolic syndrome components. Similarly, diabetes but not impaired fasting glucose remained associated with risk of all-cause and vascular dementia when adjusting for the other metabolic syndrome components.

CONCLUSIONS — In this prospective study of French noninstitutionalized elderly subjects aged ≥65 years, the presence of metabolic syndrome (NCEP ATP III criteria) at baseline was associated with an increased risk of incident vascular de-

mentia but not all-cause dementia and Alzheimer's disease over 4 years, independently of sociodemographic characteristics and the apoE ε4 allele. High triglyceride level at baseline was the only metabolic syndrome component that was significantly associated with all-cause dementia and vascular dementia, even after adjustment of the apoE genotype. On the other hand, a high waist circumference was associated with a decreased risk of Alzheimer's disease. Diabetes, but not impaired fasting glucose, was significantly associated with all-cause dementia and vascular dementia.

Our findings suggest that the concept of metabolic syndrome may not give any additive value in predicting the development of dementia compared with its components considered separately. Indeed, when we tested the contribution of each metabolic syndrome component by putting them together into a single model, the results were similar to those obtained with one regression for each component, suggesting that the association of each component with dementia risk was independent. Moreover, we found no statistically significant association between the number of metabolic syndrome components and the risk of incident dementia (data not shown). This result is in agreement with the study of Yaffe et al. (10), in which the number of metabolic syndrome components did not affect the risk of cognitive decline. Accordingly, the concept of metabolic syndrome is controversial and the metabolic syndrome would be "a set of statistical associations believed to carry an excess of cardiovascular risk" (20) and then of vascular dementia.

The association between high triglyceride level at baseline and risk of incident dementia is an original finding. Few studies have focused on hypertriglyceridemia and its relation to dementia. A transversal study (21) made known the potential relationship between elevated triglyceride levels and poorer cognitive function in patients with diabetes. A similar association was found in a longitudinal study with a long-term follow-up (in the Honolulu-Asia Aging Study, a 1 SD increase in triglyceride levels during mid-life increased the risk of dementia 25 years later [9]). In our study, high triglyceride level was only associated with incident vascular dementia (even if there were only 40 cases) but not with Alzheimer's disease. Whether moderate hypertriglyceridemia is an independent risk factor for cardiovascular disease remains a debate, but a meta-analysis of thousands of patients followed-up for >10 years showed that a triglyceride elevation of 1 mmol/l increased the risk of cardiovascular disease, independently of HDL cholesterol (22). However, the precise mechanisms, especially in the brain, by which hypertriglyceridemia might increase dementia risk still have to be elucidated. Few studies have examined the relationship between HDL cholesterol and incidence of dementia, most focusing on total or LDL cholesterol with conflicting results (23).

The fact that diabetes itself (and not impaired fasting glucose) was associated with all-cause and vascular dementia but not Alzheimer's disease reinforces the hypothesis that vascular risk factors are involved. Vascular pathophysiological mechanisms are more involved in diabetes than in impaired fasting glucose. Indeed, "diabetes" is defined by risk of microvascular complications (18) (as occurrence of microanevrysms).

In opposition with our results, higher waist circumference was found to be associated with higher risk of Alzheimer's disease but only in individuals aged <76 years (24). Conversely, some studies found that patients might lose weight before Alzheimer's disease diagnosis, and this has been interpreted as a consequence of the disease rather than a risk factor. So, the inverse association between adiposity, measured by waist circumference, and Alzheimer's disease could be explained by weight loss due to preclinical disease in our participants.

In contrast to other studies (3), we found no association between hypertension and risk of developing dementia. This could be due to the high frequency of hypertension in the whole 3C Study cohort. Therefore, the relationship between hypertension at middle age and risk of dementia (25) may no longer hold at older ages. Moreover, in our study, the duration of the presence of the various components of metabolic syndrome was not known and may have influenced the risk of dementia. Indeed, risk factors that are already present at mid-life might have a stronger impact on dementia risk (e.g., hypertension) (25). Results from several studies indicate that the relation between these factors and disease become increasingly complex with advancing age (24). Findings may therefore be different when the risk factors are measured at mid-life, in particular for hypertension and low HDL cholesterol but also for BMI (25). Another explanation for the lack of association in our study may lie in the fact that the thresholds currently used for defining metabolic syndrome might not be suitable for an older population, as suggested by the very high prevalence of hypertension found in our sample of rather healthy participants.

Nevertheless, several limitations may affect the interpretation of our results. Selective survival might explain some paradoxical results in the oldest elderly subjects, in whom metabolic syndrome was found to be associated with slower cognitive decline. The association between metabolic syndrome and dementia might indeed be underestimated as a result of censoring for death since subjects with metabolic syndrome are more likely to die from cardiovascular disease before developing dementia. It would be interesting, in a future study, to explore the causes of death in patients with metabolic syndrome. Similarly, 651 subjects with no follow-up did not differ significantly from 7,087 subjects having at least one reexamination in terms of metabolic syndrome components, except for HDL cholesterol, which could be explained by a worse nutritional status linked to higher cumulative mortality rates (data not shown).

Our results emphasize the need for early detection and treatment of hypertriglyceridemia and diabetes in older individuals in order to delay the onset of clinical dementia. However, the concept of metabolic syndrome as a whole does not seem to have any added value regarding dementia risk in this population. The putative interactions between single metabolic risk factors (high triglyceride level and diabetes) and dementia need to be further studied.

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