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**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 (MetS), and its individual components, with risk of incident dementia, and its different subtypes, are inconsistent.

## **RESEARCH DESIGN AND METHODS**

The 7087 community-dwelling subjects aged 65 yr and over were recruited from the French Three-City (3C) cohort. Hazard ratios of incident dementia over four years – and its subtypes (vascular dementia and Alzheimer’s disease (AD)) - associated with MetS (defined according to the NCEP ATP III Criteria) - and its individual components (hypertension, large waist circumference, high triglycerides, low HDL-cholesterol, elevated fasting glycemia) - were estimated in separate Cox proportional hazard models.

## **RESULTS**

MetS was present in 15.8% of the study participants. The presence of MetS increased the risk of incident vascular dementia but not AD over four years independently of socio-demographic characteristics and Apolipoprotein E  $\epsilon$ 4 allele. High triglycerides level was the only component of MetS that was significantly associated with the incidence of all-cause dementia (HR = 1.45 [1.05 – 2.00];  $p = 0.02$ ) and vascular dementia (HR = 2.27 [1.16 – 4.42];  $p = 0.02$ ), even after adjustment on Apolipoprotein E genotype. Diabetes, but not impaired fasting glycemia, was significantly associated with all-cause dementia (HR = 1.58 [1.05 – 2.38];  $p = 0.03$ ) and vascular dementia (HR = 2.53 [1.15 – 5.66];  $p = 0.03$ ).

## **CONCLUSIONS**

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

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, personality change), with a significant impact on activities of daily living (1). Eighteen percent of people over 75 yr have dementia. Its most frequent form is Alzheimer's disease (AD) (about 50-60% of cases,(1)), vascular dementia accounting for most of the other causes (1). The underlying pathophysiological mechanisms – and hence risk factors - of AD 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 (MetS) which is a cluster of five cardiovascular risk factors including hypertension, abdominal obesity, dyslipidemia: elevated triglycerides, low HDL-cholesterol and elevated fasting glycemia (impaired fasting glucose or diabetes) (7).

MetS is associated with increased risk of cardiovascular disease (8). If MetS 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 MetS, or its individual components, and dementia has received little attention (9-14). Three longitudinal studies showed that MetS as a whole is related to higher risk of cognitive decline, but they did not examine the association with the risk of dementia (10-12).

While a cross-sectional study (13) found a higher prevalence of dementia in women with MetS, the single published prospective study (14) showed no association between MetS and incident dementia. On the other hand, only some components of the MeS – and not MetS itself - might be associated with an increased risk of incident dementia. In particular, several prospective studies evidenced that presence of diabetes was associated with increased incidence of AD and vascular dementia (6, 14). However, the role of hyperglycemia in the absence of diabetes (impaired fasting glucose) needs to be well-defined (15).

We therefore aimed to estimate the prospective association between MetS, or its individual components, with the risk of incident dementia – and the potential differences according to the subtype of dementia: AD or vascular dementia - in a large prospective epidemiological study conducted in community-dwelling older persons. We focused on the component “elevated fasting glycemia” to study the specific role of diabetes *versus* impaired fasting glucose.

## **RESEARCH DESIGN AND METHODS**

### **Study population**

The subjects included in the present study were a sub-sample 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 (CCPPRB) of the University Hospital of Kremlin-Bicêtre (Paris, France). All participants gave their written informed consent. Briefly, non-institutionalized persons aged 65 yr and older 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 four 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 1341 subjects because of incomplete data for defining MetS (623 persons with no blood sample and 971 with no waist circumference measurement). This gave a baseline sample of 7738 subjects. At the second round of the study (2001-2002), 6964 (90.0%) were examined again, 134 were deceased, and 640 refused to participate or were lost to follow-up. At the third round (2003-2004), 6262 were examined (84.9% of the survivors after the second round), the cumulated number of deaths was 358, and 1118 refused to participate or were lost to follow-up. Finally, 7087 (91.6%) participants had at least one follow-up examination over the four 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 (MRI) or CT-Scan were collected (16). Second, the participants who were suspected of having dementia on the basis of their neuropsychological performance (in

particular Mini Mental Status Examination, Benton Visual Retention Test and Isaac's Set Test administered uniformly in all three study centres at each follow-up (16)) were examined by a neurologist in the three study centres (16). Finally, all suspected dementia cases were analyzed by a common independent committee of neurologists according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV) (16). This committee of neurologists reviewed by teleconference all potential cases of dementia of the three study centres 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 the committee: AD according to NINCDS-ADRDA criteria (16) and vascular dementia based on history of vascular disease, Hachinski score (16) and MRI whenever possible.

### **Definition of MetS**

Baseline MetS was defined according to the National Cholesterol Education Program Adult Treatment Panel III Criteria (NCEP ATP III), 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) elevated triglycerides ( $\geq 150$  mg/dL), 4) low HDL-cholesterol (men  $< 40$  and women  $< 50$  mg/dL), and 5) elevated fasting glycemia ( $\geq 110$  mg/dL) or non-fasting glycemia  $\geq 200$  mg/dl or antidiabetic medication (17).

In order to better understand the specific role of diabetes *versus* impaired fasting glucose, we made further analyses distinguishing subjects with diabetes (fasting glycemia  $\geq 126$  mg/dl or non-fasting glycemia  $\geq 200$  mg/dl or antidiabetic medication) (definition of WHO, 1999) (23),



subjects with impaired fasting glucose (fasting glycemia  $\geq 110$  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 MetS 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  $-80^{\circ}\text{C}$ ) and centralized measurements of fasting blood glucose, HDL-cholesterol and triglycerides were performed. As we had to include only Type 2 diabetes patients in the definition of MetS component (17), we excluded patients who were considered to have Type 1 diabetes based on the definition of WHO, 1999 (18) and who were treated by insulin alone ( $n = 26$ ).

### **Potential confounders and effect modifiers**

Socio-demographic information recorded at baseline during a face-to-face interview included age, gender, and educational level (in two classes: subjects who received primary or no education vs the others (6 years of schooling or more), 10 missing data). Determination of Apolipoprotein E (ApoE) genotype was carried out at the Lille Genopole located in Lille, France (<http://www.genopole-lille.fr/spip/>). All these characteristics are potential risk factors of

dementia (1) and might be associated with some MetS components, thus acting as potential confounders.

### **Statistical analysis**

Baseline characteristics of the subjects were compared according to the presence of MetS using Student and Pearson Chi square tests for continuous and categorical variables respectively.

Associations between MetS, or each of its components, with incident dementia over four years were estimated using separate proportional hazards models with delayed entry and age as time scale (19). This model allowed estimation of the strength of the association between MetS and each of its components with age at onset of dementia, taking censoring by death or loss-to-follow-up into account, over the four years of follow-up. All MetS 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 then its different subtypes (Alzheimer's disease / vascular dementia). Models were adjusted for socio-demographic characteristics: age (already taken into account by the model), gender, education level, and study centre. We tested the potential interactions between each component of the MetS and ApoE genotype (presence of at least one *vs* no  $\epsilon 4$  allele) on the risk of incident dementia. If no significant interaction was detected, analysis was further adjusted on ApoE genotype. We also tested the interaction between age and waist circumference. All statistical tests were two-sided and a *p* value of less than 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 Inc., Cary, NC, USA).

## **RESULTS**

### **General baseline characteristics**

The study sample consisted of 4323 women and 2764 men who had at least one re-examination over four years and for whom all MetS components were measured at baseline. The 651 subjects with no follow-up did not differ significantly from the 7087 subjects having at least one re-examination in terms of MetS 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, and according to the presence of MetS, are reported in Table 1. Mean age was 73.4 (4.9) yr. According to the NCEP-ATP III Criteria, MetS was present in 15.8% of the study participants. Subjects with MetS were more often men, slightly older and less educated than those without MetS. There were no differences in prevalence of ApoE  $\epsilon 4$  allele between the two groups. High blood pressure was the most frequent MetS component, followed by high waist circumference, high triglycerides, low HDL-cholesterol, and elevated fasting glycemia. About two thirds of participants with so defined hyperglycemia had diabetes.

## **Associations between MetS at baseline, its components, and incident dementia during follow-up**

During the four 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 MetS (44 cases) and 0.78 (0.66 – 0.90) in the others (164 cases). The incidence of AD (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 MetS (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 MetS (13 cases) and 0.13 (0.08 – 0.18) in the others (27 cases).

Subjects with MetS at baseline had a non-significant increased risk of all-cause dementia over four years (Table 2). Table 2 also reports the association between each component of MetS and the risk of all-cause dementia over the four years of follow-up in separate models. High triglycerides 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 (HR = 1.47 [1.06 – 2.03];  $p = 0.02$ ). Regarding the link between MetS and the risk of dementia sub-types, no association was found between MetS at baseline and the risk of AD over four years (Table 2). None of the MetS components was associated with a significantly increased risk of AD. On the contrary, a high waist circumference was associated with a decreased risk of AD (Table 2). This association remained unchanged after additional adjustment on ApoE genotype (HR = 0.62 [0.41 – 0.92];  $p = 0.02$ ).

Subjects with MetS at baseline had a significantly increased risk of vascular dementia over four years (Table 2) even after additional adjustment on ApoE4 genotype (HR = 2.44 [1.25 – 4.77];  $p = 0.01$ ). High triglycerides level was the only component significantly associated with vascular dementia. This significant association persisted after additional adjustment on ApoE genotype (HR = 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 AD, 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 AD 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 ( $p = 0.78$ ), AD ( $p = 0.24$ ) or vascular dementia ( $p = 0.23$ ) (data not shown).

The results remained unchanged when all five MetS components were entered simultaneously as explanatory variables in a single model (Table 2 bottom, single model). In this analysis, the results for each MetS 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 MetS components. Similarly, diabetes but not impaired fasting glucose, remained associated with risk of all-cause and vascular dementia when adjusting for the other MetS components.

## CONCLUSIONS

In this prospective study of French non-institutionalized elderly subjects aged 65 yr and over, the presence of MetS (NCEP ATP III criteria) at baseline was associated with an increased risk of incident vascular dementia but not all-cause dementia and AD over four years, independently of socio-demographic characteristics and ApoE  $\epsilon$ 4 allele. High triglycerides level at baseline was the only MetS component that was significantly associated with all-cause dementia and vascular dementia, even after adjustment on ApoE genotype. On the other hand, a high waist circumference was associated with a decreased risk of AD. Diabetes, but not impaired fasting glucose, was significantly associated with all-cause dementia and vascular dementia.

Our findings suggest that the concept of MetS may not give any additive value in predicting the development of dementia compared to its components considered separately. Indeed, when we tested the contribution of each MetS 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 MetS components and the risk of incident dementia (data not shown). This result is in agreement with the study of Yaffe *et al* (10) where the number of MetS components did not affect the risk of cognitive decline. Accordingly, the concept of MetS is controversial and the MetS 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 triglycerides level at baseline and risk of incident dementia is an original finding. Few studies have focused on hypertriglyceridemia and its relations to dementia. A transversal study made known the potential relations between elevated triglyceride levels and poorer cognitive function in patients with diabetes (21). A similar association was found in a longitudinal study with a long-term follow-up: in the Honolulu-Asia Aging Study, an 1 SD increase in triglycerides levels during mid-life increased the risk of dementia 25 years later (9). In our study, high triglycerides level was only associated with incident vascular dementia (even if there were only 40 cases) but not with AD. Whether moderate hypertriglyceridemia is an independent risk factor for cardiovascular disease remains a debated question but a metanalysis of thousands of patients followed up for more than 10 yr showed that a triglycerides 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 relations between HDL-cholesterol and incidence of dementia, most focusing on total cholesterol 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 AD, 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 microanevrysts).

In opposition with our results, higher waist circumference was found to be associated with higher risk of AD but only in persons younger than 76 years (24). Conversely, some studies found that

patients might lose weight prior to AD 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 AD could be explained by weight loss due to pre-clinical 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 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 MetS was not known and may have influenced the risk of dementia. Indeed, risk factors which are already present at mid-life might have a stronger impact on dementia risk, e.g. hypertension (25). Results from several studies indicate that relations 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 to the lack of association in our study may lie in the fact that the thresholds currently used for defining MetS 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 old, in whom MetS was found to be associated with slower cognitive decline. The association between MetS and dementia might



indeed be underestimated by censoring by death since subjects with MetS 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 MetS.

Similarly, the 651 subjects with no follow-up did not differ significantly from the 7087 subjects having at least one re-examination in terms of MetS 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 persons in order to delay the onset of clinical dementia. However, the concept of MetS 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 triglycerides level and diabetes - and dementia need to be further studied.

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## TABLES

**Table 1. Baseline characteristics according to the presence of metabolic syndrome (MetS) and associations between the different components of the MetS. The Three City Study, France, 1999-2004. N = 7087.**

	Total	MetS	No MetS	<i>p</i>	<i>Components of the MetS</i>				
	Cohort				High BP	High Waist	High TG	Low HDL-chol	High Gly
	N = 7087	N = 1121	N = 5966		N = 6064	N = 2049	N = 1247	N = 741	N = 816
Age, yr, mean (SD)	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 BP (%)	85.6	98.2	83.2	<0.0001	na	91.6	90.0	88.3	95.2
High Waist (%)	28.9	78.5	19.6	<0.0001	31.0	na	44.2	50.4	50.2
High TG (%)	17.6	66.4	8.4	<0.0001	18.5	26.9	na	50.5	32.0
Low HDL-chol (%)	10.5	47.6	3.5	<0.0001	10.8	18.3	30.2	na	22.8
High Gly (%)	11.5	47.6	4.7	<0.0001	12.9	20.0	20.9	25.0	na
IFG 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

High BP: SBP > 130 mm Hg or DBP > 85 mm Hg or medication; SBP: systolic blood pressure, DBP: diastolic blood pressure

High Waist: Waist circumference > 88 cm in women or > 102 cm in men

High TG: TG  $\geq$  150 mg/dl; TG: triglycerides

Low HDL-chol: HDL-chol < 50 mg/dl in women or < 40 mg/dl in men; HDL-chol: HDL-cholesterol

High Gly: Fasting glycemia  $\geq$  110 mg/dl or non-fasting glycemia  $\geq$  200 mg/dl or antidiabetic medication

IFG: Impaired fasting glucose: fasting glycemia  $\geq$  110 mg/dl without diabetes

Diabetes: fasting glycemia  $\geq$  126 mg/dl or non-fasting glycemia  $\geq$  200 mg/dl or antidiabetic medication

MetS was defined by the National Cholesterol Education Program Adult Treatment Panel III criteria.

*p* value : Student and Pearson Chi square tests used for continuous and categorical variables respectively to compare baseline characteristics between subjects with MetS and those with no MetS.

ApoE  $\epsilon$ 4: presence of at least one allele  $\epsilon$ 4 in ApoE genotype.

na: non applicable.



**Table 2. Association between the metabolic syndrome (MetS) at baseline, or each of its components - in separate models and then in a single model - and risk for incident dementia over four years. The Three-City study, France, 1999-2004. Models are adjusted on age, gender, educational level and city center: N = 7077, without missing data.**

	All-cause dementia N = 7077	<i>p</i>	Alzheimer's disease N = 7077	<i>p</i>	Vascular dementia N = 7077	<i>p</i>
	Hazard ratio (95% CI)		Hazard ratio (95% CI)		Hazard ratio (95% CI)	
<i>Separate models</i>						
MetS	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 BP	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	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 TG	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-chol	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 Gly	1.28 [0.88 – 1.88]	0.20	1.04 [0.62 – 1.74]	0.89	1.89 [0.89 – 4.02]	0.10
<i>Variable "High Gly" split into two variables</i>						
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
<i>Single model</i>						
High BP	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	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 TG	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-chol	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 Gly	1.21 [0.82 – 1.80]	0.34	1.13 [0.67 – 1.92]	0.65	1.61 [0.74 – 3.50]	0.23

Regressions analyzed by proportional hazards models with delayed entry and age as time scale. Results expressed as hazard ratios and 95% CI.

BP: blood pressure, TG: triglycerides, HDL-chol: HDL-cholesterol, Gly: glycemia.

High BP: SBP > 130 mm Hg or DBP > 85 mm Hg or medication; SBP: systolic blood pressure, DBP: diastolic blood pressure

High Waist: Waist circumference > 88 cm in women or > 102 cm in men

High TG: TG  $\geq$  150 mg/dl; TG: triglycerides

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Diabetes: fasting glycemia  $\geq$  126 mg/dl or non-fasting glycemia  $\geq$  200 mg/dl or antidiabetic medication

