Long-term dysglycemia as a risk factor for faster cognitive decline during aging: a 12-year follow-up study

Sanna Papunen, MD[1,6], Juha Auvinen, MD, PhD[1,2], Aini Bloigu, BSc[1], Pirjo Härkönen, PhD[1], Jari Jokelainen, MSc [3,4], Markku Timonen, MD, PhD[1,4], Sirkka Keinänen-Kiukaanniemi, MD, PhD[1,4,5]

Authors affiliations

[1]Centre for Life Course Health Research, Faculty of Medicine, University of Oulu, Finland

[2]Medical Research Center Oulu, Oulu University Hospital, Oulu, Finland

[3] Infrastructure for Population Studies, Faculty of Medicine, University of Oulu, Finland

[4]Unit of Primary Care, Oulu University Hospital and Medical Research Center Oulu, Oulu, Finland

[5]Healthcare and Social Services of Selänne, Pyhäjärvi, Finland

[6]Oulunkaari Health Center, Ii, Finland

Corresponding author

Sanna Papunen, Centre for Life Course Health Research, Faculty of Medicine,

P.O. Box 5000, FI-90014 University of Oulu, Finland

Email: sanna.papunen@oulu.fi

Abstract

Aims

This longitudinal study evaluated associations between glucose metabolism and cognitive performance during a 12-year follow-up.

Methods

We included 714 subjects, which were followed from the age 55 to 70 years. Using oral glucose tolerance tests the population was classified as normoglycemic (NGT) and based on WHO diagnostic criteria for diabetes and prediabetes. Cognitive performance was assessed with a verbal fluency (category) test and wordlist learning tests of CERAD-nb, a verbal fluency (letter) test, and trail-making tests A and B.

Results

Compared to the normal group subjects with long-lasting prediabetes showed significantly greater decline (4.6 versus 2.9 words) on the verbal fluency (category) test ($p = 0.041$); subjects with long-lasting type 2 diabetes showed significantly greater decline (13 versus 6 s) on the trail making A test ($p=0.021$) and on the wordlist learning test (3.3 versus 1.7 words) ($p = 0.013$); and a combined group of subjects with prediabetes or incident type 2 diabetes showed significantly greater cognitive decline (3.8 versus 2.9 words) in the verbal fluency (category) test ($p = 0.039$).

Conclusion

Prediabetes was associated with cognitive decline during aging. This finding should be incorporated into prevention strategies, because both type 2 diabetes and dementia are increasing world-wide.

Keywords cognition, cognitive decline, cohort, glucose tolerance

1. Introduction

Type 2 diabetes has convincingly proven to be associated with accelerated cognitive decline and is a risk factor for dementia (1)(2)(3). Cross-sectional studies (4) (5) and previous systematic reviews (6) (7) have shown that also prediabetes (i.e., impaired fasting glucose [IFG], impaired glucose tolerance [IGT], or both) and elevated glycated haemoglobin (HbA1c) -levels were associated with impaired cognitive function. However, less is known about the longitudinal association between prediabetes and cognitive changes during aging. Our systematic review (6), of longitudinal population based studies in age groups over 65 years showed conflicting results on the association. We found that only four of the 13 articles reported results focusing on prediabetes and cognitive decline. Three of these studies reported positive association (8) (9) (10)and one (11) reported no detrimental effect on cognition. In Rouch et al`s (8) study prediabetes was reported to be linked to a decline in one of the tests they used, and Marseglia et al (9) reported an independent association with accelerated cognitive decline measured by MMSE. Xu et al `s (10)study showed that prediabetes accelerated the progression from mild cognitive impairment to dementia. These studies defined prediabetes according to fasting or random blood glucose level, or by using Hba1c measurement. In none of them oral glucose tolerance test was used as a marker of prediabetes. The discrepancies between the results of those studies might have been due to variations in study design, in follow-up times and in measures of different domains of cognitive function. Follow-up times in these studies varied from 6.4 to 9 years and the age of participants from > 60 to >75 years. Moreover, only two studies used several cognitive tests in assessment of cognition (8) (11) , and two studies (9) (10)used only the Mini-mental State Examination (MMSE) as measure of cognitive function. . The studies of our review evaluated cognitive decline in dementia free populations, targeting to find out if normal cognitive decline during aging is accelerated by diabetes or prediabetes.

The present study aimed to evaluate longitudinal associations between glucose metabolism and cognitive function and population based Oulu 45 cohort study in which time period spanned 12 years. Oral glucose tolerance tests (OGTTs) and five different cognitive tests, both at baseline and at the end of follow-up. Our hypothesis was that early onset of diabetes and prediabetes might accelerate cognitive decline during aging.

2. Materials and Methods

2.1 Study Population

Our study cohort, called the Oulu 45 cohort, is a prospective population-based health survey of an aging population including all individuals born in 1945 and residing in the city of Oulu, in northern Finland, on 31 December 2001. The study aimed to find factors for maintaining individual health, well-being, and functional abilities. At baseline, 1332 individuals living in Oulu in 2001 were invited to the survey, and 993 participated. Twelve years later, 922 individuals were alive and invited to a follow-up survey, and 714 participated (77%). Finally, data were available on cognitive tests and OGTTs at both time points for 664 individuals (72%; Figure1.). The characteristics of the study population at baseline and at follow-up compared to characteristics of those who were lost during the follow-up are shown in Table 1.

The Oulu 45 cohort was followed from an initial average age of 56.8 (standard deviation [SD]: 0.5) years in 2001-2003 until the average age of 68.9 (SD: 0.5) years in 2013-2015. The average follow-up time was 12.1 years (SD: 0.5).

This follow-up study was approved by the Ethics Committee of the Northern Ostrobothnia Hospital District in Oulu, Finland (EETTMK 12/2013). It was performed in accordance with the Declaration of Helsinki. The participants were given oral and written information about the study, and all who participated provided written consent to use data for research, including consent to link the data to hospital registries. All data were analyzed only at the group level, and the personal identification codes were replaced with research id-numbers.

The data were collected by trained study nurses through interviews, structured questionnaires on health and well-being, and clinical measurements, both at baseline and at follow-up. Clinical measurements were performed on two separate days. The first examination day included the basic anthropometric measurements (weight, height, hip, and waist circumference), clinical measurements, and blood sampling, after an overnight fasting period. The second examination day included cognitive function and performance tests in a restful room, at noon and in the afternoon to standardize the testing conditions.

2.1.1 Sociodemographic characteristics, health behavior, and self-reported factors

Interviews and structured questionnaires were conducted to collect data on marital status, basic education, professional education, employment, smoking and alcohol use, subjective health and

well-being, life satisfaction, self-experienced physical condition, and physical activity. Marital status was divided into four categories: unmarried, married, widowed, and divorced. The level of education was used to measure the socioeconomic status of the study population. The educational level was classified according to professional education. Basic education was divided into three categories: primary school, middle school, and undergraduate. Professional education was divided into four categories: no education/courses, vocational school, college/polytechnic, and academy/university.

Tobacco smoking was categorized as a non-smoker, current smoker, or former smoker. Alcohol consumption was measured with standardized questions, and the weekly amount (g/d) of alcohol was calculated. Information was collected on the frequency of use and typical quantity per occasion for three different alcoholic beverages: mild drinks; wines; and spirits. The frequency of use was measured on a 10-point scale (1 = never to 10 = daily). Information was collected on the quantities consumed on a typical occasion for the three beverage types, as follows: the number of 0.33-L bottles of mild drinks; the number of glasses (=16 cL) or 0.75-L bottles of wine; and the number of 4-cL shots or 0.5-L bottles of spirits. The typical quantities were evaluated on a 9-point scale (1 = none to 9 = 15 bottles or more). One bottle of mild drink was assumed to contain one standard unit of alcohol (=12 g ethanol); wine was assumed to contain 13% alcohol; and spirits were assumed to contain 38% alcohol. Based on these stipulations, the consumption of alcohol was calculated in grams per day (g/d) for each beverage type by multiplying the frequency by the quantity. Then all the beverage types were summed to determine the total amount of alcohol consumed daily (12). Self-reported general health was categorized as: very good, good, or acceptable/weak. Life satisfaction was categorized as: very satisfied, satisfied, quite satisfied, or not satisfied. Self-reported physical condition was categorized as: very good, quite good, average, or poor. Physical activity was categorized according to the frequency of physical exercises performed on a monthly or weekly basis.

2.1.2 Clinical measurements

Depression status was classified with 21-Item Beck`s Depression Scale (BDI-21, 0-13 = normal, ≥14 = depression) (13). Seated systolic (SBP) and diastolic (DBP) blood pressure and heart rate were measured after at least five minutes rest twice with an automatic electronic blood pressure monitor (Omron M4, HEM-722C1-E) on their upper left arm, and the mean of the two measurements was used in the analyses. Subjects were classified according to whether they had been diagnosed with hypertension, and the mean blood pressure was calculated. Blood pressure was classified according to blood pressure measurements, and blood pressure changes were categorized

as follows (systolic/diastolic, in mmHg): >140/90 at both baseline and at follow-up; >140/90 at baseline and decreased during follow-up; <140/90 at baseline and increased during follow-up; or <140/90 at both baseline and at follow-up. Weight and height were measured with standard protocols and the body mass index (BMI, kg/m^2) was calculated..

2.2 Glucose metabolism and diabetes

All participants without a previous diagnosis of diabetes mellitus were invited to participate in a 2-h OGTT after a 10-h fasting period, at both baseline and follow-up. Blood samples were obtained in the fasting state, immediately before the intake of 75-g glucose, and then at 30, 60, and 120 min after the intake. The glucose tolerance status was classified according to WHO criteria for diabetes mellitus, as follows: diabetes = fasting plasma glucose level ≥7 mmol/L or 2-h plasma glucose level >11 mmol/L; impaired fasting glucose (IFG) = fasting plasma glucose level 6.1-6.9 mmol/L; impaired glucose tolerance (IGT) = 2-h plasma glucose level 7.8-11 mmol/L; and normal glucose tolerance (NGT) = fasting plasma glucose level ≤6.0 mmol/L and 2-h plasma glucose level <7.8 mmol/L. We classified the diabetes status mainly based on the OGTT, but when the 2-h value was missing, we used the fasting (0 h) value. Prediabetes was defined as IFG or IGT. Glucose values were determined from whole blood at baseline. However, glucose measures differ between whole blood and venous plasma samples; therefore, we applied a correction factor of 1.11 to convert baseline fasting blood glucose to plasma glucose values (14).

Participants were classified as: normal (normal blood glucose in both 2003 and 2015, N=264); new prediabetes (NewPre: normal blood glucose in 2003 and prediabetes in 2015, N= 204); ~~previous~~ stable prediabetes (~~Prev~~StabPre: prediabetes in both 2003 and 2015, N=47); new diabetes (NewDiab: normal blood glucose or prediabetes in 2003, and diabetes in 2015, N= 116); and ~~previous~~ stable diabetes (~~Prev~~StabDiab: diabetes in 2003, and in 2015, N= 33). In this context ~~previous~~ stable prediabetes or ~~previous~~ diabetes means that prediabetes or diabetes was diagnosed both at baseline and at the follow-up point.

2.3 Cognitive assessment

The cognitive tests applied at baseline were: the verbal fluency (category) test, and the wordlist learning test, created by the Consortium to Establish a Registry for Alzheimer's Disease (*CERAD*), neuropsychological battery (CERAD-nb). We also applied the verbal fluency (letter) test, and the trail making tests, parts A and B (TMA and TMB, respectively). At follow-up, the study population completed the entire CERAD test battery, the TMA and TMB, the MMSE, the modified Wechsler

Adult Intelligence Scale, 3rd edition, and the Stroop-test. The test battery applied at baseline was less extensive than that applied at follow-up, due to the young age and generally good health and well-being of the population at baseline. The assumption was that, at age 55 years, participants should not display any major deficits in cognitive performance. To assess changes in cognitive performance during the follow-up, we compared results from the tests that were performed at both baseline and follow-up.

In the verbal fluency (category) test, individuals were asked to list all the animals they could think of for one minute. The threshold value for a large decline was 7 animals. In the wordlist learning test, individuals had to memorize a list of 10 words, with three attempts. The threshold value for a large decline was 4 words. In the verbal fluency (letter) test, individuals were asked to list as many words as possible beginning with a certain letter for one minute. The threshold for a large decline was 9 words. The TMA consisted of 25 numbered circles distributed over a sheet of paper, and individuals were asked to draw lines to connect the numbers in ascending order. In the TMB, the circles included both numbers (1-13) and letters (A-L), and individuals were asked to connect the both the numbers and letters in ascending order, alternating between numbers and letters. The circles had to be connected as rapidly as possible, and the time to completion was measured. The thresholds for large declines were 14 s in the TMA test and 42 s in the TMB test. The wordlist tests (naming and learning) and recall tests measured different fields of memory function, and the trail making tests measured cognitive processing speed and executive functioning. The definition for "large decline" is explained in the statistical analysis.

2.4 Statistical analysis

Individuals who continued to follow-up and those who dropped out of the survey were compared with the chi-square test, for categorical variables, and the independent samples t-test or Mann-Whitney U-test, for continuous variables, as appropriate. Characteristics at baseline and follow-up were compared with paired analyses; i.e., the McNemar Bowker test, for categorical variables, and the paired-samples t-test or Wilcoxon signed ranks test for continuous variables, as appropriate. Unadjusted changes in test scores from baseline to follow-up were analyzed with paired-samples t-test. The main aim of our statistical analysis was to explore whether the changes in test scores between the beginning and end of follow-up were different between distinct glucose status groups. We implemented a General Linear Model, adjusted with covariates, for regressions between the

follow-up test score and the baseline test score. Education level, depression status (categories described above), alcohol consumption (grams/day), change in blood pressure (categories described above), LDL cholesterol, BMI (<25, 25-29.99 and ≥30 kg/m^2) and smoking status (non-smoker, ex-smoker, smoker) were considered for inclusion in the model. Inclusion in the final multivariable model was based on the clinical relevance and statistical significance of covariates. In addition to the baseline test score, the final multivariable model included the education level and the change in blood pressure as covariates. We included baseline test score as covariate to control for any baseline imbalance between groups and considered the regression to the mean (subjects with high scores generally have larger declines than subjects with low scores). Before the analyses, multicollinearity was tested with the variance inflation factor. We also dichotomized the changes in test scores, where the threshold was the third quartile of the test score change in the normal glucose status group. The proportion of cases with large declines in each test score was compared between groups with the chi -square test. All analyses were performed with IBM SPSS Statistics 24.0 (Armonk, NY: IBM Corp.). P-values <0.05 were considered statistically significant.

3. Results

At the baseline we had 993 participants, 438 (44.1 %) men and 555 (55.9%) women. The follow-up study included 714 participants who had participated both the baseline and follow-up data (Figure 1.). Data on diabetes status and cognitive test results were obtained for 664 individuals. The clinical characteristics of the study group are shown in Table 1. During the follow-up, 204 individuals developed prediabetes (NewPre), and 116 developed diabetes (NewDiab, self-reported or OGTT confirmed). Thus, the incidence of prediabetes was 31% and the incidence of diabetes was 18%. The incidence of diabetes was higher among men than among women (24 % versus 13 % respectively, $p < 0.0001$).

3.1 Change in diabetes status and cognitive function

During the follow-up period, cognitive function significantly declined in all glucose status groups of participants, based on all five cognitive tests; among Normal, ~~Prev~~StabPre, NewPre and NewDiab groups the significance of decline was $p < 0.0001$ in all the tests and among ~~Prev~~StabDiab group the significance of decline was = 0.004 in the verbal fluency (category) test, = 0.003 in TMB test and $p < 0.0001$ in the other tests.

The numerical declines in test scores - adjusted for the baseline test score, education level, and blood pressure - are shown in Figure 2. The test results showed significant numerical declines in the verbal fluency (category) test (p = 0.041) in the ~~Prev~~StabPre group (prediabetes during the entire 12-year follow-up), compared to the normal group.

Table 2. gives the information concerning the cognitive test results in each group at baseline and at follow-up and also the change in the test results during the follow-up. The ~~Prev~~StabDiab group showed a significantly greater decline in the TMA (p = 0.021) and in the word-list learning test (p = 0.013) compared to the normal group. The ~~Prev~~StabDiab group had larger proportions of participants that showed relatively significant declines on at least two cognitive tests (60.7%) and at least three cognitive tests (25.0%), compared to the normal group (35.2%, p=0.008 and 11.7%, p = 0.05, respectively).

After adjustments, we compared the normal group to the ~~Prev~~StabPre + NewPre + NewDiab groups . This combined group showed significant cognitive decline on the verbal fluency (category) test (p = 0.039) compared to the normal group. Moreover, the proportions of participants in the ~~Prev~~StabPre + NewPre + NewDiab group that showed relatively significant declines on at least one cognitive test (79.0%) and on at least two cognitive tests (43.0%) were larger than the corresponding proportions in the normal group (72.2%, p = 0.049 and 35.2%, p = 0.056, respectively).

3.2 Characteristics of those who were lost to follow-up

Table 3. shows that those who dropped out (N=279) showed worse clinical measurements and health and well-being indicators compared to those that continued the study (N=714). These groups were significantly different in all characteristics, except alcohol consumption, BDI-21 scale, HDL and LDL cholesterol and one cognitive test result (verbal fluency category).

4. Discussion

In the Oulu 45 population, we observed a significant difference in cognitive performance between individuals with prediabetes and individuals with normal blood glucose levels, based on the verbal fluency (category) test. In addition, we observed clear numerical declines in all cognitive test results

during the follow-up, which is a remarkable finding in this rather small cohort. Adjustments for alcohol consumption and depression status (BDI) did not affect the results. Moreover, the association remained significant after adjusting for hypertension, education, and baseline cognitive test results. The adjustment for baseline cognitive test results was made because we wanted to evaluate the change in test results apart from the baseline level of cognitive performance.

We also compared individuals with prediabetes at baseline that did not develop diabetes at the follow up to individuals with normal glucose tolerance. We found that prediabetes was associated with a marked decline in cognitive test results, and the numeral differences between these groups were clinically relevant (Figure 2).

Few previous studies have investigated the association between prediabetes and cognitive decline, and those studies reported conflicting results. Rouch et al. (8) conducted a two-year follow-up study, where individuals were surveyed with a large neuropsychological test battery. They found that prediabetes was related to cognitive decline, based on the verbal fluency (letter) test. Xu et al. (10) performed a nine-year follow-up, where individuals were surveyed with the MMSE. They showed that prediabetes accelerated the progression from mild cognitive impairment to dementia. Similarly, Marseglia et al. performed a nine-year follow-up, where individuals were surveyed with the MMSE. They found that prediabetes was independently associated with accelerated cognitive decline (9). In contrast, Samaras et al. performed a two-year follow-up study, where individuals were tested with a wide variety of cognitive tests. They found that stable IFG had no detrimental effect on cognition (11). Similarly, Cholerton et al. conducted a study, where individuals were surveyed with several cognitive tests. After a mean follow-up of 21 years, they found that IFG was not significantly associated with cognitive decline (15). Apparently different cognitive tests measure different cognitive domains, maybe effecting the results. The tests we used and the cognitive domains they measure are explained in the methods.

In the present study, we observed a significant decline in cognitive performance among individuals that had diabetes during the entire 12-year follow up. This result supported previous studies, which indicated that diabetes was an independent risk factor for cognitive decline during aging. According to our results from the present study, a glucose metabolism disorder (prediabetes or diabetes) independently lowered cognitive performance.

Clear evidence from prospective cohort studies have supported the relationship between cardiovascular risk factors and cognitive deficits. Smoking (16) (17), obesity (18), (19), (20), (21), (22), (23), diabetes (24), (25), (26), (27), high cholesterol in midlife (22) (28), and hypertension in midlife (19), (22), (29), (30), (31) were associated with increased risks of cognitive decline and dementia. In our study those who had diabetes at the baseline performed statistically significantly weaker in word list learning (p 0.005) and in TMA test (p 0.026) compared to those who developed diabetes during the follow-up, suggesting long lasting diabetes to be a risk factor for cognitive decline.

The main strength of this study was that the OGTT was performed at baseline and at follow-up to determine diabetes status in the participants. Additionally, the follow-up time was sufficiently long to observe possible changes as the population aged from late middle age to older age. Moreover, we adjusted the analyses for covariates to rule out the effects of some common confounders. We used the longitudinal change in blood pressure as a covariate because the change in blood pressure during the follow up associated with cognitive change more apparently than baseline blood pressure alone. In addition, we chose cognitive tests that would be sufficiently challenging for a study population that was relatively young and cognitively intact at baseline. In contrast, for follow-up, we chose a test battery that was relatively broad to test different areas of cognitive ability. Our cognitive tests were comprehensive enough (5 different tests) even though they did not evaluate the global cognition.

Some potential limitations of this study were the small group sizes at follow-up. Additionally, our test battery does not give the information about the global cognition but certain cognitive domains. Another potential limitation was the population-based study design, which is often prone to selection bias during follow -up (32). This bias could have been present in our study, because individuals with worse diabetes status or other difficult health issues tended to drop out during the follow up. This bias might have affected the results. Indeed, the decline in cognitive ability might have been more marked, if individuals in worse condition had been included in the analyses. Furthermore because the study group was aware of their prediabetes status, they might have changed their lifestyle during the follow up. This potential intervention could have impacted our ability to detect distinct changes over time.

In conclusion, we found that both prediabetes and diabetes diagnosed at mid-life accelerated cognitive decline during aging. Importantly, the clinical relevance of our results could be

meaningful, even in the absence of statistical significance. Further studies are needed to evaluate whether insulin resistance and prediabetes are independent risk factors for cognitive decline. Common vascular risk factors are also known to be associated with cognitive decline, particularly those that become influential in middle age. Further study is needed to assess their roles in weakening cognitive performance later in life.

Funding:

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The authors declare no conflict of interest.

References

References

1. Cukierman T, Gerstein HC, Williamson JD. Cognitive decline and dementia in diabetes - Systematic overview of prospective observational studies. Diabetologia. 2005;48(12):2460-9.

2. 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.

3. Zhang J, Chen C, Hua S, Liao H, Wang M, Xiong Y, et al. An updated meta-analysis of cohort studies: Diabetes and risk of Alzheimer's disease. Diabetes Res Clin Pract. 2017;124:41-7.

4. Hiltunen LA, Keinänen-Kiukaanniemi SM, Läärä EM. Glucose tolerance and cognitive impairment in an elderly population. Public Health. 2001;115(3):197-200.

5. 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):658-63.

6. Papunen S, Mustakallio-Könönen A, Auvinen J, Timonen M, Keinänen-Kiukaanniemi S, Sebert S. The association between diabetes and cognitive changes during aging. Scand J Prim Health Care. 2020;38(3):281-90.

7. Biessels G, Strachan MW, Visseren F, Kapplelle LJ, Whitmer RA. Dementia and cognitive decline in tye 2 diabetes and prediabetic stages: towards targeted interventions. Lancet Diabetes Endocrinol. 2014;2:246-55.

8. Rouch I, Roche F, Dauphinot V, Laurent B, Antérion CT, Celle S, et al. Diabetes, impaired fasting glucose, and cognitive decline in a population of elderly community residents. Aging Clin Exp Res. 2012;24(4):377-83.

9. Marseglia A, Fratiglioni L, Kalpouzos G, Wang R, Bäckman L, Xu W. Prediabetes and diabetes accelerate cognitive decline and predict microvascular lesions: A population-based cohort study. Alzheimer's Dementia. 2019;15(1):25-33.

10. Xu W, Caracciolo B, Wang H-, Winblad B, Bäckman L, Qiu C, et al. Accelerated progression from mild cognitive impairment to dementia in people with diabetes. Diabetes. 2010;59(11):2928-35.

11. Samaras K, Lutgers HL, Kochan NA, Crawford JD, Campbell LV, Wen W, et al. The impact of glucose disorders on cognition and brain volumes in the elderly: The Sydney Memory and Ageing Study. Age. 2014;36(2):977-93.

12. Vladimirov D, Niemelä S, Auvinen J, Timonen M, Keinänen-Kiukaanniemi S, Ala-Mursula L, et al. Changes in alcohol use in relation to sociodemographic factors in early midlife. Scand J Public Health. 2016;44(3):249-57.

13. Beck AT, Steer RA, Ball R, Ranieri WF. Comparison of Beck depression inventories -IA and -II in psychiatric outpatients. J Pers Assess. 1996;67(3):588-97.

14. D'Orazio P, Burnett RW, Fogh-Andersen N, Jacobs E, Kuwa K, Külpmann WR, et al. Approved IFCC recommendation on reporting results for blood glucose. Clin Chem Lab Med. 2006;44(12):1486-90.

15. Cholerton B, Omidpanah A, Verney SP, Nelson LA, Baker LD, Suchy-Dicey A, et al. Type 2 diabetes and later cognitive function in older American Indians: The Strong Heart Study. Int J Geriatr Psychiatry. 2019;34(7):1050-7.

16. Anstey KJ, Von Sanden C, Salim A, O'Kearney R. Smoking as a risk factor for dementia and cognitive decline: A meta-analysis of prospective studies. Am J Epidemiol. 2007;166(4):367-78.

17. Rusanen M, Kivipelto M, Quesenberry Jr. CP, Zhou J, Whitmer RA. Heavy smoking in midlife and long-term risk of Alzheimer disease and vascular dementia. Arch Intern Med. 2011;171(4):333-9.

18. Whitmer RA, Gustafson DR, Barrett-Connor E, Haan MN, Gunderson EP, Yaffe K. Central obesity and increased risk of dementia more than three decades later. Neurology. 2008;71(14):1057-64.

19. Kivipelto M, Ngandu T, Fratiglioni L, Viitanen M, Kåreholt I, Winblad B, et al. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. Arch Neurol. 2005;62(10):1556-60.

20. Xu WL, Atti AR, Gatz M, Pedersen NL, Johansson B, Fratiglioni L. Midlife overweight and obesity increase late-life dementia risk: A population-based twin study. Neurology. 2011;76(18):1568-74.

21. Fitzpatrick AL, Kuller LH, Lopez OL, Diehr P, O'Meara ES, Longstreth Jr. WT, et al. Midlife and late-life obesity and the risk of dementia: Cardiovascular health study. Arch Neurol. 2009;66(3):336-42.

22. Rönnemaa E, Zethelius B, Lannfelt L, Kilander L. Vascular risk factors and dementia: 40-year follow-up of a population-based cohort. Dementia Geriatr Cogn Disord. 2011;31(6):460-6.

23. Luchsinger JA, Cheng D, Tang MX, Schupf N, Mayeux R. Central obesity in the elderly is related to late-onset alzheimer disease. Alzheimer Dis Assoc Disord. 2012;26(2):101-5.

24. Ohara T, Doi Y, Ninomiya T, Hirakawa Y, Hata J, Iwaki T, et al. Glucose tolerance status and risk of dementia in the community: The Hisayama Study. Neurology. 2011;77(12):1126-34.

25. Reitz C, Brayne C, Mayeux R. Epidemiology of Alzheimer disease. Nat Rev Neurol. 2011;7(3):137-52.

26. Ahtiluoto S, Polvikoski T, Peltonen M, Solomon A, Tuomilehto J, Winblad B, et al. Diabetes, Alzheimer disease, and vascular dementia: A population-based neuropathologic study. Neurology. 2010;75(13):1195-202.

27. Cheng D, Noble J, Tang MX, Schupf N, Mayeux R, Luchsinger JA. Type 2 diabetes and late-onset Alzheimer's disease. Dementia Geriatr Cogn Disord. 2011;31(6):424-30.

28. Solomon A, Kivipelto M, Wolozin B, Zhou J, Whitmer RA. Midlife serum cholesterol and increased risk of Alzheimer's and vascular dementia three decades later. Dementia Geriatr Cogn Disord. 2009;28(1):75-80.

29. Launer LJ, Ross GW, Petrovitch H, Masaki K, Foley D, White LR, et al. Midlife blood pressure and dementia: The Honolulu-Asia aging study. Neurobiol Aging. 2000;21(1):49-55.

30. Ninomiya T, Ohara T, Hirakawa Y, Yoshida D, Doi Y, Hata J, et al. Midlife and late-life blood pressure and dementia in japanese elderly: The hisayama study. Hypertension. 2011;58(1):22-8.

31. Debette S, Seshadri S, Beiser A, Au R, Himali JJ, Palumbo C, et al. Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. Neurology. 2011;77(5):461-8.

32. Chanelle J Howe , Stephen R Cole, Bryan Lau, Sonia Napravnik, Joseph J Eron Jr. Selection Bias Due to Loss to Follow Up in Cohort Studies. . 2016 Jan;1:91-7.