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Insulin and Sex Interactions in Older Adults with Mild Cognitive Impairment

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Abstract

Alzheimer's disease (AD) and other dementias are likely preceded by a protracted preclinical state. Thus, identification of biomarkers that signal potential points of intervention during this prodromal phase (during which patients are largely able to compensate for their cognitive deficits) is of paramount importance. Insulin is a pancreatic hormone with potent central nervous system effects, and insulin dysregulation has been implicated in the pathogenesis of both AD and vascular dementia. The aim of the current study was to determine whether circulating insulin differs as a function of mild cognitive impairment (MCI) diagnosis, and whether this relationship is mediated by sex and apolipoprotein E (APOE) genotype. A sample of 549 nondemented participants aged 65 and over from the Adult Changes in Thought community-based cohort underwent cognitive testing and blood draw to determine fasting levels of plasma insulin. Subjects were categorized as having normal cognitive functioning, amnesic MCI, or nonamnesic MCI. Results showed that the relationship between insulin and diagnostic category is moderated by sex, such that men with nonamnesic or amnesic MCI have higher fasting plasma insulin than cognitively normal men, while women with amnesic MCI have lower fasting plasma insulin than cognitively normal women. Exploratory analyses suggest that APOE 4 genotype may further influence the relationship between sex and insulin. Future research will help determine whether insulin dysregulation results in differential effects on vascular function and AD pathology as a function of sex and/or APOE genotype.

Keywords

Age-related memory disorders; aging; Alzheimer's disease; cognition; dementia; hyperinsulinemia; insulin; vascular

INTRODUCTION

An expanding body of evidence links insulin resistance, a reduction in the capacity of insulin to effectively carry out its biologic actions, to an increased risk for cognitive impairment and dementia [1–3]. Chronic peripheral hyperinsulinemia, a compensatory reaction to insulin resistance, leads to reduced insulin levels in brain [4]. Insulin has been shown to modulate amyloid- (A β) peptide [5], and impaired brain insulin function is associated with reductions in A β clearance [6–9]. In addition to the likely independent effects of chronic hyperinsulinemia on Alzheimer's disease (AD)-related pathophysiology, the insulin resistance syndrome also greatly increases the risk for several chronic disease conditions, including type 2 diabetes, cardio- and cerebrovascular disease, obesity, hyperlipidemia, and hypertension [10–14]. Such insulin resistance-related syndromes are associated with an increased likelihood of developing both AD and vascular dementia [15–19]. The negative effects of insulin resistance may be present years before patients are diagnosed with frank diabetes, as the pancreas is typically able to compensate for glucose disruptions for some time by producing sufficient amounts of insulin to keep glucose levels low. Thus, for some people, high fasting levels of insulin during this “silent” phase may signal the presence of insulin resistance, and in turn the beginning of a cascade of negative events in the brain associated with AD and other dementias. Conversely, reduced insulin secretory capacity as a result of pancreatic beta cell dysfunction is an early feature of type 2 diabetes [20], and thus abnormally low fasting insulin may also be a marker that presages the onset of diabetes. Indeed, recent evidence suggests the possibility of multiple pathways to diabetes characterized by differences in insulin sensitivity and secretion [21]. Thus, pre-diabetes states may result in higher or lower levels of circulating insulin depending upon which particular mechanism underlies the insulin dysfunction.

Because insulin resistance and diabetes are associated with early vascular and AD-related neuropathological processes, negative effects of insulin resistance on cognitive functioning may arise prior to the development of the clinical dementia syndrome. The term mild cognitive impairment (MCI) refers to mild reductions in memory and/or other cognitive abilities in the absence of significant functional impairments [22, 23]. Often conceptualized as prodromal dementia, the diagnosis of MCI is associated with a significantly increased risk for developing AD and other dementia syndromes [24]. Thus, a primary focus of dementia research is identifying effective therapeutic interventions during this prodromal phase, when patients are capable of self-care and remain able to engage in an independent lifestyle. The complex and heterogeneous nature of MCI, however, has led to a recognized need for identification of specific cognitive patterns (e.g., amnesic versus nonamnesic impairment) and biomarkers that are most predictive of dementia risk [22].

Given the relationship between insulin resistance, cognitive impairment, and dementia, reports that fasting plasma insulin may differentiate between cognitively normal and impaired individuals fuel speculation that insulin resistance may represent an important point of intervention in older adults. The literature is rife, however, with contradictory reports concerning the relationship between circulating plasma insulin and cognitive functioning. High fasting plasma insulin has been associated with poorer cognition, cognitive decline over time, and dementia risk in both middle age and late life [25–29]. Others have shown that fasting plasma insulin has a nonlinear relationship with regard to

cognitive function and dementia risk [30], findings that suggest either too little or too much circulating insulin may be harmful. These seemingly incongruous reports raise the possibility that other factors may interact with insulin to produce group-specific effects on cognition. For example, there is increasing evidence that sex may play an important role in the development and presentation of insulin resistance-related conditions (e.g., metabolic syndrome) [31, 32], and sex differences in insulin sensitivity have been reported in adults with AD [33]. In addition to sex, several previous studies suggest that insulin-related effects on cognition and dementia risk may be in part dependent upon genetic factors, such that peripheral insulin resistance may be more characteristic of adults with AD without an APOE 4 allele [34–36]. One such study demonstrated that in older adults with AD, those without an APOE 4 allele showed lower glucose-mediated insulin disposal rates (indicating greater insulin resistance) during a hyperinsulinemic clamp procedure; female subjects also demonstrated lower insulin-mediated glucose disposal rates than male subjects, independent of APOE genotype [33]. These results suggest that insulin resistance may be more likely to be an underlying factor in AD pathology in certain patient groups, which in turn may be more likely to benefit cognitively from insulin-sensitizing treatments.

The current study examines the relationship between fasting plasma insulin and MCI and its subtypes in a population-based sample of older adults, with the goal of reconciling these seemingly incongruous reports. Given that the effects of insulin resistance on chronic disease are potentially modulated by both sex and APOE genotype, we examined the association between these factors and fasting plasma insulin in older adults with and without cognitive impairment.

MATERIALS AND METHODS

Subjects

The sample consisted of 549 participants from the Adult Changes in Thought (ACT; E. Larson, PI) study. Study methods for ACT have been published in detail elsewhere [37, 38]. Briefly, this population-based cohort, recruited from a random sample of Seattle area Group Health subscribers, consists of adults aged 65 and older who were nondemented at the time of enrollment. At study entry and biennially thereafter, participants undergo cognitive screening, physical function and functional status assessments, and general medical history review. In addition to tests of specific cognitive abilities, participants are administered a global measure of cognitive functioning, the Cognitive Abilities Screening Instrument (CASI) [39]. Participants who obtain scores falling below a cutoff of 86 out of 100 total possible points on the CASI are subsequently referred for a full dementia evaluation. Such cases are adjudicated at a consensus diagnosis conference consisting of physicians and psychologists with expertise in dementia diagnosis. Dementia diagnosis is made using standard diagnostic criteria for dementia (DSM-IV) [40] and probable/possible Alzheimer's disease (NINCDS-ADRDA criteria) [41].

During an 18-month period (June 1, 2008 – December 31, 2010), all nondemented subjects who presented for their biennial ACT study visit were approached to undergo a fasting blood draw in order to measure plasma levels of insulin. A total of 1,494 subjects completed a study visit during this time, 1,385 of whom were nondemented. Of these, 638 (43%) received a fasting plasma blood draw. Five participants were missing sufficient test data such that a determination of the presence or absence of MCI could not be made and thus were excluded from all analyses. Subjects who reported a diagnosis of type 2 diabetes ($n = 84$) were also excluded, as these participants are likely to have variations in fasting plasma insulin according to their treatment regimens and stage of metabolic disease. The resulting sample of 549 participants was demographically representative of the overall nondiabetic

sample ($n = 1,101$, excluding 214 diabetics and 70 with missing cognitive data) (see Table 1).

This study was conducted in compliance with guidelines on human experimentation and approved by the institutional review boards of the University of Washington, Group Health Research Institute (GHRI), and the VA Puget Sound Healthcare System. All participants provided written consent for participation in study procedures via consent processes authorized by these review boards.

Cognitive examination

All ACT participants underwent cognitive testing at their biennial examination in the following areas: immediate and delayed verbal recall (Logical Memory from the Wechsler Memory Scale-revised [WMS-R] [42]), visual recall (Constructional Praxis-Delayed from the Consortium to Establish a Registry for Alzheimer's Disease [CERAD] neuropsychological battery [43]), visuospatial abilities (CERAD Constructional Praxis), attention/concentration (Trailmaking Test, Parts A & B [44]), and verbal fluency (letter and supermarket items [45, 46]). Z-scores were calculated from raw test scores using published normative data [49].

MCI diagnosis

Nondemented participants were assigned an MCI diagnosis if any cognitive test z-score fell 1.5 standard deviations (sd) or more below published normative means. A functional assessment scale [50] was administered to determine whether the presence of significant deficits in the ability to perform activities of daily living warranted further investigation of dementia status. This scale was reviewed by a neuropsychologist; participants who endorsed impaired functional status were referred for a full dementia evaluation. Subjective cognitive complaints were assessed in order to rule out dementia, but were not required for diagnosis. MCI diagnosis was further divided by subtype: a diagnosis of *amnesic MCI* (MCI-a) was assigned if the participant's score was at least 1.5 sd below the standard normative mean for age on either delayed verbal recall or recall of designs, and a diagnosis of *nonamnesic MCI* (MCI-na) was assigned if the participant had normal scores on recall measures but was determined to be impaired (at least 1.5 sd below the normative mean) on one or more nonamnesic measures. Participants who had both amnesic and nonamnesic deficits were categorized as having MCI-a.

Fasting plasma insulin

Plasma was collected by study phlebotomists during a morning visit either at the participant's home or in the GHRI clinic following a 12-hour fast. Samples were immediately placed on ice and spun in a cold centrifuge for 15 minutes; after which time plasma was aliquoted into storage tubes and flash frozen at -70°C . Insulin assays were carried out as previously described [33, 35].

APOE genotyping

APOE genotyping was performed as part of the ACT study procedures in accordance with accepted methods [51]. APOE genotype was available for 455 subjects (83% of the sample). The APOE sample participants did not differ from the overall ACT sample or the insulin study sample in terms of age, education, CASI score, body mass index (BMI), or waist-hip ratio.

Analyses

Distribution of insulin values was skewed, thus these values were log-transformed. Insulin levels were analyzed using analysis of variance (ANOVA), with MCI diagnosis (normal, MCI) and sex as independent variables. Insulin levels were then similarly analyzed using MCI subtype (normal, MCI-a, MCI-na) in place of the combined MCI group. Subsequently, insulin levels within the APOE subgroup were subjected to a three-way ANOVA, with diagnosis, sex, and APOE genotype (ϵ 4 ϵ -, 4 ϵ +) included in the model. Following a significant omnibus diagnosis by sex by APOE interaction, subgroup analyses by APOE genotype were performed using ANOVA to determine whether the insulin-sex interaction was present for both groups. For all analyses, age, BMI, and education were entered as covariates. Pairwise comparisons of adjusted means were performed using *t*-tests. *T*-tests and chi-square tests were performed to examine differences between groups on demographic variables and study population characteristics. All statistical analyses were conducted using Stata 11 (Stata Corp., College Station, TX).

RESULTS

Prevalence of MCI

Prevalence of MCI (either amnesic or non-amnesic) in the overall nondiabetic sample ($n = 1101$) was 44.7% (15.4% amnesic, 29.3% nonamnesic). Prevalence of MCI in the plasma insulin sample ($n = 549$) was 42.9% (13.8% amnesic, 29.1% non-amnesic), which was consistent with the overall group ($\chi^2 = 0.36$, $p = 0.55$). The proportion of males diagnosed with MCI (39.4%) did not differ significantly from the proportion of females diagnosed with MCI (44.8%), again consistent with the overall nondiabetic sample (43.4% and 45.6%, respectively).

Participant characteristics

Demographic and clinical characteristics of the sample are presented in Table 1. Cognitively normal participants had more years of education than participants with either MCI-a or MCI-na, and the MCI-a group was significantly older than both the cognitively normal and nonamnesic groups ($p < 0.01$). The cognitively normal group had higher CASI scores than both the MCI-a and MCI-na groups ($p < 0.001$), and the MCI-na group had higher average CASI scores than the MCI-a group ($p < 0.001$). Within each diagnostic group, male and female participants had similar distributions of age, CASI score, and BMI. As expected, waist-hip ratio was significantly higher for men than for women ($p < 0.001$), and males had more years of education than females ($p < 0.001$), patterns that were consistent across diagnostic groups.

Mean (sd) fasting plasma insulin for the overall group was 15.0 (6.8) mU/L. In comparison, mean (sd) fasting plasma insulin for the excluded diabetic group ($n = 84$) was 24.4 (17.6) mU/L. Group mean differences for fasting plasma insulin with regard to diagnosis, gender, and APOE status are discussed in the following sections.

Fasting plasma insulin and MCI diagnosis

BMI was a significant covariate in all analyses, while age and education were not. A low variable inflation factor ($VIF = 1.01$) suggests that the magnitude of multicollinearity between BMI and insulin did not substantially influence the results. The analysis of fasting insulin indicated a significant diagnosis by sex interaction for both overall MCI diagnosis ($F_{(1,505)} = 6.72$, $p = 0.01$; Cohen's $f = 0.12$) and when MCI subtypes were included ($F_{(2,503)} = 4.42$, $p = 0.01$; Cohen's $f = 0.13$). Overall, men with MCI had higher fasting plasma insulin than cognitively normal men ($p = 0.01$), and than women with MCI ($p = 0.02$). Relative to cognitively normal men, fasting insulin levels were higher in men with MCI-na

($p < 0.05$), and trended higher in men with MCI-a ($p = 0.08$). In contrast, women with MCI-a had significantly *lower* fasting plasma insulin levels than cognitively normal women ($p = 0.01$) and men with MCI-a ($p = 0.005$). There was a trend for higher insulin in women with MCI-na as compared to their MCI-a counterparts ($p = 0.07$) (Fig. 1). Despite sex differences in waist-hip ratio, when this variable was entered in the analysis of insulin as a covariate, the observed diagnosis by sex interaction remained unchanged.

Fasting plasma insulin, sex, and APOE

The analyses of fasting insulin with APOE in the model indicated a significant diagnosis by sex by APOE (4−, 4+) interaction for both overall MCI diagnosis ($F_{(4,414)} = 2.45$, $p = 0.05$; Cohen's $f = 0.15$) and when subtypes were included ($F_{(7,410)} = 2.37$, $p = 0.02$; Cohen's $f = 0.20$). In subgroup analyses by APOE genotype, there was a significant diagnosis by sex interaction for the 4− group only, again for both overall MCI diagnosis ($F_{(1,306)} = 7.41$, $p = 0.01$) and when MCI subtypes were included ($F_{(2,304)} = 5.13$, $p = 0.007$; Cohen's $f = 0.18$), indicating that the two-way interaction described above (diagnosis by sex) holds true for the 4− adults but not the 4+ adults. In the 4− group, women with MCI-a had lower plasma insulin levels than their normal counterparts ($p = 0.05$), while men with MCI-a had significantly higher levels than cognitively normal men ($p = 0.03$) or women with MCI-a ($p = 0.007$). In contrast, there was a main effect of diagnosis in the 4+ group ($F_{(2,103)} = 4.83$, $p = 0.01$; Cohen's $f = 0.31$) only when subtypes were included in the analyses; these results were not qualified by a sex-diagnosis interaction. Post hoc analyses indicated that the MCI-na group had significantly higher plasma insulin levels than either the cognitively normal group ($p = 0.01$) or the MCI-a group ($p = 0.005$) (Fig. 2).

DISCUSSION

Results from the current study demonstrate that fasting insulin levels vary according to MCI diagnostic subtype and sex, and thus suggest a complex relationship between insulin and cognitive functioning in nondiabetic older adults. Multiple observational studies demonstrate a connection between diabetes and increased risk for cognitive impairment and dementia [52, 53]; however, reports from nondiabetic cohorts that examine markers of insulin resistance such as hyperinsulinemia have been less consistent. Several studies report that cognitive decline coincides with increasing hyperinsulinemia [25–29], while others have shown a nonlinear relationship, such that both high and low levels of circulating insulin are associated with poorer cognitive functioning and increased dementia risk [30]. A recent prospective study (combining the PROSPER and Rotterdam cohorts) however, found no association between insulin resistance and fasting glucose levels for baseline cognitive measures and subsequent cognitive decline [54]. In addition, reports suggest that both high and low levels of insulin secretion are related to cognitive impairment and dementia risk, resulting in an inverted U-shaped relationship between fasting insulin levels and cognitive functioning [36, 55–57]. Our results may help clarify factors that determine this U-shaped curve by suggesting that plasma insulin differs according to cognitive diagnosis, but only when diagnostic subtype, sex, and APOE genotype are taken into consideration.

Our results show that women with MCI-a had *lower* fasting plasma insulin levels than all other groups. A potential explanation for these findings, although speculative, is related to reduced insulin secretion that may occur as a result of oxidative damage to pancreatic beta cells in some people with early or pre-diabetes [20]. Along these lines, Burns and colleagues reported that adults with early AD who had lower insulin levels in response to a glucose challenge showed more cognitive impairment and brain atrophy, results that may suggest impaired insulin secretory capacity in these subjects [58, 59]. This finding supports our premise that women with MCI-a may have lower fasting insulin levels on average due to impaired insulin secretion, a hypothesis that cannot be confirmed in the present study.

Interestingly, insulin levels in brain may be reduced at an earlier stage of dementia in women. Gil-Bea et al. [60] recently reported reduced CSF insulin levels in both men and women with AD, but only in women with MCI. Conversely, our results demonstrate elevated fasting plasma insulin levels in older men with MCI-a or MCI-na, although the effect was more robust for *MCI-na*, a cognitive pattern that has been associated with impaired vascular functioning [61]. The negative impact of insulin resistance and compensatory hyperinsulinemia on vascular functioning is well-documented [62, 63], and the prevalence of vascular disease is elevated in those with consistently high insulin levels [64]. The Honolulu Heart Program, which specifically measured fasting insulin in older men, found that hyperinsulinemia was associated with increased coronary artery disease, angina, peripheral vascular disease, stroke, dyslipidemia, hypertension, and obesity [65, 66]. Our results suggest that non-diabetic men with higher plasma insulin levels may also be at greater risk for impaired cognitive function associated with vascular disease.

Our findings indicating sex differences with regard to insulin levels and cognitive functioning, although unique, are not surprising. Sex differences in the development and expression of chronic disease, including diabetes, have long been noted. Endogenous sex hormones may play a role in the relative risk for developing diabetes, such that higher circulating androgens are associated with greater diabetes risk in women and lower risk in men [31]. As visceral fat accumulates following menopause, there is an associated increase in androgen receptors, which likely influences the increased prevalence of type 2 diabetes in women in this age bracket [32]. As mentioned above, diabetes appears to raise the risk for cardiovascular disease differently in men and women. Together with our findings, it is possible that cognitive function and dementia risk are differentially affected by disruptions in insulin activity as a function of sex.

Our APOE results are consistent with reports indicating a relationship between insulin resistance, cognitive functioning, and dementia risk may be most commonly observed for adults without an $\epsilon 4$ allele [34–36]. This observation suggests that APOE- $\epsilon 4$ carriage and insulin resistance may represent two pathways that lead to similar disease endpoints. In men without an $\epsilon 4$ allele in our sample, plasma insulin was higher for MCI-a than for men with normal cognitive functioning, while women without an $\epsilon 4$ allele had lower plasma insulin as described above. These results suggest the possibility that $\epsilon 4$ - participants' risk for MCI-a (and thus AD) may be associated with sex-specific differences in plasma insulin. Interestingly, in $\epsilon 4$ + adults, elevated fasting insulin was associated with an increased prevalence of nonamnesic MCI only, irrespective of sex. Again, this suggests that hyperinsulinemia may exert negative vascular effects, independent of AD-associated neuropathology. These findings are exploratory, however, due to small cell sizes in the $\epsilon 4$ + group, and thus limit our ability to interpret these findings too strongly.

One unique aspect of this study is the relatively advanced age of the participants. There is increasing evidence that multiple chronic health conditions, including hypertension, obesity, and hyperlipidemia, are associated with adverse consequences related to cognitive function and dementia risk primarily when present during middle age. Interestingly, it appears that during perimenopause, women undergo a “metabolic shift” that occurs in conjunction with the decline in circulating sex hormones. Nondiabetic women demonstrate higher fasting insulin and decreased insulin sensitivity in comparison with their male counterparts when measured at midlife. This pattern is reversed in both older and younger subjects, with men in these age groups typically showing decreased insulin sensitivity as compared to women [68]. This dramatic and relatively sudden metabolic change occurs at the same time as the well-documented increased risk for cardiovascular disease in women. Thus, the negative associations of high fasting plasma insulin in women may be more apparent when measured during midlife. Further exploration into the role of circulating insulin at midlife and later

will help to elucidate whether age and sex differentially influence the effects of peripheral hyperinsulinemia, which in turn impact overall AD prevalence.

Due to feasibility constraints in this large, elderly sample, we were unable to obtain a more accurate estimate of insulin resistance other than fasting plasma insulin, such as a hyperinsulinemic euglycemic clamp or modified insulin suppression test, nor did we have access to fasting glucose levels which would permit calculation of the homeostasis model assessment of insulin resistance (HOMA-IR). Such techniques provide more sensitive measurement of insulin resistance than fasting plasma insulin, and may represent valuable future tools with which to further explore the association between insulin resistance and cognitive function in late life. We also did not have access to sex hormone levels in this sample; future analyses that examine the relationship between sex hormones, insulin, and cognition in older adults will help to further illuminate the nature of the sex differences described here. In addition, we were unable to obtain clinical and laboratory data regarding the presence of diabetes, and thus we relied on self-reported diabetic history. Insulin values reported throughout the literature are consistently skewed to the right, suggesting that most “normal” samples include participants with undiagnosed diabetes. Our nondiabetic sample had mean insulin values that were significantly lower than the excluded diabetic group by self-report; nonetheless, the skewed distribution suggests that the study sample likely included participants with as yet undiagnosed diabetes. This method of relying on self-reported diabetes, however, is consistent with other similar studies [27, 28], and permits the exclusion of people for whom fasting insulin may be affected by anti-diabetic medication use.

Another limitation of this study is the cross-sectional design, which does not permit examination of the effects of plasma insulin on cognition over time in either men or women. Longitudinal follow up of this sample, once available, will undoubtedly provide valuable information concerning the effects of baseline fasting plasma insulin on cognition over time, and eventually help to clarify whether higher plasma insulin levels lead to a differential relative risk for dementia with regard to sex and APOE status. Also given the large sample size, participants were diagnosed with MCI based on psychometric performance, and were not examined by a clinician unless their CASI score fell below a pre-determined threshold or unless they reported notable functional problems that warranted a full evaluation to identify dementia (as opposed to identifying MCI). Finally, when the sample was divided into groups on the basis of diagnostic subtype, sex, and APOE genotype, some of the resulting cell sizes were quite small, thus limiting confidence regarding the results of subgroup analyses.

Our findings demonstrating that men and women with amnesic and nonamnesic MCI had different fasting plasma insulin levels, suggest that either too much or too little circulating insulin may have detrimental consequences on cognitive functioning in older adults, and that this relationship may depend upon sex and APOE genotype. If confirmed, these results may indicate disparate processes by which insulin resistance can exert a negative influence in the brains of older adults. Future studies will help determine whether insulin resistance, diabetes, and cardiovascular disease produce differential effects on cognition and dementia risk in men and women.

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Fig. 1.

Log mean insulin values by MCI diagnostic subtype (normal, MCI-a, MCI-na) and sex, with standard errors of the mean represented in the error bars. Means are statistically adjusted for age, education, and BMI.

Fig. 2.

Log mean insulin values by MCI diagnostic subtype (normal, MCI-a, MCI-na), sex, and APOE genotype, with standard errors of the mean represented in the error bars. Means are statistically adjusted for age, education, and BMI.

Table 1

Demographic characteristics of the overall nondiabetic ACT participant sample and the study sample

	General sample (<i>n</i> = 1,101)	Insulin sample (<i>n</i> = 549)	Cognitively normal		Amnesic MCI		Nonamnesic MCI	
			Male (<i>n</i> = 146)	Female (<i>n</i> = 167)	Male (<i>n</i> = 30)	Female (<i>n</i> = 46)	Male (<i>n</i> = 69)	Female (<i>n</i> = 91)
Age								
Mean (sd)	79.4 (7.4)	79.0 (7.1)	78.0 (7.1)	78.7 (7.0)	82.5 (7.5)	81.2 (7.2)	79.2 (7.1)	78.9 (7.0)
Education								
Mean (sd)	15.5 (3.1)	15.8 (3.1)	17.2 (3.0)	16.1 (2.5)	15.9 (3.3)	14.2 (2.8)	15.5 (3.4)	14.1 (2.8)
CASI								
Mean (sd)	94.3 (4.5)	94.8 (4.2)	96.2 (2.8)	96.5 (2.7)	91.5 (5.5)	91.2 (4.7)	93.6 (5.0)	93.1 (4.6)
BMI								
Mean (sd)	27.1 (7.2)	27.1 (5.1)	26.8 (5.1)	27.2 (5.5)	26.8 (3.0)	26.5 (6.1)	27.4 (4.0)	27.6 (5.4)
Waist-hip ratio								
Mean (sd)	0.90 (0.1)	0.90 (0.1)	0.95 (0.1)	0.87 (0.1)	0.94 (0.1)	0.86 (0.1)	0.96 (0.1)	0.86 (0.1)
4								
± (<i>n</i>)	657/233	337/118	102/31	101/33	17/8	27/9	42/14	48/23