

The Metabolic Syndrome, Inflammation, and Risk of Cognitive Decline

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CARDIOVASCULAR AND METABOLIC risk factors such as hypertension and diabetes have been hypothesized to play a role in the pathogenesis of Alzheimer disease (AD) as well as in development of vascular dementia.¹⁻⁴ The metabolic syndrome,⁵ a clustering of several commonly occurring disorders that include (1) abdominal obesity, (2) hypertriglyceridemia, (3) low high-density lipoprotein (HDL) level, (4) hypertension, and (5) hyperglycemia, has not been specifically investigated as a risk factor for cognitive decline in elderly individuals. The metabolic syndrome may be a risk factor for cognitive decline because it summarizes the joint effects of these risk factors. As obesity and sedentary lifestyle rise in the United States, identification and explanation of the role of these modifiable behaviors in increasing risk for developing deleterious outcomes such as cognitive impairment is critical. If the metabolic syndrome is associated with increased risk of developing cognitive impairment, then early identification and treatment of these individuals might offer avenues for disease course modification.

High levels of inflammation increase the risk of the development of

Context Several studies have reported an association between the metabolic syndrome and cardiovascular disease. Despite an increasing awareness that cardiovascular risk factors increase risk of cognitive decline and dementia, there are few data on the metabolic syndrome and cognition.

Objective To determine if the metabolic syndrome is a risk factor for cognitive decline and if this association is modified by inflammation.

Design and Setting A 5-year prospective observational study conducted from 1997 to 2002 at community clinics at 2 sites.

Participants A total of 2632 black and white elders (mean age, 74 years).

Main Outcome Measures Association of the metabolic syndrome (measured using National Cholesterol Education Program guidelines) and high inflammation (defined as above median serum level of interleukin 6 and C-reactive protein) with change in cognition (Modified Mini-Mental State Examination [3MS]) at 3 and 5 years. Cognitive impairment was defined as at least a 5-point decline.

Results Compared with those without the metabolic syndrome ($n=1616$), elders with the metabolic syndrome ($n=1016$) were more likely to have cognitive impairment (26% vs 21%, multivariate adjusted relative risk [RR], 1.20; 95% confidence interval [CI], 1.02-1.41). There was a statistically significant interaction with inflammation and the metabolic syndrome ($P=.03$) on cognitive impairment. After stratifying for inflammation, those with the metabolic syndrome and high inflammation ($n=348$) had an increased likelihood of cognitive impairment compared with those without the metabolic syndrome (multivariate adjusted RR, 1.66; 95% CI, 1.19-2.32). Those with the metabolic syndrome and low inflammation ($n=668$) did not exhibit an increased likelihood of impairment (multivariate adjusted RR, 1.08; 95% CI, 0.89-1.30). Stratified multivariate random-effects models demonstrated that participants with the metabolic syndrome and high inflammation had greater 4-year decline on 3MS ($P=.04$) compared with those without the metabolic syndrome, whereas those with the metabolic syndrome and low inflammation did not ($P=.44$).

Conclusion These findings support the hypothesis that the metabolic syndrome contributes to cognitive impairment in elders, but primarily in those with high level of inflammation.

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diabetes and atherosclerosis and are thought to be a possible mechanism for the adverse consequences of the metabolic syndrome.^{6,7} Indeed, level of inflammation in the setting of the meta-

bolic syndrome may help identify those at especially high risk for adverse outcomes. Furthermore, subclinical inflammation might be an underlying factor for an association between the

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metabolic syndrome and cognitive decline since inflammatory mechanisms are also hypothesized to be involved in the pathogenesis of cognitive impairment.⁸⁻¹⁰ Thus, we conducted this study to investigate whether the metabolic syndrome is associated with cognitive decline and modified by level of inflammation. Our hypothesis was that presence of the metabolic syndrome would be associated with more cognitive decline and greater risk of developing cognitive impairment and that this association would be modified by inflammation.

METHODS

Study Population

Participants were part of the Health, Aging and Body Composition (ABC) study, a prospective cohort study conducted from 1997 to 2002 of 3075 community-dwelling elders aged 70 to 79 years living in Memphis, Tenn, and Pittsburgh, Pa. Elders were recruited from a random sample of white and all black Medicare-eligible adults living in designated ZIP codes. Race was defined by self-report and was assessed because rates of cognitive impairment have been shown to differ by race. Sampled participants were mailed a brochure describing the study and then contacted by telephone to establish functional status and to recruit eligible residents to join the study. Community-based activities were also used to enhance the recruitment of black participants. Well-functioning was determined by self-report and was defined as having no difficulty in walking a quarter of a mile or going up 10 steps without resting reported during 2 separate interviews prior to enrollment into the study.

Exclusion criteria included (1) any difficulty with activities of daily living, (2) clinical dementia (based on *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* criteria), (3) inability to communicate with the interviewer, (4) intention of moving out of the vicinity in the next year, (5) active treatment for cancer in the previous 3 years, and (6) participation in a trial involving a lifestyle intervention.

Data on the metabolic syndrome were missing for 40 participants, 70 had missing inflammatory marker data, and 16 had missing baseline cognitive data, leaving 2949 participants. Our analytic cohort includes the 2632 participants who had at least 1 cognitive follow-up assessment. Of the remaining 317 participants, 164 died, 69 were lost to follow-up, and 84 did not have repeat cognitive testing. Those with and without the metabolic syndrome had similar rates of follow-up (90.2% vs 89.2%, $P = .40$). All participants signed an informed written consent, approved by the institutional review boards of the clinical sites. This study was approved by the University of California, San Francisco Committee of Human Research.

Measurements

Cognitive Test. The Teng Modified Mini-Mental State Examination (3MS) was administered to all participants during the baseline visit and repeated at the year 3 and 5 follow-up visits. It is a brief, general cognitive battery with components for orientation, concentration, language, praxis, and immediate and delayed memory with a maximum (best) score of 100.¹¹ The 3MS is more sensitive than the traditional 30-point Mini-Mental State Examination, especially for mild cognitive change.¹¹ Cognitive impairment was defined as a 3MS change of 5 or more points at either follow-up visit as has been previously recommended.¹²

The Metabolic Syndrome. Presence of the metabolic syndrome at baseline was calculated by sex as defined by the National Cholesterol Education Program Third Adult Treatment Panel guidelines of at least 3 of the following: (1) waist measurement (greater than 88 cm for women and greater than 102 cm for men); (2) hypertriglyceridemia (150 mg/dL or higher [≥ 1.69 mmol/L]), (3) low HDL cholesterol (less than 40 mg/dL [< 1.03 mmol/L] in men and less than 50 mg/dL [1.29 mmol/L] in women), (4) high blood pressure (systolic, ≥ 130 mm Hg; diastolic, ≥ 85 mm Hg using the average of 2 seated measurements or cur-

rently using an antihypertensive medication), and (5) high fasting glucose (110 mg/dL or higher [≥ 6.10 mmol/L] or currently using antidiabetic [insulin or oral agents] medication).⁵ Lipid levels were measured after fasting.

To focus on those without clinically evident disease, we constructed an alternate definition for the metabolic syndrome, excluding those participants with overt diabetes (either by self-report, using antidiabetic medication, or fasting glucose ≥ 126 mg/dL [6.99 mmol/L]), frank hypertension (blood pressure $\geq 140/90$ mm Hg), or clinically significant hyperlipidemia (triglycerides ≥ 200 mg/dL [2.26 mmol/L]).

Inflammatory Markers. Measurements for interleukin 6 (IL-6) and for C-reactive protein (CRP) were obtained from frozen stored plasma or serum taken at baseline. Blood samples were obtained in the morning and, after processing, the specimens were aliquoted, frozen at -70°C , and shipped to the Health ABC Core Laboratory at the University of Vermont. Plasma IL-6 levels were measured in duplicate by enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis, Minn). The detectable limit for IL-6 (HS600 Quantikine kit, R & D Systems) was 0.10 pg/mL. Serum levels of CRP were also measured in duplicate by ELISA based on purified protein and polyclonal anti-CRP antibodies (Calbiochem, EMD Biosciences Inc, Darmstadt, Germany). The CRP assay was standardized according to the World Health Organization First International Reference Standard with a sensitivity of 0.08 $\mu\text{g/mL}$. Assays of blind duplicates collected for 150 participants yielded an average interassay coefficient of variation of 10.3% for IL-6 and 8.0% for CRP. We defined "high" inflammation as present if a participant had higher than the median values for both CRP (≥ 2.0 mg/L) and IL-6 (≥ 2.0 pg/mL). The correlation between CRP and IL-6 was 0.40.

Covariates. Covariates included characteristics previously shown in the literature to be associated with cognitive function or with the metabolic syndrome. At baseline, we obtained infor-

mation on participants' age, race, sex, years of education, current smoking, and alcohol use during the past year (percentage with >1 drink per day). At each clinic examination, we measured weight and height; body mass index was defined as weight in kilograms divided by the square of height in meters. In addition, standardized algorithms were used to assess prevalent myocardial infarction (by self-report) and stroke (by self-report). Participants were also asked to rate their overall health compared with others as excellent, good, fair, poor, or very poor. Depressive symptoms were assessed with the Center for Epidemiologic Studies-Depression (CES-D) Scale,¹³ with higher scores indicating greater number of symptoms. An inventory of prescription and over-the-counter medications was obtained by checking the participants' medication container(s). We classified current use of medications as those regularly taken in the past 2 weeks and coded them according to the Iowa Drug Information System (IDIS) code.¹⁴ Using this drug inventory, we documented daily current use of anti-inflammatory drugs (IDIS code 2808) and statins (IDIS code 2406).

Statistical Analyses

χ^2 Analyses or *t* tests were conducted to assess baseline characteristics by presence of the metabolic syndrome. We conducted unadjusted and multivariate adjusted logistic regression analyses to determine if presence of the metabolic syndrome was associated with odds of cognitive impairment. We then corrected for possible overestimation of odds ratios by adjusting to approximate risk ratios according to the method of Zhang and Yu.¹⁵ All models contained baseline cognitive score as a covariate. The multivariate adjusted logistic regression model included covariates that were associated with cognitive impairment ($P < .10$) and were entered into the model using backward elimination. We added an interaction term to these models to assess whether inflammation modified the association of the metabolic syndrome with cognitive outcomes. Since

this term was statistically significant, we conducted stratified analyses by inflammation level.

We used random-effects models to analyze the association between the metabolic syndrome and 4-year change on 3MS score. Random-effects models account for between-subject variation and within-subject correlations between repeated cognitive measurements.¹⁶ The Bayesian Information Criterion was used to determine which random effects to include.¹⁷ Candidates for the random-effect terms included both the intercept and the slope of cognitive scores over time. Fixed effects were chosen by backward elimination until all were associated with cognitive scores at $P < .05$. The candidates for fixed-effect terms included all baseline covariates plus their interactions with time and with a missing pattern indicator. Time was considered as a continuous covariate, measured in days from baseline to follow-up test. By including the missing pattern indicator and its interaction with other covariates, we performed a simplified pattern-mixture model to help account for possible nonrandom dropout. Pattern-mixture models jointly model observed responses and dropout times, thus reducing the effect of biases that would result if dropout was assumed to be independent of unobserved responses.¹⁸ All analyses were conducted with SAS (version 8.2, SAS Institute, Cary, NC).

RESULTS

The mean (SD) age of the participants at baseline was 73.6 (2.9) years; 52% were women, 40% were black, and 25% had high markers of inflammation. Compared with participants without the metabolic syndrome ($n = 1616$), those with the metabolic syndrome ($n = 1016$) were more likely to be women, and white, and to smoke; to have higher depression scores, higher BMI, and a history of a myocardial infarction; to use statins and nonsteroidal anti-inflammatory drugs; and to have high markers of inflammation. In addition, several baseline characteristics were statistically sig-

nificantly different when comparing participants by inflammatory status and presence of the metabolic syndrome (TABLE 1). Among those with the metabolic syndrome, 56% met 3, 33% met 4, and 11% met 5 of the National Cholesterol Education Program criteria. The most common criterion met was hypertension (92%), followed by large waist circumference (86%), hypertriglyceridemia (65%), low HDL cholesterol (62%), and high fasting glucose/antidiabetic medication use (49%).

Overall, the mean (SD) baseline 3MS score was 90.5 (8.0), and cognitive impairment (3MS decline ≥ 5 points) occurred in 598 (22.7%) of the 2632 participants. Baseline 3MS scores did not differ significantly for those with and without the metabolic syndrome (90.6 [7.6] vs 90.4 [8.3], respectively; $P = .46$). However, compared with those without the metabolic syndrome, elders with the metabolic syndrome were somewhat more likely to have cognitive impairment (260 [26%] vs 338 [21%], multivariate adjusted relative risk [RR], 1.20; 95% confidence interval [CI], 1.02-1.41).

We assessed for presence of an interaction between high inflammation and the metabolic syndrome on risk of cognitive impairment. The *P* for interaction was .05 in the unadjusted models and .03 in the adjusted models (adjustment for age, education, race, baseline cognitive score, depression score, alcohol use, stroke, and statin use). Given this significant interaction, we stratified the remainder of our analyses by inflammation. Those participants with the metabolic syndrome and high inflammation were significantly more likely than those without the syndrome to develop cognitive impairment (105 [30%] vs 67 [21%]; multivariate-adjusted RR, 1.66; 95% CI, 1.19-2.32) (TABLE 2). However, those elders with the metabolic syndrome and low inflammation were not more likely to develop impairment (155 [23%] vs 271 [21%]; adjusted RR, 1.08; 95% CI, 0.89-1.30) (Table 2). We repeated these analyses after excluding patients with baseline

stroke (n=55) and found almost identical results. Those participants without the metabolic syndrome but with high inflammation (n=317) did not have an elevated risk of developing cognitive impairment (adjusted RR, 0.81; 95% CI, 0.60-1.08) compared with those without the metabolic syndrome and low inflammation.

When further stratified by race, the association between the metabolic syndrome and cognitive impairment re-

mained elevated for blacks and whites with high inflammation but not for those with low inflammation (for blacks with high inflammation, adjusted RR, 1.67; 95% CI, 1.11-2.53; with low inflammation, adjusted RR, 1.04; 95% CI, 0.80-1.36; and for whites, with high inflammation adjusted RR, 1.75; 95% CI, 0.99-3.08; with low inflammation, adjusted RR, 1.17; 95% CI, 0.89-1.54).

In the stratified, unadjusted, and multivariate-adjusted random-effects

models, within the high inflammation group, scores for those with the metabolic syndrome declined significantly more than for those without the syndrome (TABLE 3). We next determined whether the association remained between the metabolic syndrome and cognitive impairment after excluding participants with clinically significant diabetes, hypertension, or hyperlipidemia. After excluding these elders (n=797), the risk of developing cognitive impairment remained elevated among participants with the metabolic syndrome and high inflammation but was no longer statistically significant (adjusted RR, 1.35; 95% CI, 0.83-2.19); the power was reduced with only 118 elders with both the metabolic syndrome and high inflammation. The metabolic syndrome and cognitive impairment were not associated with low inflammation.

Finally, we assessed whether the association between the metabolic syndrome and inflammation and cognitive decline was related to the number of components of the metabolic syndrome and degree of inflammation. For participants with high inflammation and the metabolic syndrome, the number of components of the metabolic syndrome did not affect the risk of cognitive decline (for the 185 participants meeting 3 criteria, RR, 1.64; 95% CI, 1.13-2.38, whereas for the 163 participants meeting 4 or 5 criteria, RR, 1.49; 95% CI, 1.01-2.21). However, more inflammation (assessed as tertiles) was associated with greater cognitive decline. For participants with 1 or both low tertiles of inflammation (n=743), the adjusted RR for presence of the metabolic syndrome vs no presence of the metabolic syndrome was 1.09 (95% CI, 0.84-1.40); for 1 or both medium tertiles of inflammation (n=1442), the adjusted RR was 1.26 (95% CI, 1.00-1.59); and for 1 or both high tertiles of inflammation (n=447), the adjusted RR was 1.62 (95% CI, 1.10-2.38).

COMMENT

Among high-functioning elders, those with the metabolic syndrome show an

Table 1. Baseline Characteristics of the 2632 Health ABC Participants by Presence of the Metabolic Syndrome

Characteristic*	Low Inflammation		High Inflammation		P Value†
	Without the Metabolic Syndrome (n = 1299)	With the Metabolic Syndrome (n = 668)	Without the Metabolic Syndrome (n = 317)	With the Metabolic Syndrome (n = 348)	
Black	494 (38)	208 (31)	174 (55)	169 (49)	<.001
Female	634 (49)	367 (55)	160 (51)	207 (60)	.001
Age, mean (SD), y	73.7 (2.9)	73.4 (2.8)	73.4 (2.9)	73.5 (2.8)	.09
Education ≤high school	440 (34)	243 (36)	142 (45)	161 (47)	<.001
BMI, mean (SD)	25.8 (4.0)	28.7 (4.3)	27.3 (5.4)	31.0 (4.9)	<.001
Current smoker	197 (15)	71 (11)	88 (31)	51 (16)	<.001
>1 Alcoholic drink per day	102 (8)	32 (5)	36 (12)	24 (7)	.002
Self-reported health (poor/fair)	136 (11)	91 (14)	70 (22)	81 (23)	<.001
Depression score, mean (SD)	4.5 (5.1)	4.5 (5.0)	4.2 (5.2)	5.5 (6.4)	.009
Myocardial infarction history	116 (9)	78 (12)	40 (13)	52 (15)	.004
Stroke history	17 (1)	16 (2)	10 (3)	12 (4)	.03
Current statin use	132 (10)	118 (18)	37 (12)	62 (18)	<.001
Current NSAID use	269 (21)	168 (25)	65 (21)	75 (22)	.15
Baseline 3MS score, mean (SD)	90.7 (8.0)	91.2 (6.9)	89.0 (9.2)	89.5 (8.5)	<.001

Abbreviations: BMI, body mass index calculated as weight in kilograms divided by the square of height in meters; NSAID, nonsteroidal anti-inflammatory drug; 3MS, Modified Mini-Mental State Examination.

*Data are expressed as number and percentage unless otherwise indicated.

†P value analysis of variance for continuous variables and χ^2 for dichotomous variables.

Table 2. Risk of Developing Cognitive Impairment Over 4 Years According to the Metabolic Syndrome and Inflammation Status

	Cognitive Impairment, No. (%)		Risk Ratio (RR) (95% Confidence Interval)*
	No Presence of the Metabolic Syndrome (n = 1616)	Presence of the Metabolic Syndrome (n = 1016)	
Entire cohort (n = 2632)	338 (20.9)	260 (25.6)	Unadjusted RR = 1.21 (1.03-1.43) Adjusted RR = 1.20 (1.02-1.41)
High inflammation (n = 665)	67 (21.1)	105 (30.2)	Unadjusted RR = 1.57 (1.13-2.18) Adjusted RR = 1.66 (1.19-2.32)
Low inflammation (n = 1967)	271 (20.9)	155 (23.2)	Unadjusted RR = 1.08 (0.89-1.31) Adjusted RR = 1.08 (0.89-1.30)

*Reference is the group without the metabolic syndrome. Unadjusted for characteristics other than for baseline cognitive score; adjusted for age, education, race, baseline cognitive score, depression, alcohol use, stroke, and statin use.

increased risk of developing cognitive impairment and decline over 4 years. This association remained after adjustment for possible confounders such as demographics, lifestyle variables, and chronic health conditions. The increased rate of cognitive impairment was primarily observed in those elders who had high levels of serum markers of inflammation, suggesting that at least some of the increased risk associated with the metabolic syndrome is modified by inflammation. To our knowledge, this is the first study to document that the metabolic syndrome is associated with poor cognitive outcomes.

Several components of the metabolic syndrome have been individually related to cognitive outcomes. Mid- or late-life hypertension,^{19,20} hyperlipidemia,^{4,21,22} and diabetes^{3,23,24} have been reported to increase risk of developing dementia or cognitive decline, both due to vascular disease and AD. Our findings are also consistent with results from a study of middle-aged Japanese American men, in which a composite score of 7 cardiovascular risk factors was associated with increased risk of developing vascular dementia but not with increased AD²⁵ and another study of mid- to late-life black and white Americans in which diabetes and hypertension were associated with increased risk of developing cognitive decline.²⁰ The finding that the metabolic syndrome without clinically significant diabetes, hypertension, or hyperlipidemia shows the same pattern of increased risk of cognitive impairment implies that the adverse effect of the metabolic syndrome is related, but not solely, due to the contribution of these conditions.

In many observational studies and animal models, inflammation is associated with AD and vascular disease.^{9,26-28} We previously have shown that elevated CRP and IL-6 is associated with accelerated cognitive decline.⁸ Similarly, those with elevated CRP and IL-6 are at greater risk for developing diabetes, atherosclerosis, and other complications.^{6,7,29} How may inflammation account for the deleterious effect of the metabolic syn-

Table 3. Association Between the Metabolic Syndrome at Baseline and Cognitive Scores Over Time, Adjusted Random-Effects Models*

Model Term	Participants With High Inflammatory Markers (n = 665)		Participants With Low Inflammatory Markers (n = 1967)	
	β Estimated (SE)	P Value	β Estimated (SE)	P Value
The metabolic syndrome	1.666 (1.456)	.25	-0.759 (2.955)	.10
The metabolic syndrome \times time				
Unadjusted†	-0.002 (0.001)	.03	0.000 (0.001)	.49
Adjusted	-0.002 (0.001)	.04	0.000 (0.001)	.47

*Models adjusted for age, education, race, sex, depression, smoking, alcohol use, self-reported health, myocardial infarction, stroke, missing pattern, and statin use. Results are based on random-effects models with the interaction of the metabolic syndrome \times time (days) indicating that, when statistically significant, there is an independent effect of the metabolic syndrome on cognitive decline over time. Reference is the group without the metabolic syndrome.

†Unadjusted for characteristics other than for baseline cognitive score.

drome on cognition? Given the range of possible inclusion criteria for the metabolic syndrome, it may be that level of inflammation may serve as a marker of active pathologic process. For example, an individual with well-controlled hypertension and borderline dyslipidemia may have a markedly different risk for adverse outcomes than an elder with poorly controlled hypertension, obesity, and hyperglycemia. We find some evidence for this hypothesis, as the association between the metabolic syndrome and cognitive impairment was lessened somewhat when we excluded those with clinically significant diseases such as diabetes, hypertension, and hyperlipidemia. Most likely, the metabolic syndrome contributes to accelerated atherosclerosis that is associated with an inflammatory response and in turn, either the atherosclerosis or inflammation or both, contribute to cognitive decline.^{30,31} However, the direction of an association between inflammation and the metabolic syndrome is controversial, with some advocating that the metabolic syndrome is due to subclinical inflammation.³² Alternatively, genetic predisposition to a heightened inflammatory response that may predispose to adverse outcomes of the metabolic syndrome, including cognitive impairment.

The strengths of our study include that we studied high-functioning elders who did not have dementia at baseline, thereby allowing us to prospectively investigate whether the metabolic syndrome influenced cognitive impair-

ment and decline. This high-functioning status most likely explains the lack of a difference on baseline cognitive scores among those with and without the metabolic syndrome. The 39% prevalence of the metabolic syndrome in the Health ABC cohort is similar to that observed in other studies of elderly individuals.^{33,34} Due to carefully assessed data on the participants, we were able to adjust statistically for a number of possible confounding variables. Finally, because our cohort was biracial, we were able to determine that the link between the metabolic syndrome and cognitive impairment was similar among blacks and whites.

Several limitations of our study may affect the interpretation of our results. Those individuals without follow-up cognitive testing were older and had lower baseline cognitive scores; exclusion of these individuals could lead to bias. However, we used random-effects models to reduce the bias that comes from having missing outcome values. While we used a standard measure of global cognitive function, the 3MS may be insensitive to subclinical cognitive impairment and thus, there may have been some individuals included in Health ABC at baseline who had some cognitive dysfunction. In addition, the physiology underlying the cognitive impairment was not assessed, so we do not know etiology of cognitive impairment and if the underlying pathophysiology is more consistent with vascular disease or AD or yet another cause. Finally, our cohort con-

sisted of elders who were relatively well-functioning at baseline and therefore we cannot generalize to community-dwelling elders who are initially more functionally impaired.

We found that high-functioning elders with the metabolic syndrome had an increased risk of developing cognitive impairment and that this remained after accounting for demographics, health habits, and comorbidities. This was primarily true for those elders with high serum markers of inflammation.

Future studies will need to address whether preventing the metabolic syndrome or lowering inflammation prevents cognitive impairment in elderly individuals.

Author Contributions: Dr Yaffe had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Yaffe, Tylavsky, Newman.
Acquisition of data: Simonsick, Harris, Tylavsky, Newman.

Analysis and interpretation of data: Yaffe, Kanaya, Lindquist, Simonsick, Shorr, Tylavsky.

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