Published in final edited form as:

Neurobiol Aging. 2008 January ; 29(1): 78–83. doi:10.1016/j.neurobiolaging.2006.09.010.

PPAR γ pro12Ala genotype and risk of cognitive decline in elders

K. Yaffe, MD^a, A.M. Kanaya, MD^a, K. Lindquist, MS^a, W.C. Hsueh, PhD, MPH^a, S.R. Cummings, MD^b, B. Beamer, MD^c, A. Newman, MD, MPH^d, C. Rosano, MD, MPH^d, R. Li, MD, PhD, MPH^e, T. Harris, MD^f, and for the Health ABC Study

^a Department of Psychiatry and Neurology (Dr Yaffe), Epidemiology (Drs Yaffe and Kanaya), Geriatrics (Ms Lindquist), Medicine (Drs Kanaya and Hsueh), University of California, San Francisco; San Francisco VA Medical Center (Dr. Yaffe), San Francisco, CA

^b California Pacific Medical Center, San Francisco, CA;

^c Department of Medicine, Johns Hopkins University, Baltimore, MD

^d Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA

^e Center for Genomics and Bioinformatics, Department of Preventive Medicine, University of Tennessee Health Science Center, Memphis, TN

^f Laboratory of Epidemiology, Demography, and Biometry, National Institute on Aging, Bethesda, MD

Abstract

Background— The Pro12Ala polymorphism of peroxisome proliferator-activated receptor- γ (PPAR- γ) has been associated with decreased risk of diabetes and obesity, both disorders linked to cognitive impairment. We tested whether this polymorphism is associated with cognition.

Methods— 2,961 participants (mean age, 74.1; 41% black; 52% women) were administered the Modified Mini-Mental State Examination (3MS) and Digit Symbol Substitution Test (DSST) at baseline and 4 year follow-up. Test scores were adjusted for age, sex, education, cerebrovascular disease, *depression* and APOE genotype and additionally for race. We determined the association between Ala allele and development of cognitive *decline* (3MS decline of ≥ 5 points).

Results— At baseline, unadjusted scores on both cognitive tests were higher for Ala carriers compared to non-carriers (3MS, 94.2 vs 92.5, $p < 0.001$; DSST, 40.2 vs 34.5, $p < 0.001$). Similarly, follow-up scores were higher for Ala carriers. *Multivariable* adjustment led to similar results; additional adjustment for race attenuated the baseline 3MS results. After 4 years, 17.5% of Ala carriers developed cognitive *decline* compared to 25% among non-carriers (unadjusted OR=0.61 95% CI 0.46–0.82; adjusted OR=0.75 95% CI 0.55–1.02). Further adjustment for metabolic variables including fasting blood glucose and lipid level did not change the results.

Conclusions— The PPAR- γ Ala12 allele carriers may have less risk of developing cognitive *decline*.

Corresponding Author/Author for Reprints: Kristine Yaffe, MD, c/o University of California, San Francisco, Box 181, 4150 Clement Street, San Francisco, CA 94121, Phone: +01 (415) 221-4810, FAX: +01 (415) 750-6641, E-mail: Kristine.yaffe@ucsf.edu.

Financial Disclosure: There are no conflicts of interest for any of the authors.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

cognitive function; PPAR- γ ; cognitive impairment; dementia; metabolism

1. Introduction

The peroxisome proliferator-activated receptor-gamma (PPAR- γ) is a critical transcription factor in the development and function of adipose tissue. PPAR- γ plays an important role in several age-associated changes in body composition and metabolism, including obesity, insulin resistance and type 2 diabetes. It is well recognized as the molecular target of the thiazolidinediones class of insulin-sensitizing class [18]. The Pro12Ala PPAR- γ 2 variant was first identified in 1997 and is relatively common in White populations [29]. The Ala allele has been associated with higher body mass index [19] but also a reduced risk of type 2 diabetes [1,24].

PPAR- γ is also expressed in the central nervous system in microglial cells and monocytes [4]. PPAR- γ activation has been shown to inhibit microglial mediated neurotoxicity and cytokine expression in both *in vitro* [7] and *in vivo* [13] experiments. A recent trial that tested the effects of PPAR- γ agonists on patients with early Alzheimer disease (AD) and mild cognitive impairment (MCI) yielded favorable short-term results [26]. No studies to date have determined whether common polymorphisms of PPAR- γ are associated with cognitive function. However, obesity, *insulin resistance*, and diabetes are increasingly recognized as important risk factors for dementia and cognitive decline [8,12,19,27,28,11].

We examined the relationship between Ala allele carrier status in the Pro12Ala polymorphism of PPAR- γ with performance on two tests of cognitive function at baseline and after approximately 4 years of follow-up in a large biracial cohort of older adults. Since the Ala allele has been associated with decreased risk of diabetes in several populations [1], we hypothesized *a priori* that the Ala allele would be associated with better cognitive test performance and less cognitive decline over time. Moreover, we postulated that an association between PPAR- γ polymorphisms and cognitive function might be mediated by metabolic variables including obesity, diabetes, and dyslipidemia.

2. Methods

2.1. Study population

Participants enrolled in the Health, Aging, and Body Composition study (Health ABC) were well-functioning men and women between the ages of 70 and 79 years who were recruited from April 1997 to June 1998 from a random sample of Medicare beneficiaries residing in the areas surrounding Pittsburgh, Pennsylvania and Memphis, Tennessee. To be eligible for inclusion in the study, participants had to report no difficulty in walking ¼ mile, climbing 10 steps, or performing basic activities of daily living. Individuals requiring assistive devices for ambulation, subjects with difficulty performing activities of daily living or life-threatening cancers, and those planning to leave the area within 3 years were excluded from the study.

We first performed a cross-sectional study using the baseline medical history, physical exam measurements, laboratory tests, and cognitive function tests gathered in 1997–1998. We then performed a prospective analysis for change in cognitive function with a mean length of follow-up of 3.7 ± 0.9 years. Of the 3,075 participants enrolled in Health ABC, we excluded 100 who were missing PPAR γ genotype information and another 14 who did not have cognitive testing at the baseline examination. Thus, our analytic sample included 2,961 participants.

The study was approved by the institutional review boards of the University of California, San Francisco, University of Pittsburgh, and University of Tennessee. All of the study participants provided written informed consent to participate in the study.

2.2. Measurements

PPAR- γ genotype—From genomic DNA, the Pro12Ala PPAR- γ 2 variant was detected by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis as previously described [2,29]. Briefly, genomic DNA was subjected to PCR using upstream primer 5' GCCAATTCAAGCCCAGTC-3' and mutagenic downstream primer 5'-GATATGTTTGCAGACAGTGTATCAGTGAAGGAATCGCTTTCCG-3' using standard reagents and cycling conditions to yield a 270 base pair product. If the C→G substitution at nucleotide 34 of the PPAR γ gene was present, the mutagenic downstream primer introduced a BstU-I restriction site (CG||CG). Digestion with BstU-I was performed, followed by electrophoresis on a 2.5% agarose gel, staining with ethidium bromide, and visualization by UV transillumination.

2.3. Cognitive function tests

The Modified Mini-Mental State Examination (3MS) was administered to all participants during the baseline visit and repeated at the third and fifth annual follow-up examinations. This test is a brief general cognitive battery with components for orientation, concentration, language, praxis, and immediate and delayed memory with a maximum score of 100 [25]. The 3MS test is more sensitive than the 30-point Mini-Mental State Examination, especially for mild cognitive change [25]. We examined the change in 3MS score from the baseline examination to the 4-year follow-up, and clinically significant cognitive *decline* was defined as a 3MS decline of 5 or more points over time as has been previously recommended [17].

The Digit Symbol Substitution Test (DSST) measures attention, psychomotor speed, and executive function. The DSST score was calculated as the total number of test items correctly coded in 90 seconds, with a higher score indicating better cognitive function [3]. The DSST was administered at baseline and at Year 5.

2.4. Covariates and explanatory factors

Racial group, age, sex, and education were assessed by self-report during the baseline interview. Participants reported smoking history as never, former or current smoker. Each participant had seated systolic and diastolic blood pressures measured by a manual sphygmomanometer. Hypertension was defined by self-report of a diagnosis, use of an anti-hypertensive medication, or if systolic blood pressure ≥ 140 mmHg or if diastolic blood pressure ≥ 90 mmHg. Diabetes was defined by self-report of diabetes diagnosis, use of diabetes drug or if fasting plasma glucose ≥ 126 mg/dl or 2-hour post-challenge glucose ≥ 200 mg/dl. Cerebrovascular disease was defined as history of stroke, transient ischemic attack or carotid endarterectomy. Coronary heart disease (CHD) was defined by self-reported health history or hospitalizations for prior coronary artery bypass surgery or percutaneous coronary transluminal angioplasty, prior myocardial infarction or angina with use of an anti-anginal medication. We also used definite ECG evidence of previous MI with a major Q-wave abnormality to classify participants with CHD at baseline. Depressive symptoms were measured using the Center for Epidemiologic Study Depression Scale (CES-D), with a higher score indicating presence of more depressive symptoms [23].

Weight and height were measured and body mass index (BMI) was calculated as body weight in kg divided by height in meters squared. Waist circumference was measured with a flexible tape measure at the site of maximum circumference midway between the lower ribs and the anterior superior iliac spine.

Participants had venipuncture performed at the baseline visit after an overnight fast. Serum samples were frozen at -70°C and stored at McKesson BioServices, Rockville, MD. Fasting lipoprotein levels, fasting and 2-hour post-challenge plasma glucose were measured. Apolipoprotein (APOE) genotype was assessed using standard methods and coded as $\epsilon 4$ carrier or noncarrier [14].

2.5. Statistical analyses

We calculated the allele frequency of the Pro12Ala PPAR- $\gamma 2$ variant overall and by racial subgroup and Hardy-Weinberg equilibrium was checked using exact tests. Since there were few participants who were homozygous for the Ala12Ala genotype, we combined the heterozygous Pro12Ala with the homozygous Ala12Ala groups to characterize the Ala carrier subgroup. We used χ^2 and t-tests to examine whether baseline characteristics were associated with Ala carrier status.

Baseline and Year 5 cognitive test results were transformed using $\log_2(101\text{-score})$ to *reduce the skewness of the distribution. Data were back transformed using the inverse of the original transformation.* We calculated the mean and standard deviation for each cognitive test at baseline, the fourth annual follow-up examination and the 4-year change in score by Ala carrier status. We used *multivariable* linear regression models adjusting for potential confounders including age, sex, race, education, cerebrovascular disease, *depression* and APOE ($\epsilon 4$ carrier or not) genotype. *No covariate was missing more than 5% of data.* We used *multivariable* logistic regression to estimate the odds of cognitive *decline* on the 3MS. We sequentially adjusted our models to include potential confounders including age, sex, education, cerebrovascular disease, *depression* and race. Next we added potential variables that may lie in the causal pathway between Ala carrier status and cognitive *decline* including BMI, waist circumference, hypertension, diabetes, fasting glucose, and lipoproteins.

We checked whether sex or race modified the association between Ala carrier status and baseline or change in cognition by including an interaction term to the models. Statistical analyses were performed using SAS (version 9.1, SAS Institute, Cary, NC).

3. Results

Of the 2,961 participants included in our analysis, 1,216 (41%) were Black and 1524 (52%) were women. The distribution of PPAR γ genotype varied significantly by race (Table 1). White elders were much more likely to be an Ala carrier compared to Black elders (21.1% vs. 4.6%). The Ala allele frequency in Whites was 0.11 and was in Hardy-Weinberg equilibrium ($p=0.19$) whereas the allele frequency was 0.02 in Blacks and was not in Hardy-Weinberg equilibrium ($p=0.03$).

Baseline demographic, physical examination, and medical history did not vary among Black elders with and without the Ala allele. (Table 2) Among Whites, Ala carrier status was associated with higher BMI, waist circumference, fasting glucose levels, increased prevalence of APOE $\epsilon 4$ and cerebrovascular disease.

Because there were no statistically significant interactions between Ala allele, race or gender and cognitive function, we combined all participants and included race and gender as covariates in *multivariable* analyses. Participants with the Ala allele had significantly higher baseline scores ($\pm$ sd) on both the 3MS (94.2 ± 5.2 vs 92.5 ± 6.7 , $p<0.001$) and the DSST (40.2 ± 13.0 vs 34.5 ± 14.9 , $p<0.001$) compared to those without Ala (Table 3). This difference remained statistically significant ($p<0.001$ for both tests) after adjusting for age, sex, education, cerebrovascular disease, *depression* and APOE $\epsilon 4$. However, further adjustment for race attenuated the difference in scores ($\pm$ se) for baseline 3MS between groups (93.1 ± 0.3 vs 92.8

± 0.1 , $p=0.36$) but the adjusted mean baseline DSST score remained significantly higher for those with the Ala allele (36.9 ± 0.3 vs 35.1 ± 0.1 , $p=0.007$).

Follow-up scores were also higher for carriers of the Ala allele on both cognitive tests in unadjusted models ($p<0.001$ for both) and after *multivariable* adjustment for age, sex, education, cerebrovascular disease, *depression* and APOE $\epsilon 4$ ($p<0.001$ for both) (Table 3). After additional adjustment for race, both the 3MS (93.3 ± 0.3 vs 92.7 ± 0.1 , $p=0.08$) and DSST (35.0 ± 0.6 vs 33.4 ± 0.2 , $p=0.02$) follow-up scores were higher among Ala allele carriers compared to noncarriers. The 4-year change in score ($\pm sd$ for *unadjusted* and $\pm se$ for *adjusted models*) on DSST was not significantly different across groups in the unadjusted or adjusted analyses (*unadjusted scores* -3.2 ± 9.2 vs -2.5 ± 9.9 , $p=0.25$; *adjusted scores* -2.6 ± 0.6 vs -2.5 ± 0.2 , $p=0.52$); however, the 4-year change in 3MS was less in the Ala carriers compared to non carriers (*unadjusted scores* -0.1 ± 5.3 vs. -1.0 ± 6.5 , $p=0.01$; *adjusted scores* -0.2 ± 0.3 vs -1.0 ± 0.1 , $p=0.022$).

Of the participants without the Ala allele, 554 (25.7%) developed cognitive *decline* compared to 65 (17.5%) of those with the Ala allele ($p=0.001$; OR 0.61; 95% CI 0.46–0.82). (Figure) After adjusting for potential confounders, especially race, the difference was attenuated slightly (OR 0.75; 95% CI 0.55 – 1.03). Further adjustment for variables that potentially lay in the causal pathway between Ala carrier status and cognitive *decline* such as BMI, waist circumference, hypertension, fasting glucose, and lipoproteins did not materially affect this result. (Figure) *16 participants were taking a cholinesterase inhibitor (ChI) at some time during the 5 year study and most of these met criteria for cognitive decline; ChI use did not differ by Ala carrier status.*

Non-Ala carriers were more likely than Ala carriers to be missing 5-year follow-up on the 3MS (17.7% vs. 13.9%) and on the DSST (25.2% vs. 20.3%). This association was of borderline significance for 3MS ($p=0.054$) and was significant for DSST ($p=0.029$). *For both Ala carriers and non-carriers, those with missing data had lower baseline cognitive scores ($p<0.05$ for both tests).* When we restricted our analysis to those with follow-up data, the baseline unadjusted and adjusted means for both cognitive tests were similar to those shown in Table 3.

4. Discussion

In this biracial cohort of elders, we found that the PPAR- γ Ala allele was associated with cognitive function on both of the tests we studied. Those with the Ala allele were less likely to develop clinically significant cognitive *decline* over time compared to non carriers. Parallel to this finding, participants with an Ala allele had better performance on cognitive function at baseline and during follow-up. This difference in cognitive test scores remained after adjustment for possible confounders including age, sex, education, cerebrovascular disease, *depression* and APOE $\epsilon 4$ allele. Further adjustment for race attenuated the association for 3MS; however, Ala carrier status was still independently associated with better performance on the DSST at both the baseline and follow-up examination. In addition the results were not diminished after controlling for other metabolic variables that may lie in the causal pathway such as fasting blood glucose and lipid level. To our knowledge, this is the first study that has examined a relationship between PPAR- γ genotype and cognitive function.

In our study, Whites had a higher Ala allele frequency than Blacks for the Ala polymorphism. Prior studies have found consistent results with an Ala allele frequency between 0.08–0.17 in White populations [2,6,9] and 0.01–0.03 in African Americans [11,15]. In our cohort, among Blacks, the allele frequencies were not in Hardy-Weinberg equilibrium. Since the Black American population is a mixture of African, European, and Native American ancestry [22], it is reasonable to expect that this may account for deviations from Hardy-Weinberg

equilibrium. This may also explain our finding that only among Whites, was the Ala allele associated with higher BMI, waist circumference, fasting glucose levels, all previously shown to be associated with the allele.

Potential mechanisms by which the Ala carrier status may impact cognition include a protective effect of this polymorphism on glucose and *insulin metabolism* in the central nervous system. The Ala allele has been associated with decreased risk of type 2 diabetes in several populations [1], and type 2 diabetes, *as well as insulin resistance*, has been linked with cognitive dysfunction and AD [5,8,12,19,28]. Studies of PPAR- γ agonists, thiazolidenediones, have found anti-inflammatory and neuroprotective effects [16,20]. A recent short-term trial also found better cognitive function and unchanged levels of beta-amyloid protein in subjects with mild AD or MCI randomized to rosiglitazone [26], which provides more definitive data linking PPAR- γ with cognition.

Another potential mechanism by which the Ala allele can affect cognition may be through effects on obesity. Recently, obesity has been reported to be linked with the development of dementia independently of other comorbid conditions [27]. The Ala allele has also been linked to obesity, but results have been mixed with differential effects of Ala on insulin action depending on the level of adiposity [2,10,15]. However, when we adjusted for two measures of obesity, BMI and waist circumference, and for fasting glucose and diabetes in our model examining cognitive decline, we found that these metabolic parameters did not change the association between Ala allele and risk of developing cognitive impairment. *However, we cannot fully adjust for the possible dynamic relationship between weight and cognition given the limitation of our measures.*

While this is the first study to examine the cross-sectional and prospective association between PPAR- γ Pro12Ala genotype and cognitive function in a large population-based study, we are limited in interpretation of our findings due to the types of tests of cognition that were assessed. The 3MS is a validated general test of cognition and the DSST is a test for executive function and attention, but both tests do not specifically test for memory. Participants in our cohort also did not undergo a clinical evaluation to determine whether the cognitive *decline* was due to vascular disease or AD. We also had some participants without follow-up cognitive testing which may have limited our ability to evaluate prospective associations with change in cognitive function tests. In addition, there was a differential loss to cognitive follow-up across the PPAR- γ genotype. This may have introduced a bias into our results and may explain the limited differences in 4-year change in cognitive scores, especially on the DSST, despite cross-sectional differences in cognitive test scores.

In conclusion, carriers of the PPAR- γ Ala allele have better performance on two tests of cognitive function and less risk of developing cognitive *decline* over time. However, controlling for race attenuated these results. Future studies should confirm these findings and explore the mechanisms that may explain the association between PPAR- γ and cognition.

Acknowledgements

Supported by NIA NO1-AG-6-2101, NO1-AG-6-2103, and NO1-AG-6-2106 and in part by the Intramural Research Program of the NIH, National Institute on Aging. Dr. Yaffe is supported in part by an anonymous foundation, NIA AG021918-03 and NIDDK DK070713.

References

1. Altshuler D, Hirschhorn JN, Klannemark M, Lindgren CM, Vohl MC, Nemesh J, Lane CR, Schaffner SF, Bolk S, Brewer C, Tuomi T, Gaudet D, Hudson TJ, Daly M, Groop L, Lander ES. The common

- PPARgamma Pro12Ala polymorphism is associated with decreased risk of type 2 diabetes. *Nat Genet* 2000;26(1):76–80. [PubMed: 10973253]
2. Beamer BA, Yen CJ, Andersen RE, Muller D, Elahi D, Cheskin LJ, Andres R, Roth J, Shuldiner AR. Association of the Pro12Ala variant in the peroxisome proliferator-activated receptor-gamma2 gene with obesity in two Caucasian populations. *Diabetes* 1998;47(11):1806–1808. [PubMed: 9792554]
 3. Beres CA, Baron A. Improved digit symbol substitution by older women as a result of extended practice. *J Gerontol* 1981;36(5):591–597. [PubMed: 7264244]
 4. Bernardo A, Levi G, Minghetti L. Role of the peroxisome proliferator-activated receptor-gamma (PPAR-gamma) and its natural ligand 15-deoxy-Delta12, 14-prostaglandin J2 in the regulation of microglial functions. *Eur J Neurosci* 2000;12(7):2215–2223. [PubMed: 10947800]
 5. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. *Lancet Neurol* 2006;5(1):64–74. [PubMed: 16361024]
 6. Clement K, Hercberg S, Passenge B, Galan P, Varroud-Vial M, Shuldiner AR, Beamer BA, Charpentier G, Guy-Grand B, Froguel P, Vaisse C. The Pro115Gln and Pro12Ala PPAR gamma gene mutations in obesity and type 2 diabetes. *Int J Obes Relat Metab Disord* 2000;24(3):391–393. [PubMed: 10757637]
 7. Combs CK, Johnson DE, Karlo JC, Cannady SB, Landreth GE. Inflammatory mechanisms in Alzheimer's disease: inhibition of beta-amyloid-stimulated proinflammatory responses and neurotoxicity by PPARgamma agonists. *J Neurosci* 2000;20(2):558–567. [PubMed: 10632585]
 8. Craft S, Watson GS. Insulin and neurodegenerative disease: shared and specific mechanisms. *Lancet Neurol* 2004 Mar;3(3):169–78. [PubMed: 14980532]
 9. Deeb SS, Fajas L, Nemoto M, Pihlajamaki J, Mykkanen L, Kuusisto J, Laakso M, Fujimoto W, Auwerx J. A Pro12Ala substitution in PPARgamma2 associated with decreased receptor activity, lower body mass index and improved insulin sensitivity. *Nat Genet* 1998;20(3):284–287. [PubMed: 9806549]
 10. Ek J, Urhammer SA, Sorensen TI, Andersen T, Auwerx J, Pedersen O. Homozygosity of the Pro12Ala variant of the peroxisome proliferation-activated receptor-gamma2 (PPAR-gamma2): divergent modulating effects on body mass index in obese and lean Caucasian men. *Diabetologia* 1999;42(7):892–895. [PubMed: 10440134]
 11. Fornage M, Jacobs DR, Steffes MW, Gross MD, Bray MS, Schreiner PJ. Inverse effects of the PPAR (gamma)2 Pro12Ala polymorphism on measures of adiposity over 15 years in African Americans and whites. *The CARDIA study Metabolism* 2005;54(7):910–917.
 12. Grodstein F, Chen J, Wilson RS, Manson JE. Type 2 diabetes and cognitive function in community-dwelling elderly women. *Diabetes Care* 2001;24(6):1060–1065. [PubMed: 11375371]
 13. Heneka MT, Klockgether T, Feinstein DL. Peroxisome proliferator-activated receptor-gamma ligands reduce neuronal inducible nitric oxide synthase expression and cell death in vivo. *J Neurosci* 2000;20(18):6862–6867. [PubMed: 10995830]
 14. Hixson JE, Vernier DT. Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. *J Lipid Res* 1990;31(3):545–548. [PubMed: 2341813]
 15. Kao WH, Coresh J, Shuldiner AR, Boerwinkle E, Bray MS, Brancati FL. Pro12Ala of the peroxisome proliferator-activated receptor-gamma2 gene is associated with lower serum insulin levels in nonobese African Americans: the Atherosclerosis Risk in Communities Study. *Diabetes* 2003;52(6):1568–1572. [PubMed: 12765972]
 16. Kielian T, Drew PD. Effects of peroxisome proliferator-activated receptor-gamma agonists on central nervous system inflammation. *J Neurosci Res* 2003;71(3):315–325. [PubMed: 12526021]
 17. Kuller LH, Lopez OL, Newman A, Beauchamp NJ, Burke G, Dulberg C, Fitzpatrick A, Fried L, Haan MN. Risk factors for dementia in the cardiovascular health cognition study. *Neuroepidemiology* 2003;22(1):13–22. [PubMed: 12566949]
 18. Lehmann JM, Moore LB, Smith-Oliver TA, Wilkison WO, Willson TM, Kliewer SA. An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPAR gamma). *J Biol Chem* 1995;270(22):12953–12956. [PubMed: 7768881]
 19. Luchsinger JA, Tang MX, Shea S, Mayeux R. Hyperinsulinemia and risk of Alzheimer disease. *Neurology* 2004 Oct 12;63(7):1187–92. [PubMed: 15477536]
 20. Luna-Medina R, Cortes-Canteli M, Alonso M, Santos A, Martinez A, Perez-Castillo A. Regulation of inflammatory response in neural cells in vitro by thiazolidinones derivatives through

- peroxisome proliferator-activated receptor gamma activation. *J Biol Chem* 2005;280(22):21453–21462. [PubMed: 15817469]
21. Masud S, Ye S. Effect of the peroxisome proliferator activated receptor-gamma gene Pro12Ala variant on body mass index: a meta-analysis. *J Med Genet* 2003;40(10):773–780. [PubMed: 14569127]
 22. McKeigue PM, Carpenter JR, Parra EJ, Shriver MD. Estimation of admixture and detection of linkage in admixed populations by a Bayesian approach: application to African-American populations. *Ann Hum Genet* 2000;64(Pt 2):171–86. [PubMed: 11246470]
 23. Radloff LS. The CES-D scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement* 1977;1:385–401.
 24. Stumvoll M, Haring H. The peroxisome proliferator-activated receptor-gamma2 Pro12Ala polymorphism. *Diabetes* 2002;51(8):2341–2347. [PubMed: 12145143]
 25. Teng EL, Chui HC. The Modified Mini-Mental State (3MS) examination. *J Clin Psychiatry* 1987;48(8):314–318. [PubMed: 3611032]
 26. Watson GS, Cholerton BA, Reger MA, Baker LD, Plymate SR, Asthana S, Fishel MA, Kulstad JJ, Green PS, Cook DG, Kahn SE, Keeling ML, Craft S. Preserved cognition in patients with early Alzheimer disease and amnesic mild cognitive impairment during treatment with rosiglitazone: a preliminary study. *Am J Geriatr Psychiatry* 2005;13(11):950–958. [PubMed: 16286438]
 27. Whitmer RA, Gunderson EP, Barrett-Connor E, Quesenberry CP Jr, Yaffe K. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. *Bmj* 2005;330(7504):1360. [PubMed: 15863436]
 28. Yaffe K, Blackwell T, Kanaya AM, Davidowitz N, Barrett-Connor E, Krueger K. Diabetes, impaired fasting glucose, and development of cognitive impairment in older women. *Neurology* 2004;63(4):658–663. [PubMed: 15326238]
 29. Yen CJ, Beamer BA, Negri C, Silver K, Brown KA, Yarnall DP, Burns DK, Roth J, Shuldiner AR. Molecular scanning of the human peroxisome proliferator activated receptor gamma (hPPAR gamma) gene in diabetic Caucasians: identification of a Pro12Ala PPAR gamma 2 missense mutation. *Biochem Biophys Res Commun* 1997;241(2):270–274. [PubMed: 9425261]

Figure. Likelihood of developing cognitive *decline* (odds ratio and 95% confidence interval) according to PPAR- γ Ala carrier status (reference group is non carrier) in unadjusted and adjusted models.

Table 1

Distribution of genotypes for the Health ABC participants by race

Subgroup	Pro12Pro n (%)	Pro12Ala n (%)	Ala12Ala n (%)	<i>p</i> [*]
Blacks (n=1216)	1160 (95.4)	53 (4.4)	3 (0.3)	<0.001
Whites (n=1745)	1377 (78.9)	340 (19.5)	28 (1.6)	

* p-value by χ^2 test

Table 2

Baseline characteristics (*mean (sd) or N (%)*) of the 2961 Health ABC participants by race and PPAR γ genotype (Ala carrier vs non carrier).

	Blacks		<i>p</i> [*]	Whites		<i>p</i> [*]
	Non carrier n=1160	Ala carrier n=56		Non carrier n=1377	Ala carrier n=368	
Age, years	73.5 (2.9)	73.2 (2.7)	0.44	73.7 (2.8)	73.8 (2.9)	0.81
Female sex (%)	661 (57.0)	33 (58.9)	0.77	669 (48.6)	161 (43.8)	0.05
Education <high school (%)	501 (43.3)	17 (30.3)	0.05	157 (11.4)	54 (14.7)	0.08
Current smoker (%)	190 (16.4)	7 (12.5)	0.44	84 (6.1)	25 (6.8)	0.63
BMI, kg/m ²	28.7 (5.5)	27.8 (4.6)	0.23	26.5 (4.1)	26.9 (4.2)	0.05
Waist circumference, cm	100.6 (13.6)	98.1 (12.1)	0.18	98.6 (11.8)	100.2 (11.8)	0.02
Hypertension (%)	855 (73.7)	35 (62.5)	0.06	770 (55.9)	210 (57.1)	0.69
Diabetes (%)	337 (30.4)	19 (35.9)	0.40	259 (19.3)	76 (20.8)	0.54
Cerebrovascular disease (%)	99 (8.7)	5 (9.1)	0.81	88 (6.4)	44 (12.1)	<0.001
Coronary heart disease (%)	256 (22.7)	12 (21.8)	0.87	299 (21.9)	70 (19.3)	0.29
Depression score	4.2 (3.6)	4.3 (4.1)	0.87	4.1 (3.6)	3.9 (3.4)	0.30
Fasting glucose, mg/dl	104.3 (29.5)	104.7 (24.4)	0.91	97.9 (20.9)	100.7 (23.6)	0.04
HDL-cholesterol, mg/dl	54.7 (15.8)	56.8 (17.0)	0.35	49.6 (14.9)	49.5 (14.9)	0.89
Triglycerides, mg/dl	107.3 (45.2)	102.1 (33.5)	0.26	134.6 (65.0)	135.2 (66.5)	0.87
APOE ϵ 4 carrier (%)	415 (36.6)	15 (27.8)	0.19	300 (22.3)	102 (28.6)	0.01

* p-value by χ^2 or Fisher's exact test for categorical variables and t-tests for continuous variables

Table 3
3MS and DSST scores at baseline and Year 5 by PPAR γ genotype

	Pro12Pro	Unadjusted Mean (SD) Ala Carrier	$P^{\dagger}$	Pro12Pro	Adjusted* Mean (SE) Ala Carrier	$P^{\dagger}$
3MS score: Baseline	92.5 (6.7)	94.2 (5.2)	<0.001	92.6 (0.1)	93.9 (0.3)	<0.001
Year 5	92.6 (7.3)	94.6 (5.1)	<0.001	92.6 (0.1)	94.2 (0.3)	<0.001
DSST score: Baseline	34.5 (14.9)	40.2 (13.0)	<0.001	34.7 (0.3)	39.3 (0.6)	<0.001
Year 5	33.7 (14.7)	38.2 (12.9)	<0.001	33.3 (0.3)	37.3 (0.7)	<0.001

* Adjusted for age, sex, education, cerebrovascular disease, depression and APOE ϵ 4.

† P-value from t-test for unadjusted means and *multivariable* regression for adjusted means