

Published in final edited form as:

*Neurobiol Aging*. 2014 March ; 35(3): 585–589. doi:10.1016/j.neurobiolaging.2013.09.033.

## Impaired glycemia increases disease progression in mild cognitive impairment

Jill K. Morris<sup>1,2</sup>, Eric D. Vidoni<sup>1,2</sup>, Robyn A. Honea<sup>1,2</sup>, and Jeffrey M. Burns<sup>1,2</sup> for the Alzheimer's Disease Neuroimaging Initiative\*

<sup>1</sup>University of Kansas Medical Center, Alzheimer's Disease Center

<sup>2</sup>University of Kansas Medical Center Department of Neurology

### Abstract

Insulin resistance and Type 2 Diabetes are associated with cognitive decline and increased risk for Alzheimer's disease (AD). Relatively few studies have assessed the impact of metabolic dysfunction on conversion to AD in mild cognitive impairment (MCI), and it is unclear whether glycemic status is associated with clinically-relevant measures of cognitive decline and brain structure in MCI. This study used the Alzheimer's Disease Neuroimaging Initiative (ADNI) database to examine the relationship of baseline glycemia with conversion to AD and longitudinal clinical, cognitive, and imaging measures of decline. MCI subjects (n=264) with baseline and 2-year clinical dementia rating (CDR) data available were classified according to American Diabetes Association (ADA) criteria for fasting glucose at baseline. These groups were "normoglycemic" (FG<100mg/dL; n= 167) or "impaired glycemia" (FG ≥ 100mg/dL, n=97). The "impaired glycemia" group included individuals with fasting glucose that either reached the ADA cut-point for impaired fasting glucose or individuals with diagnosed diabetes. Two-year change in CDR sum of boxes (CDR-SB), cognitive performance testing ("global cognition"), brain volume (whole brain and hippocampal volume), FDG-PET, and conversion to AD were assessed. Subjects with normoglycemia at baseline had less functional (CDR-SB) and global cognitive decline over 2 years than subjects with impaired glycemia. Normoglycemic subjects also lost less whole brain volume and exhibited lower conversion from MCI to AD. There was no difference in hippocampal volume change or FDG-PET between groups. These results suggest that baseline glycemia is related to cognitive decline and progression to AD.

---

© 2013 Elsevier Inc. All rights reserved.

Correspondence: Jeffrey M. Burns, MD, MS, KU Alzheimer's Disease Center, Mail Stop 6002, 4350 Shawnee Mission Parkway, Fairway, KS 66205, (P): 913-945-5022, (F): 913-945-5035, jburns2@kumc.edu.

\*Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: [http://adni.loni.ucla.edu/wp-content/uploads/how\\_to\\_apply/ADNI\\_Acknowledgement\\_List.pdf](http://adni.loni.ucla.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf)

**Disclosures:** The authors report no conflicts of interest.

All authors have contributed to the development of and take full responsibility for the content of this manuscript, and agree with its content and agree to the Authorship and Contributorship statement. This submission is not in review at any other journal.

This study was conducted according to Good Clinical Practice guidelines. Informed consent was obtained from all study subjects prior to performing any procedures.

**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.

## Introduction

The etiology of sporadic Alzheimer's Disease (AD), the most common type of dementia, remains unknown. However, risk factors for sporadic AD include insulin resistance and Type 2 Diabetes (T2D)(De Felice, 2013). The prevalence of both insulin resistance and AD increase with age, and over half of individuals over 65 have either diabetes or pre-diabetes. (Cowie, et al., 2006) Thus, an increasing number of individuals will suffer from co-morbid AD and T2D. It is important to understand not only the effect of impaired glycemia on AD risk, but also on AD progression, beginning in mild cognitive impairment (MCI).

Studies suggest that diabetes may accelerate conversion from MCI to dementia, (Velayudhan, et al., 2010,Xu, et al., 2010) warranting further study of metabolic dysfunction on cognitive decline in MCI. This report supports and extends prior work using stringent definitions of MCI (amnesic MCI) and impaired glycemia (American Diabetes Association (ADA) guidelines). Analysis of MCI subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI) allowed analysis of clinically-relevant outcomes that may contribute to increased conversion, the latest methods for indexing decline, and biomarkers. This study is the largest to examine the relationship between glycemia and disease progression in amnesic MCI. We hypothesized that impaired glycemia would be associated with longitudinal functional, cognitive, and structural changes, and may represent a modifiable risk factor for MCI to AD progression.

## Methods

### Sample and recruitment

Data were obtained from ADNI ([www.loni.ucla.edu/ADNI](http://www.loni.ucla.edu/ADNI)) on January 5<sup>th</sup>, 2012. The ADNI is conducted by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, pharmaceutical companies and nonprofits with the goal of testing whether biological, neuroimaging, clinical and neuropsychological assessments can be combined to measure progression to AD. 264 subjects with amnesic Mild Cognitive Impairment (MCI) and baseline and 24-month CDR assessments were included. One subject that qualified was excluded due to very high fasting glucose (>400mg/dL). Imaging data (MRI and FDG-PET) was available for a subset of individuals and was also analyzed.

### Classification of groups

We classified subjects as either "normoglycemic" (NG; fasting glucose < 99mg/dL, n=167) or "impaired glycemia" (IG; fasting glucose >= 100mg/dL, n=97) using ADA criteria. Subjects with diagnosed diabetes (n=4) were classified as IG. For ADNI, MCI subjects scored 24–30 (inclusive) on the MMSE, had a memory complaint, abnormal memory function (WMS-R Logical Memory II score < 8 for more than 16y education, < 4 for 8–15y education, < 2 for less than 7y education), CDR of 0.5, and did not meet criteria for dementia.

### Clinical and cognitive assessment

Clinical and neuropsychometric assessment included the Clinical Dementia Rating (CDR) and cognitive tests used in the Uniform Data Set (UDS). The CDR assessment considered 6 independent domains, (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care) the sum of which is referred to as CDR sum of boxes (CDR-SB). (Burke, et al., 1988) The UDS neuropsychological test battery consists of the Mini-Mental State Examination, Logical Memory (I and II), Digit Span Forward and Backward, Category Fluency (Animals and Vegetables), Trailmaking A and B, WAIS Digit Symbol, and Boston Naming Test. A web-based normative calculator (Shirk, et al., 2011)

was used to compute sex, age, and education-adjusted scores for each test. A “global cognition” score was generated from the average of all normed scores.

### Laboratory measures and genotyping

Plasma was collected and analyzed for insulin on a 190 analyte multiplex immunoassay panel (Human Discovery Map; Rules-Based Medicine, TX) per ADNI protocol. For this study, only plasma insulin values above the assay least detectable dose (LDD) for insulin (n=257) were used; readings below the LDD (0.66 $\mu$ U/mL) were excluded. Further information is available from the Biomarkers Consortium Data Primer (<http://adni.loni.ucla.edu/>). Insulin sensitivity (Quantitative Insulin Sensitivity Check Index; QUICK I) was calculated as described (Katz, et al., 2000) with higher values indicative of greater insulin sensitivity. Apolipoprotein  $\epsilon$ 4 (APOE  $\epsilon$ 4) genotyping was performed at the University of Pennsylvania (ADNI Biomarker Core Laboratory). Subjects were APOE  $\epsilon$ 4 positive if they carried at least one allele. CSF was analyzed by ADNI for A $\beta$  and pTau using the multiplex xMAP Luminex platform (Luminex Corp, Austin, TX) as described (Shaw, et al., 2009).

### MRI and FDG-PET Imaging

All MRI and PET analyses were of previously processed secondary data obtained from ADNI. Hippocampal and whole brain volume (HBV) data from the Anders Dale Lab (UCSD) were used and details on their processing methods are published elsewhere (Holland, et al., 2009). For normalization we used total-intracranial volumes calculated automatically from FreeSurfer (Fischl, et al., 1999). A subgroup of subjects also presented for an FDG-PET scan after a 4-hr fast. A 5.0 $\pm$ 0.5mCi dose of [<sup>18</sup>F]FDG was injected IV and quantitative imaging was performed over 60 min. Mean FDG values were calculated as described (Landau, et al., 2011) from the average of 5 regions of interest (MetaROI's; bilateral posterior cingulate cortex, right and left inferior temporal region, and right and left lateral parietal region) chosen based on previous studies using FDG-PET in subjects with MCI and AD.

### Statistical analyses

Categorical variables (sex, 2-year conversion, and APOE  $\epsilon$ 4 genotype) were analyzed using the chi squared test. All other data were analyzed using ANOVA. Change scores were computed by subtracting the 24 mo value from baseline. Age, sex, education, and genotype were included as covariates for all variables except Global Cognition. Age, sex, and education were included in the calculation of the Global Cognition z-score and thus only genotype was included as a covariate. Fasting glucose and fasting insulin values were non-normally distributed and were log-transformed prior to analysis.

### Results

The glycemia groups did not differ in years of education (F=0.472, p=0.493), sex ( $\chi^2=2.8$ , p=0.093), proportion of APOE carriers ( $\chi^2=1.47$ , p=0.226), age (F=3.5, p=0.061), body mass index (BMI; F=1.48, p=0.309), or body weight (F=0.196, p=0.769). Although there was a trend for a difference in age, this did not reach significance and analyses were corrected for age. NG subjects had lower fasting glucose and were more insulin sensitive (QUICK I) than IG subjects (F=6.3, p<0.001). Triglyceride levels were lower in NG subjects (F=3.59, p<0.001). Fasting insulin (F=1.43, p=0.076) and cholesterol (F=7.5, p=0.95) were not different based on glycemic status. CSF amyloid beta 1–42 and phosphorylated tau were also not different between groups (F=7.0, p=0.298 and F=3.9, p=0.860, respectively; Table 1). Subjects with IG exhibited a greater increase in CDR-SB over 2 years compared to NG individuals (F=3.1, p=0.028). In addition, decline in global

cognition over 2-years was also significantly greater for IG subjects than NG subjects; individuals with IG performed more poorly compared to NG individuals ( $F=3.8$ ,  $p=0.023$ ). In line with greater clinical and cognitive decline, subjects with IG exhibited greater conversion from MCI to AD over 2 years (48.5%; 24.3%/yr) than NG subjects (32.3%; 16.2%/yr  $\chi^2=6.749$ ,  $p=0.009$ ; Table 2). IG subjects exhibited greater loss of whole brain volume over 2 years compared to NG individuals ( $F=4.3$ ,  $p=0.046$ ). This was significant only for whole brain and not hippocampus ( $p=0.350$ ). Furthermore, 2-year change in brain glucose metabolism (global FDG-PET) was not different between groups ( $p=0.695$ ).

## Discussion

In this retrospective longitudinal analysis of MCI subjects in the ADNI, subjects with IG at baseline had more 2-year functional decline, global cognitive decline, and whole brain atrophy. Most notably, IG was associated with a higher rate of conversion from MCI to AD (~24%/yr) than NG (~16%/yr). These findings are clinically relevant, as over half of elderly adults in the United States (>65 yrs of age) meet criteria for either impaired fasting glucose or diabetes, (Cowie, et al., 2006) the same criteria used to define our IG group.

MCI subjects are at greater risk of cognitive decline than nondemented subjects (Bennet, 2002). The MCI population is also enriched in APOE  $\epsilon 4$  positive individuals and thus at greater genetic risk for AD (Matsuzaki, et al., 2011). This likely contributes to the high rate of conversion in this cohort overall (ranging from 6–25% per year in previous studies (Petersen, et al., 2001)). However, few studies have investigated the role of modifiable risk factors in mediating MCI to AD progression. Two studies have shown that diabetes or pre-diabetes accelerates progression from MCI to AD (Xu, et al., 2010) (Velayudhan, et al., 2010). Our study in a larger cohort of subjects with amnesic MCI, using stringent definitions for both MCI and IG, and is consistent with this finding. Moreover, we include additional measures of decline (functional, cognitive, neuroimaging) and characterize potential contributing factors (genetics, biomarkers, lipid metabolism).

Several factors may mediate decline in subjects with IG. For instance, insulin resistance is associated with inflammation and oxidative stress (Hotamisligil, 2005), and hyperglycemia is linked to cognitive dysfunction in diabetics (Knowler, et al., 2002). In this study, subjects with IG were less insulin sensitive (lower QUICK I) in the absence of high insulin. Insulin levels increase to compensate for rising glucose in early-stage insulin resistance, (Puglielli, et al., 2003) but decline with increased disease severity. Insulin is important for cell growth and survival, and high insulin may be beneficial in early AD (Burns, et al., 2007). Subjects with IG also exhibited higher triglycerides, which impair cognitive performance in individuals with high levels of inflammation. (van den Kommer, et al., 2012) While neuropathology ( $A\beta$  1-42 and pTau) is greater in MCI than cognitively-normal individuals (Shaw, et al., 2009), our data demonstrate that within the MCI group, CSF  $A\beta$  and pTau are not different based on glycemia. Thus, the increased decline in IG subjects is not due to an increased biomarker load. Rather, our results suggest a combination of factors characteristic of IG (high glucose, insulin resistance, high triglycerides) in subjects who as a whole already have increased AD pathology ( $A\beta$  1-42, pTau) may contribute to greater cognitive decline and conversion to AD. Our data supports studies which suggest that the combinatorial effect of AD brain pathology together with vascular factors may produce a greater effect than either process alone (Viswanathan, et al., 2009).

We did not observe differences in 2-year hippocampal atrophy or FDG-PET between groups. This is somewhat discordant from our other results, but it is possible that the impact of metabolic dysfunction on these measures is more evident earlier in the disease, as our analysis included subjects that already exhibit MCI. Longitudinal studies of nondemented

subjects at risk for AD (i.e. individuals that exhibit genetic risk or maternal family history) may be most sensitive to these changes (Bateman, et al., 2012, Honea, et al., 2011, Mosconi, et al., 2009). Thus, glycemia-mediated effects on these measures may be more evident in longitudinal studies performed in subjects at risk for AD, rather than MCI subjects.

We also did not observe a significant difference in BMI or body weight between glycemia groups, although it is worth noting that the average BMI in both cohorts was >25, the cut-point for designation of “overweight.” More sensitive measures of body composition may have revealed key differences in adipose distribution (i.e. visceral vs. subcutaneous fat) that have been shown to affect glycemia (Yamashita, et al., 1996). It should also be noted that when all MCI subjects were considered together (regardless of glycemic status), “converters” did not exhibit higher glucose, insulin, or triglyceride levels than “non-converters” ( $p>0.05$ ). However, individuals who converted from MCI to AD over 2 years were more likely to be APOE e4 carriers, regardless of glycemic status ( $\chi^2=10.16$ ,  $p=0.01$ ), and individuals with IG were more likely to convert from MCI to AD than subjects with normal glucose levels, regardless of APOE e4 status ( $\chi^2=6.749$ ,  $p=0.009$ ). This supports a previous report that APOE e4 genotype is not associated with insulin resistance, (Ragogna, et al., 2012) and suggests that genotype and glycemic impairment may represent independent risk factors for disease conversion.

Strengths of our study include use of a well-characterized cohort and diverse and robust longitudinal outcome measures, and weaknesses include lack of 2-year longitudinal plasma measures and limited measures of body composition and lifestyle factors. In fact, recent reviews underscore the fact that several factors including diet, physical activity, and distribution of body fat that are related to impairment of glucose metabolism (Neeland, et al., 2012, Salas-Salvado, et al., 2011, Solomon and Thyfault, 2013). Future studies are warranted to investigate the role of additional factors in progression of MCI to AD. Nevertheless, this is the first study to assess MCI progression using the ADA accepted cut-point for fasting glucose, and the largest to assess amnesic MCI. Overall, our consistent results that encompass diverse outcome measures, such as greater 2-year functional and cognitive decline, decreased whole brain volume, and increased progression from MCI to AD suggest a relationship between impaired glucose metabolism and disease progression in MCI. This study supports and extends previous work that suggests impaired glucose metabolism in MCI is associated with increased progression to AD and represents a potentially modifiable risk factor for increased cognitive decline in this cohort.

## Acknowledgments

Data collection and sharing was funded by ADNI (NIH U01 AG024904). ADNI is funded by the NIA, NIBIB, the Alzheimer’s Association; Alzheimer’s Drug Discovery Foundation; BioClinica, Inc.; Biogen Idec Inc; Bristol-Myers Squibb Co., F. Hoffmann-LaRoche Ltd and Genetech, Inc; GE Healthcare; innogenetics, N.V.; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development LLC.; Medpace, Inc.; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Novartis Pharmaceuticals, Co, Pfizer, Inc.; Piramal Imaging; Servier; Synarc inc.; and Takeda Pharmaceutical Co. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the NIH ([www.fnih.org](http://www.fnih.org)). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer’s Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of California, Los Angeles. This research was also supported by P30 AG010129, KL2 TR000119, K01 AG030514, and the KUMC Biomedical Research Training Program.

## References

Bateman RJ, Xiong C, Benzinger TL, Fagan AM, Goate A, Fox NC, Marcus DS, Cairns NJ, Xie X, Blazey TM, Holtzman DM, Santacruz A, Buckles V, Oliver A, Moulder K, Aisen PS, Ghetti B, Klunk WE, McDade E, Martins RN, Masters CL, Mayeux R, Ringman JM, Rossor MN, Schofield

- PR, Sperling RA, Salloway S, Morris JC. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N Engl J Med*. 2012; 367(9):795–804.10.1056/NEJMoa1202753 [PubMed: 22784036]
- Bennet D, Wilson RS, Schneider JA, et al. Natural history of mild cognitive impairment. *Neurology*. 2002; 59(2):198–205. [PubMed: 12136057]
- Burke WJ, Miller JP, Rubin EH, Morris JC, Coben LA, Ducheck J, Wittels IG, Berg L. Reliability of the Washington University Clinical Dementia Rating. *Archives of Neurology*. 1988; 45:31–2. [PubMed: 3337672]
- Burns JM, Donnelly JE, Anderson HS, Mayo MS, Spencer-Gardner L, Thomas G, Cronk BB, Haddad Z, Klima D, Hansen D, Brooks WM. Peripheral insulin and brain structure in early Alzheimer disease. *Neurology*. 2007; 69(11):1094–104. [PubMed: 17846409]
- Cowie CC, Rust KF, Byrd-Holt DD, Eberhardt MS, Flegal KM, Engelgau MM, Saydah SH, Williams DE, Geiss LS, Gregg EW. Prevalence of diabetes and impaired fasting glucose in adults in the U.S. population: National Health And Nutrition Examination Survey 1999–2002. *Diabetes care*. 2006; 29(6):1263–8.10.2337/dc06-0062 [PubMed: 16732006]
- De Felice FG. Alzheimer's disease and insulin resistance: translating basic science into clinical applications. *The Journal of clinical investigation*. 2013; 123(2):531–9.10.1172/JCI64595 [PubMed: 23485579]
- Fischl B, Sereno MI, Tootell RB, Dale AM. High-resolution intersubject averaging and a coordinate system for the cortical surface. *Hum Brain Mapp*. 1999; 8(4):272–84. [pii]. 10.1002/(SICI)1097-0193(1999)8:4<272::AID-HBM10>3.0.CO;2-4 [PubMed: 10619420]
- Holland D, Brewer JB, Hagler DJ, Fennema-Notestine C, Dale AM. Subregional neuroanatomical change as a biomarker for Alzheimer's disease. *Proc Natl Acad Sci U S A*. 2009; 106(49):20954–9. [PubMed: 19996185]
- Honea RA, Swerdlow RH, Vidoni ED, Burns JM. Progressive regional atrophy in normal adults with a maternal history of Alzheimer disease. *Neurology*. 2011; 76(9):822–9.10.1212/WNL.0b013e31820e7b74 [PubMed: 21357834]
- Hotamisligil GS. Role of endoplasmic reticulum stress and c-Jun NH2-terminal kinase pathways in inflammation and origin of obesity and diabetes. *Diabetes*. 2005; 54(Suppl 2):S73–8. [PubMed: 16306344]
- Katz A, Nambi SS, Mather K, Baron AD, Follmann DA, Sullivan G, Quon MJ. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. *The Journal of clinical endocrinology and metabolism*. 2000; 85(7):2402–10. [PubMed: 10902785]
- Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002; 346(6):393–403.10.1056/NEJMoa012512 [PubMed: 11832527]
- Landau SM, Harvey D, Madison CM, Koeppe RA, Reiman EM, Foster NL, Weiner MW, Jagust WJ. Alzheimer's Disease Neuroimaging I. Associations between cognitive, functional, and FDG-PET measures of decline in AD and MCI. *Neurobiology of aging*. 2011; 32(7):1207–18.10.1016/j.neurobiolaging.2009.07.002 [PubMed: 19660834]
- Matsuzaki T, Sasaki K, Hata J, Hirakawa Y, Fujimi K, Ninomiya T, Suzuki SO, Kanba S, Kiyohara Y, Iwaki T. Association of Alzheimer disease pathology with abnormal lipid metabolism: the Hisayama Study. *Neurology*. 2011; 77(11):1068–75.10.1212/WNL.0b013e31822e145d [PubMed: 21911734]
- Mosconi L, Mistur R, Switalski R, Brys M, Glodzik L, Rich K, Pirraglia E, Tsui W, De Santi S, de Leon MJ. Declining brain glucose metabolism in normal individuals with a maternal history of Alzheimer disease. *Neurology*. 2009; 72(6):513–20.10.1212/01.wnl.0000333247.51383.43 [PubMed: 19005175]
- Neeland IJ, Turer AT, Ayers CR, Powell-Wiley TM, Vega GL, Farzaneh-Far R, Grundy SM, Khera A, McGuire DK, de Lemos JA. Dysfunctional adiposity and the risk of prediabetes and type 2 diabetes in obese adults. *JAMA : the journal of the American Medical Association*. 2012; 308(11):1150–9.10.1001/2012.jama.11132 [PubMed: 22990274]
- Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST. Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the

- Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2001; 56(9):1133–42. [PubMed: 11342677]
- Puglielli L, Ellis BC, Saunders AJ, Kovacs DM. Ceramide stabilizes beta-site amyloid precursor protein-cleaving enzyme 1 and promotes amyloid beta-peptide biogenesis. The Journal of biological chemistry. 2003; 278(22):19777–83.10.1074/jbc.M300466200 [PubMed: 12649271]
- Ragogna F, Lattuada G, Ruotolo G, Luzi L, Perseghin G. Lack of association of apoE epsilon4 allele with insulin resistance. Acta diabetologica. 2012; 49(1):25–32.10.1007/s00592-011-0255-3 [PubMed: 21290252]
- Salas-Salvado J, Martinez-Gonzalez MA, Bullo M, Ros E. The role of diet in the prevention of type 2 diabetes. Nutrition, metabolism, and cardiovascular diseases : NMCD. 2011; 21(Suppl 2):B32–48.10.1016/j.numecd.2011.03.009
- Shaw LM, Vanderstichele H, Knapik-Czajka M, Clark CM, Aisen PS, Petersen RC, Blennow K, Soares H, Simon A, Lewczuk P, Dean R, Siemers E, Potter W, Lee VM, Trojanowski JQ. Cerebrospinal fluid biomarker signature in Alzheimer’s disease neuroimaging initiative subjects. Ann Neurol. 2009; 65(4):403–13.10.1002/ana.21610 [PubMed: 19296504]
- Shirk SD, Mitchell MB, Shaughnessy LW, Sherman JC, Locascio JJ, Weintraub S, Atri A. A web-based normative calculator for the uniform data set (UDS) neuropsychological test battery. Alzheimer’s research & therapy. 2011; 3(6):32.10.1186/alzrt94
- Solomon TP, Thyfault JP. Type 2 diabetes sits in a chair. Diabetes, obesity & metabolism. 2013.10.1111/dom.12105
- van den Kommer TN, Dik MG, Comijs HC, Jonker C, Deeg DJ. Role of lipoproteins and inflammation in cognitive decline: do they interact? Neurobiology of aging. 2012; 33(1):196, e1–12.10.1016/j.neurobiolaging.2010.05.024 [PubMed: 20594617]
- Velayudhan L, Poppe M, Archer N, Proitsi P, Brown RG, Lovestone S. Risk of developing dementia in people with diabetes and mild cognitive impairment. The British journal of psychiatry : the journal of mental science. 2010; 196(1):36–40.10.1192/bjp.bp.109.067942 [PubMed: 20044657]
- Viswanathan A, Rocca WA, Tzourio C. Vascular risk factors and dementia: how to move forward? Neurology. 2009; 72(4):368–74.10.1212/01.wnl.0000341271.90478.8e [PubMed: 19171835]
- Xu W, Caracciolo B, Wang HX, Winblad B, Backman L, Qiu C, Fratiglioni L. Accelerated progression from mild cognitive impairment to dementia in people with diabetes. Diabetes. 2010; 59(11):2928–35.10.2337/db10-0539 [PubMed: 20713684]
- Yamashita S, Nakamura T, Shimomura I, Nishida M, Yoshida S, Kotani K, Kameda-Takemura K, Tokunaga K, Matsuzawa Y. Insulin resistance and body fat distribution. Diabetes care. 1996; 19(3):287–91. [PubMed: 8742584]

**Table 1**

Baseline demographic and biomarker characteristics of MCI subjects based on glycemic status. Data is presented as means  $\pm$ SD.

	Normoglycemic	Impaired Glycemia	p-value
<b>Age</b>	74.1 (7.6)	75.8 (6.5)	0.061
<b>Sex (#, % male)</b>	98 (58.7%)	67 (69.1%)	0.093
<b>Education</b>	15.9 (2.9)	15.6 (3.2)	0.493
<b>APOE <math>\epsilon</math>4 carriers (#, %)</b>	87 (52.1%)	58 (59.8%)	0.226
<b>Glucose (mg/dL)</b>	89.1 (6.9)	118.3 (23.1)	<0.001*
<b>CSF glucose (mg/dL)</b>	55.9 (13.3)	61.2 (8.8)	0.025*
<b>Insulin (<math>\mu</math>U/mL)</b>	2.53 (2.3)	3.22 (3.4)	0.076
<b>QUICK I</b>	0.449 (0.05)	0.415 (0.05)	<0.001*
<b>Triglycerides</b>	135.5 (60.2)	178.1 (131.5)	<0.001*
<b>Cholesterol</b>	198.8 (39.1)	195.4(39.3)	0.950
<b>CSF A<math>\beta</math> (1-42)</b>	160.3 (54.4)	151.9 (48.4)	0.298
<b>pTau</b>	35.9 (18.2)	36.2 (14.1)	0.860
<b>BMI</b>	25.7 (3.6)	26.4 (4.4)	0.366
<b>Body Weight</b>	165.0 (28.6)	168.6 (32.1)	0.769

\* p<0.05



**Table 2**

Longitudinal functional, cognitive, and neuroimaging characteristics of MCI subjects based on glycemic status. Data is presented as means  $\pm$ SD.

Measure	Timepoint	Normoglycemic	Impaired Glycemia	p-value (2yr $\Delta$ )
<b>MCI to AD converters</b>	Baseline	N/A	N/A	<b>0.009*</b>
	2yr $\Delta$	32.3% (16.2%/yr)	48.5% (24.3%/yr)	
<b>CDR-SB</b>	Baseline	1.56 (0.87)	1.61 (0.83)	<b>0.028*</b>
	2yr $\Delta$	1.33 (1.9)	1.91 (1.9)	
<b>Global Cognition</b>	Baseline	-0.615 (0.55)	-0.761 (0.61)	<b>0.023*</b>
	2yr $\Delta$	-0.194 (0.56)	-0.363 (0.58)	
<b>Whole Brain Volume</b>	Baseline	0.677 (0.027)	0.672 (0.023)	<b>0.046*</b>
	2yr $\Delta$	-0.012 (0.007)	-0.0152 (0.009)	
<b>Hippocampal Volume</b>	Baseline	0.656 (0.89)	0.640 (0.08)	<b>0.350</b>
	2yr $\Delta$	-0.0149 (-.016)	-0.0198 (0.019)	
<b>FDG-PET</b>	Baseline	1.22 (0.14)	1.17 (0.11)	<b>0.695</b>
	2yr $\Delta$	-0.047 (0.07)	-0.037 (0.077)	

\*  
p<0.05