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Insulin Resistance is Associated with Increased Levels of Cerebrospinal Fluid Biomarkers of Alzheimer's Disease and Reduced Memory Function in At-Risk Healthy Middle-Aged Adults

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Abstract

Background—Type 2 diabetes is associated with an increased risk for Alzheimer disease (AD). Regulation of normal insulin function may be important in reducing the prevalence of dementia due to AD, particularly in individuals who harbor genetic risk for or have a parental family history of AD. The relationship between insulin resistance (IR) and AD pathology remains poorly understood, particularly in midlife prior to the onset of clinical metabolic disease or cognitive decline.

Objective—We examined associations between IR as indexed by HOMA-IR, cerebral spinal fluid (CSF) biomarkers of AD pathology and memory in middle-aged adults enriched for AD. We postulated that higher HOMA-IR and *APOE* ϵ 4 carriage would be associated with greater CSF AD pathology and poor memory performance.

Methods—Cognitively asymptomatic middle-aged adults (N=70, mean age=57.7 years) from the Wisconsin Alzheimer's Disease Research Center with a parental family history of dementia due to AD underwent lumbar puncture, blood draw and neuropsychological testing. CSF AD biomarkers

including soluble amyloid precursor protein β (sAPP- β), β -amyloid₄₂ (A β ₄₂) and phosphorylated tau (P-tau₁₈₁) were examined with respect to HOMA-IR and *APOE* ϵ 4 status. Delayed memory performance was examined with respect to HOMA-IR, CSF AD biomarkers and *APOE* ϵ 4 status.

Results—Higher HOMA-IR was associated with higher sAPP- β and A β ₄₂. *APOE* ϵ 4 carriers had significantly higher levels of sAPP- α , sAPP- β and P-tau₁₈₁/A β ₄₂ compared to noncarriers. The concurrent presence of higher HOMA-IR and CSF AD pathology predicted worse delayed memory performance.

Conclusion—Overall, the findings suggest that IR and *APOE* ϵ 4 are contributing factors to the development of AD pathology in midlife, and provide support for targeting insulin function as a potentially modifiable risk factor for AD.

Keywords

insulin resistance; CSF AD biomarkers; *APOE* ϵ 4; memory function

1. Introduction

Epidemiological studies indicate that type 2 diabetes and related conditions such as insulin resistance (IR) are associated with an increased risk of developing dementia due to Alzheimer disease (AD) [1–6]. Over the past fifty years, the rate of type 2 diabetes mellitus has increased alarmingly with approximately 387 million individuals diagnosed with the disease as of 2014 [7]. While several animal studies link IR to specific features of AD [8], the relationship between IR and development of neuropathology among cognitively healthy individuals is less clear, especially among individuals who have not yet developed type 2 diabetes. Such studies are needed, given that IR may induce neurodegeneration prior to the onset of marked cognitive or behavioral impairment, and that the window for effectively modifying IR precedes the clinical diagnosis of type 2 diabetes [9].

Insulin is increasingly recognized as playing an integral role in normal brain function and plays a central role in learning and memory [10,11]. Regions of the brain that are dense with insulin receptors, including the medial temporal and frontal lobes, are preferentially sensitive to insulin signaling and among the first to be adversely effected in AD [12–14]. Cognitively healthy individuals with reduced peripheral insulin function show subtle cognitive deficits, reduced cerebral glucose metabolism, and diminished cerebrocortical activity [15,16]. Among cognitively intact middle-aged and older adults, reduced glucose tolerance has been associated with poor memory performance and hippocampal atrophy [17,18]. Glucose metabolism is also reduced, particularly among regions affected by AD [15,19]. Postmortem and cerebrospinal fluid biomarker studies indicate that type 2 diabetes and IR are associated with amyloid deposition [20] and tau pathology [21], although some studies have failed to find a relationship [22] and others have found an inverse effect [23]. It has been particularly difficult to determine whether IR contributes to amyloid pathology, with en vivo imaging studies showing differential effects [24–26].

The proteolytic processing of amyloid precursor protein (APP) is one of many neurobiological processes negatively affected by IR. APP is typically processed by two

competing pathways: the amyloidogenic β -secretase (BACE1)-mediated and the nonamyloidogenic α -secretase-mediated pathways. Cleavage of APP by α -secretase occurs within the A β sequence and precludes the formation of A β peptides; this process mitigates the accumulation of extracellular amyloid plaques [27]. By contrast, APP cleavage by BACE1 produces a membrane-bound fragment of APP (commonly referred to as C99) that, upon further cleavage by γ -secretase, yields different A β species, which range between 38 and 43 amino acids in length [28,29]. Both α and β cleavage of APP will release the N-terminal ectodomain of APP (sAPP- α and sAPP- β , respectively) in the extracellular milieu.

Among the different A β species normally produced, the 40- (A β_{40}) and 42- (A β_{42}) amino acids long peptides are highly enriched in neuritic plaques, an important hallmark of AD neuropathology. Furthermore, over the past decade, several studies have shown that A β soluble oligomers have neurotoxic effects that include disruption of synaptic integrity and synaptic plasticity [30,31], as well as alteration of molecular and cellular pathways integral to memory formation [32–34]. Transgenic mouse models provide evidence that IR promotes beta cleavage of APP [35,36]; they also show that increased beta cleavage of APP is associated with disrupted synaptic transmission and plasticity in the hippocampus [33]. Congruent with these findings, a study of diet-induced IR in Tg2576 transgenic mice showed that IR promoted amyloidogenic A β production, increased AD-type amyloid plaque burden, and impaired performance on hippocampal-dependent memory tasks [37].

Several risk factors for AD have been associated with increased neuropathology, including nonmodifiable factors such as genetic risk, parental family history of dementia due to AD (i.e., FH+ individuals), and age. *APOE* ϵ 4 carriage is associated with hypometabolism [38–40], higher amyloid burden [41] and gray matter atrophy in AD-sensitive regions [42], and as shown by animal studies, may be particularly deleterious to the hippocampus and hippocampal-dependent tasks such as the Morris Water Maze, object recognition, and context fear conditioning [43]. Carriage of the ApoE4 isoform also impairs A β clearance [44], facilitates neuronal degeneration and interferes with synaptic stability [45]. Likewise, parental family history of dementia due to AD is associated with pathological changes in AD-sensitive brain regions, even among individuals who are cognitively asymptomatic [46–52]. Neurodegeneration and neuropathology observed in FH+ individuals is consistent with pathology observed in mild cognitive impairment (MCI) and AD patients, although substantially less severe. Pathological changes observed in FH+ individuals likely confer additional risk for development of late-onset AD [52,53]. The direct relationship between parental family history of dementia due to AD and development of AD in later life is not well understood. While carriage of the ϵ 4 allele and parental family history of dementia due to AD are known to increase AD risk, moderating effects of these factors on molecular mechanisms alone may not be sufficient to cause the disease. As genetic and familial risk factors are invariable, modifiable factors that may decrease the risk of developing AD are of clinical importance. Although IR has been implicated in an increased risk for developing AD, the effects of IR on AD-like pathology and memory function in healthy middle-aged individuals is currently poorly understood, although important given that midlife is a critical time period during which lifestyle factors that confer risk for AD may be altered [54].

Thus, the current study investigated associations between IR, *APOE* ϵ 4 carriage, and cerebrospinal fluid (CSF) biomarkers of AD including CSF sAPP- β , A β ₄₂, P-tau₁₈₁ and P-tau₁₈₁/A β ₄₂, as well as hippocampal-dependent memory function among middle-aged participants with parental family history of dementia due to AD. Specifically, we examined the effects of IR as assessed by the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) and *APOE* ϵ 4 status on CSF biomarkers of AD and performance on the Rey Auditory Verbal Learning Test (RAVLT), delayed recall. Given prior studies showing that the effects of IR may depend on *APOE* ϵ 4 carriage, we also tested for interactions between HOMA-IR and *APOE* ϵ 4 on CSF biomarkers and memory function. We hypothesized that higher HOMA-IR and *APOE* ϵ 4 would be associated with: 1) increased CSF biomarkers of neural injury and amyloid burden and 2) decreased memory function.

2. Materials and Methods

2.1. Participants

We examined 70 asymptomatic middle-aged adults (mean age= 57.7 years, SD= 5.11, range= 46–66, 78.6% female) from the Wisconsin Alzheimer's Disease Research Center (ADRC) Investigating Memory in People At risk, Causes and Treatments (IMPACT) cohort (Table 1). All participants had a parental family history of dementia due to AD (FH+) defined as one or both biological parents meeting criteria for clinical diagnosis [55,56]. Parental family history was determined by a validated interview reviewed by a multidisciplinary diagnostic consensus panel [57] or postmortem neuropathological diagnosis of AD. Individuals underwent lumbar puncture, fasting blood draw, and comprehensive neuropsychological testing. Inclusion criteria entailed no history of a clinical diagnosis of diabetes or current diabetes treatment. Fasting plasma glucose (FPG) was evaluated to exclude individuals who met FPG criteria for diabetes diagnosis (i.e., FPG > 125 mg/dL). All participants were required to have normal cognitive function, as determined by neuropsychological evaluation and consensus review, and no current diagnosis of major psychiatric illness. Participants were defined as *APOE* ϵ 4 positive if they harbored at least one copy of the ϵ 4 allele. Hetero- and homozygous ϵ 4 allele carriers constituted 47% of the sample.

2.2. Design and Procedure

To assess IR and biomarkers of CSF AD pathology, venipuncture and lumbar puncture were performed in the morning after a 12h fast. Blood samples were collected in 9mL polypropylene tubes, allowed to clot for 30mins and centrifuged at 4 degrees Celsius at 3000 rpm for 10mins. Cell-free plasma/serum was aliquoted into 1.5mL micro centrifuge tubes and frozen at –80 degrees Celsius. Plasma and serum samples were analyzed at the University of Wisconsin Hospital and Clinics Hospital Laboratory (Madison, WI). To assess fasting glucose, plasma was assayed using hexokinase glucose method (Siemens Dimension Vista). To assess fasting insulin, serum was assayed using chemiluminescent immunoassay on an ADVIA Centaur XP Immunoassay System (Siemens Corporation, Washington DC, USA). Insulin resistance was calculated from fasting serum insulin and fasting plasma glucose using the homeostatic model assessment of insulin resistance (HOMA-IR) method [58] calculated as $HOMA-IR = [Insulin (mg/dL) \times Glucose (uIU/mL)]/405$. A log

transformation (log base 10) was performed on HOMA-IR scores to correct for a skewed distribution.

CSF was collected through gentle extraction via lumbar puncture using a Sprotte 25- or 24-gauge spinal needle at the L3/4 or L4/5 level of the spinal column. Approximately 22mL of CSF was extracted, inverted to avoid gradient, gently mixed and centrifuged at 2000g for 10mins. Supernatants were frozen in polypropylene tubes in 0.5mL aliquots and stored at -80 degrees Celsius. CSF was assayed for P-tau₁₈₁ and A β ₄₂ using commercially available enzyme-linked immunosorbent assay (ELISA) methods (INNOTEST assays, Fujiirebio, Ghent Belgium) as previously described in detail [59]. The P-tau₁₈₁/A β ₄₂ ratio (using INNOTEST) was examined as a marker of both tau and amyloid pathology. CSF sAPP- α , sAPP- β , A β ₃₈, A β ₄₀, and A β ₄₂ were measured using the MSD Multiplex Soluble APP assay (Meso Scale Discovery, Rockville, MD), as described by the manufacturer. Board-certified laboratory technicians blinded to clinical information analyzed all samples in accordance to protocols approved by the Swedish Board of Accreditation and Conformity Assessment (SWEDAC). One batch of reagents was used yielding intra-assay coefficients of <10 % variation.

APOE ϵ 4 status was determined using genetic testing at the Wisconsin Alzheimer's Disease Research Center. Genotyping was performed using a blood sample collected at baseline visit using standard polymerase chain reaction (PCR) and deoxyribonucleic acid (DNA) sequencing techniques. DNA extracted from whole blood was genotyped with the use of a homogenous Florescent Resonance Energy Transfer technology coupled to competitive allele specific PCR (LGC Genomics; Beverly, MA). The National Cell Repository for Alzheimer's disease (NCRAD) also performed genotyping. There was 100% concordance for *APOE* genotyping between these analyses.

Participants underwent a comprehensive neuropsychological battery that included the Rey Auditory Verbal Learning Test (RAVLT) [60] a widely used and well-validated assessment of memory function. The delayed component of the RAVLT is designed to examine long-term memory function and is a well-known measure for assessing cognitive changes from intact, to MCI to AD [61,62]. In the current study the RAVLT delayed task was chosen as an index of long-term hippocampal-dependent memory function.

2.7. Statistical Analyses

Linear regression analyses were conducted in SPSS (IBM SPSS Statistics for Mac, Version 21.0. Armonk, NY: IBM Corp). Regression models were conducted to test for main effects and an interaction of HOMA-IR and *APOE* ϵ 4 status on CSF sAPP- α , sAPP- β , A β ₃₈, A β ₄₀, and A β ₄₂. Each CSF biomarker of interest was selected a priori and was entered into separate models to examine unique effects of predictor variables. A linear regression was conducted to test for main effects (HOMA-IR, *APOE* ϵ 4 status, and CSF P-tau₁₈₁/A β ₄₂) and interactions (HOMA-IR x *APOE* ϵ 4; HOMA-IR x P-tau₁₈₁/A β ₄₂) on delayed memory performance. The P-tau₁₈₁/A β ₄₂ ratio was chosen a priori as a summary CSF biomarker of AD-like neuropathology. Age, sex, and body mass index (BMI) were included as covariates in all analyses. Education was added as a covariate in the memory analysis to control for interparticipant variability on the RAVLT associated with years of formal education.

3. Results

3.1. HOMA-IR, *APOE* ε4, and CSF biomarkers of AD

Linear multiple regression analyses revealed that HOMA-IR was a significant but modest predictor of CSF sAPP-β and Aβ₄₂. Higher HOMA-IR was associated with increased levels of CSF sAPP-β ($F_{[1,63]} = 4.21$, $p = 0.044$, $\eta_p^2 = 0.063$) (Figure 1), but did not show a significant relationship with CSF sAPP-α (not shown). The relationship between HOMA-IR and Aβ₄₂ as assayed by the INNOTEST kit showed a positive trend [$(F_{[1,63]} = 3.62$, $p = .062)$]; however, Aβ₄₂ assayed with the Triplex kit showed a modest but significant association with HOMA-IR, with higher HOMA-IR predicting higher Aβ₄₂ ($F_{[1,63]} = 4.26$, $p = .043$, $\eta_p^2 = 0.063$) (Figure 2). Furthermore, carriage of the ε4 allele significantly predicted higher levels of CSF sAPP-α ($F_{[1,63]} = 8.65$, $p = 0.005$, $\eta_p^2 = 0.121$), sAPP-β ($F_{[1,63]} = 7.74$, $p = 0.007$, $\eta_p^2 = 0.109$) (Figures 3 A&B) and P-tau₁₈₁/Aβ₄₂ ($F_{[1,63]} = 5.21$, $p = 0.026$, $\eta_p^2 = 0.076$) (Figure 4). No significant effects of HOMA-IR or *APOE* ε4 were observed on Aβ₃₈ or Aβ₄₀. No significant interactions between HOMA-IR and *APOE* ε4 were observed on any of the CSF measures.

3.2. HOMA-IR, *APOE* ε4, CSF biomarkers of AD, and Memory Performance

Linear multiple regression analysis yielded a significant interaction between HOMA-IR and P-tau₁₈₁/Aβ₄₂ on memory performance ($F_{[1,60]} = 6.14$, $p = 0.016$, $\eta_p^2 = 0.093$), such that higher HOMA-IR and greater P-tau₁₈₁/Aβ₄₂ predicted lower performance on the delayed RAVLT (Figure 5). No other significant main effects or interactions were observed.

4. Discussion

The current study investigated the relationship between HOMA-IR, AD pathology, and memory performance in middle-aged individuals enriched for AD. Diabetes and related conditions, such as IR, are associated with an increased relative risk for developing sporadic late-onset AD [1,5,6], and dysregulation of insulin signaling is thought to contribute to a cascade of neuropathological changes that promote amyloidogenic processing, neurotoxicity, and brain amyloidosis [13,26,63–65]. Brain changes associated with IR that may underlie or contribute to the pathogenesis of AD have not been well studied in humans, particularly in midlife in the absence of metabolic disorders or cognitive decline. IR may be a modifiable risk factor and thus regulation of normal insulin signaling is an important target for early intervention, one that may be particularly relevant to persons who harbor genetic risk or have a parental family history of dementia due to AD.

Our findings revealed that higher HOMA-IR was associated with increased CSF sAPP-β, but not sAPP-α. One possible mechanism for this is that IR may facilitate cleavage of APP through the amyloidogenic β-secretase pathway. Evidence from animal studies shows that IR upregulates levels of BACE1 and promotes amyloidogenic β-amyloid peptide production [63]. An alternative explanation is that the observed association between higher HOMA-IR and CSF sAPP-β is indicative of IR-mediated demobilization of low-density lipoprotein receptor-related protein (LRP) known to participate in the degradation of APP [66]. At least one study has provided evidence for this notion showing that intravenous insulin infusion in

AD patients resulted in modified levels of plasma APP postulated to be driven by insulin effects on mobilized LRP-mediated APP degradation [67]. Further research is needed to determine relationships between IR and LRP function.

Our findings also revealed that higher HOMA-IR was associated with higher CSF A β ₄₂ as measured with the triplex assay. It is known that cleavage of APP through the β -secretase pathway results in the formation of sAPP- β and the eventual generation and deposition of A β . While the generation of A β ₄₂ is complex and the relationship between sAPP- β and A β ₄₂ is not 1:1, it is possible that the results reflect a relationship between IR and early phase of A β ₄₂ generation prior to IR associated deposition. Prior research from our group has shown that IR predicts brain amyloid deposition in late middle-aged adults at risk for AD as indexed by [C-11] Pittsburgh compound B (PiB) positron emission tomography [26]. Some studies have failed to find a relationship between IR and amyloid pathology [21,25]; however, the participants studied here are younger than in other studied cohorts, consistent with a possible early relationship between IR and A β ₄₂ generation. Longitudinal studies that include CSF and PET-based markers of amyloid from asymptomatic state to disease state are necessary to map out longitudinal trajectories of amyloid deposition and its contribution to AD.

IR may also be linked to pathological processes via amyloidosis by decreasing availability of IDE [35]. This large zinc-binding protease has a high affinity for extracellular insulin and binds to and degrades insulin. IDE also binds to and breaks down A β proteins preventing accumulation [68,69]. Animal models have provided evidence that IR is associated with reduced IDE levels, impaired A β protein degradation and increased amyloidosis [37]. Animal studies also indicate that selective removal of the IDE gene results in more than a 50% decrease in A β degradation and a significant increase in A β deposition [35,37]. Transgenic mouse models of IR have provided evidence that IDE may not only be affected by IR through interference of IDE-mediated degradation of A β but may also decrease IDE expression and activity [37]. Furthermore, recent research has provided evidence that IDE also degrades sAPP- β in the intracellular domain [68] and that elevated levels of sAPP- β are observed in homozygous deletions of the IDE gene [35]. These results are aligned with the notion that IR may lead to increased levels of sAPP- β through mechanisms that involve diminished IDE availability and reduced sAPP- β degradation.

Carriage of the ϵ 4 allele of *APOE* was also a significant predictor of CSF markers of AD pathology. *APOE* ϵ 4 status showed a positive relationship with sAPP- α , sAPP- β , and the ratio of P-tau₁₈₁/A β ₄₂, although significant relationships between *APOE* ϵ 4 carriage and A β ₄₂ or P-tau₁₈₁ were not observed. These results suggest that P-tau₁₈₁/A β ₄₂ may be a more sensitive marker of AD pathology in preclinical populations compared to a single marker of disease. *APOE* ϵ 4 status is a strong predictor of AD pathology and is believed to act on the A β pathway. While *APOE* ϵ 4 status is primarily associated with a reduction in clearance and increased A β aggregation and deposition [70], we also found that *APOE* ϵ 4 carriers showed higher sAPP- α potentially implicating overall greater production of amyloid precursor protein. Additional studies will be needed to further assess the effect of *APOE* ϵ 4 on soluble APP.

Interestingly, we found that high HOMA-IR and P-tau₁₈₁/Aβ₄₂ concomitantly act to impair memory performance on the RAVLT delayed memory score. Long-term memory tasks, such as the one examined here, are dependent on the hippocampus, a medial temporal lobe structure negatively affected by IR [71–73] and among the first regions to show structural and functional changes in AD [74–77]. Insulin homeostasis is an instrumental component of the signal transduction cascades that underlie memory consolidation and long-term memory function [14,78,79]. Research from our group has shown that IR in midlife is associated with hypometabolism in brain regions involved in episodic memory, including the hippocampus [19]. Taken together, the findings suggest that insulin dysregulation may have deleterious effects on memory performance that precede or act in concert with early pathological AD changes leading to subclinical memory dysfunction. It is worth noting that while we found that high HOMA-IR and AD pathology interacted to impair memory function, we did not observe an interaction with ε4 allele carriage. This finding suggests that while AD pathology (i.e., P-tau/Aβ₄₂) appears to be more prominent in *APOE* ε4 carriers than noncarriers in midlife, the combined deleterious effects of IR and AD pathology on memory performance is observed across carriers and noncarriers alike.

Some limitations should be noted. Overall, the effects of HOMA-IR and *APOE* ε4 on AD pathology and memory were small. Given that the group under study is nondemented and it may be expected that only a subset will ultimately develop dementia, the findings merit replication in a larger sample, as well as evaluation in a longitudinal design. Furthermore, while we have focused on mechanisms related to insulin, the role of glucose in memory cannot be overlooked. Glucose enhances cognitive function among older adults [80], and blood glucose levels are intimately tied with insulin function. HOMA-IR provides a measure of IR calculated from fasting blood glucose and insulin levels [58]. Utilizing the euglycemic-hyperinsulinemic clamp method would provide a closer measure of insulin sensitivity. It is important to note, however, that the majority of our study sample was normoglycemic (~87%), suggesting a particular role of insulin in the pathogenesis of AD in midlife. Lastly, while the current findings provide valuable insight that IR is associated with AD-like neuropathology in midlife that may be targeted for intervention, the results are not predictive and merit longitudinal investigation.

5. Conclusions

The current results are novel, as this is one of the first studies to examine HOMA-IR, CSF biomarkers of AD pathology, and memory function in a cognitively healthy midlife sample. Overall, our findings provide evidence that in early aging IR plays a role in increased markers of pathological processes associated with AD prior to the onset of clinically significant symptoms of cognitive impairment or diagnosis of metabolic disorders. Both IR and carriage of the *APOE* ε4 allele were associated with CSF biomarkers of AD in persons with parental history of late-onset AD. Furthermore, we show that IR and AD pathology interact to impair long-term memory function in healthy middle-aged adults. Given that IR is a potentially modifiable risk factor, especially prior to a diagnosis of type 2 diabetes, the findings have implications for designing interventions that improve or maintain normal insulin signaling to potentially delay or ameliorate AD-related neuropathology in midlife.

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Figure 1. Relationship between HOMA-IR (log10) and CSF sAPP-β showed a modest but significant association across all participants. *Significant at $p < 0.05$. Units are adjusted for age, sex and BMI.

Figure 2.

Relationship between HOMA-IR (log10) and CSF Aβ₄₂ showed a modest but significant association across all participants. *Significant at $p < 0.05$. Units are adjusted for age, sex and BMI.

Figure 3.

Figure 3A. Comparison of CSF sAPP- α in *APOE* $\epsilon 4$ carriers compared to noncarriers. Error bars represent the standard error of the mean. *Significant at $p < 0.01$.

Figure 3B. Comparison of CSF sAPP- β in *APOE* $\epsilon 4$ carriers compared to noncarriers. Error bars represent the standard error of the mean. *Significant at $p < 0.01$.

Figure 4. Comparison of CSF P-tau₁₈₁/Aβ₄₂ in *APOE* ε4 carriers compared to noncarriers. Error bars represent the standard error of the mean. *Significant at $p < 0.05$.

Figure 5.

Interaction between HOMA-IR (log10) and CSF P-tau₁₈₁/Aβ₄₂ on delayed memory performance. *Significant at $p < 0.05$. Memory performance was adjusted for sex, age and education. HOMA-IR (log 10) is presented as a median split for graphing purposes only. Individuals with lower HOMA-IR are shown in blue. Individuals with higher HOMA-IR are shown in green.

Table 1

Participant demographics, glucoregulatory and genetic data

Demographic, glucoregulatory, and genetic data	
Sex	55 female, 15 male
Age (years)	57.7 ± 5.1
Education (years)	15.9 ± 2.5
BMI (kg/m ²)	28.66 ± 5.08
HOMA-IR	2.26 ± 1.24
Diabetes status	
Normoglycemic (fasting glucose < 100 mg/dL)	61
Prediabetic (fasting glucose < 126 mg/dL)	9
APOE genotype	
<i>APOE</i> ε4 (hetero- or homozygous)	33 (47%)