A 10-year follow-up of adiposity and dementia in Swedish adults aged 70-years and older

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Abstract

Background:

Adiposity measured in mid- or late-life, and estimated using anthropometric measures such as body mass index (BMI) and waist-to-hip ratio (WHR), or metabolic markers such as blood leptin and adiponectin levels, is associated with late-onset dementia risk. However, during later life this association may reverse and aging- and dementia-related processes may differentially affect adiposity measures.

Objective:

We explored associations of concurrent BMI, WHR, and blood leptin and high molecular weight adiponectin levels with dementia occurrence.

Methods:

924 Swedish community-dwelling elderly without dementia, aged 70 years and older, systematically-sampled by birth day and birth year population-based in the Gothenburg city region of Sweden. The Gothenburg Birth Cohort Studies are designed for evaluating risk and protective factors for dementia. All dementias diagnosed after age 70 for 10 years were identified. Multivariable logistic regression models were used to predict dementia occurrence between 2000-2005, 2005-2010, and 2000-2010 after excluding prevalent baseline (year 2000) dementias. Baseline levels of BMI, WHR, leptin and adiponectin were used.

Results:

Within 5 years of baseline, low BMI (<20 kg/m^2) was associated with higher odds of dementia compared to those in the healthy BMI category (≥ 20-24.9 kg/ m^2). Compared to the lowest quartile, leptin levels in the second quartile were associated with lower odds of dementia in women ($p<0.05$).

Conclusion:

In late-life, anthropometric and metabolic adiposity measures appear to be differentially associated with dementia risk. While BMI and leptin levels are highly positively correlated, our results show that their association with dementia at age ≥ 70 years, is asynchronous. These data suggest that with aging, the complexity of the adiposity exposure may increase and suggests metabolic dysregulation. Additional studies are needed to better understand this complexity.

Introduction

In later life, lower body mass index (BMI), being underweight by definition, and declining BMI (despite one's BMI level at onset of decline), are associated with greater risk of late-onset dementias [1, 2]. In mid- or adult life, higher BMI is prospectively associated with dementia risk [1]. This difference in the mid-life *versus* late-life BMI-dementia risk association is often referred to as the 'obesity paradox' and evidence of reverse causality [3].

Anthropometric characteristics are sculpted by amount and distribution of adipose tissue. Changes in this important tissue result from lifetime variations in energy balance, sociocultural background, and epigenetic phenomena, and develop secondarily to central pathophysiological changes in preclinical and clinical dementia [4]. Therefore, adiposity indicators like BMI, waist-hip ratio (WHR), and circulating blood levels of adipokines, such as leptin and adiponectin, are potential risk markers for dementia [5-8]. Since adipose tissue is the primary source of both of these adipokines, leptin and adiponectin are good biomarkers of this tissue's metabolic activity.

There is limited and ambiguous published research regarding the link between adipokine levels and sporadic, late-onset dementias [9, 10]. However, leptin is associated with insulin resistance and brain health,[11, 12] and is the adipose tissue hormone [13] most studied in association with brain structure and function. Leptin has numerous effects on brain development [14], and potentially on brain health in cognition and aging. Peripheral leptin enters the central nervous system and interacts with specific areas of the brain such as the hypothalamus and hippocampus [15]. In addition to crossing the BBB [16], several studies indicate that

leptin is also produced in the brain, for example in the hypothalamus, cortex and cerebellum [17, 18]. Leptin has been prospectively associated with dementia over 8 years [19], but not over 24 years, from mid- to late-life [20]. Leptin is positively correlated with total and central anthropometric adiposity measures [21, 22].

Adiponectin is a visceral adipose tissue marker and exists as complex multimeric isoforms comprised of high molecular weight (HMW) hexamers and trimers [23]. It is an effective insulin sensitizer, and circulating levels are inversely correlated with insulin resistance, metabolic syndrome, adiposity, type 2 diabetes, and cardiovascular diseases. Adiponectin modulates inflammatory responses, energy expenditure (CNS and periphery), food intake (CNS), and a number of metabolic processes, including glucose regulation and fatty acid catabolism in the periphery. Since blood-brain barrier (BBB) transport mechanisms for adiponectin are unclear, blood levels may not indicate potential interactions between adiponectin and the brain [24].

We investigated the association between dementia occurrence and both anthropometric and adipokine indicators of adiposity - BMI, WHR, and blood leptin and adiponectin levels - in a 10-year prospective population-based study of Swedish adults, aged 70 years and older. Moreover, we examined whether these adiposity markers predict dementia occurrence over the short- and/or long-term. This study will further reveal the complex interplay between surrogate markers of adiposity and dementia onset.

Methods

Participants

Participants comprising the Gothenburg Birth Cohort Studies, originate from two epidemiological studies in Gothenburg, Sweden: 1) the Prospective Population Study of Women (PPSW) and 2) the Gerontological and Geriatric Population Studies (H70). Both have been described in detail previously [25-27]. Eligible participants were sampled from the Swedish Population Register based on birth date. PPSW participants were born in 1908, 1914, 1918, 1922 and 1930. H70 participants were born in 1930. Adults living in private households and residential care were included. There were 1725 eligible individuals in 2000-2001, and 1018 agreed to participate (response rate 59.0%). Among these, 857 (84.2%) consented to genetic analyses. Due to the nature of PPSW and H70, women (n=700) were 70-92 years and men (n=224) 70 years. Participants included 339 H70 females at age 70, 224 H70 males at age 70, and 361 PPSW females age 70 years and older (Fig. 1). Follow-up examinations were conducted in 2005-06 and 2009-10, and 689 participated in 2005-06 (response rate among survivors, 82.2%), and 518 in 2009-10 (response rate among survivors, 76.7%).

Those who died, or declined participation during follow-up, were traced in records from hospitals and homes for the aged, inpatient and outpatient departments in psychiatric hospitals and clinics, municipal psychiatric outpatient departments in Gothenburg, the hospital-linkage system, and death certificates [28]. All participants (or their closest relatives) gave informed consent, which was conducted in accordance to the provisions of the Helsinki Declaration. The study was approved by the Ethics Committee for Medical Research at the University of Gothenburg.

Dementia assessment

Dementia diagnoses were made according to the Diagnostic and Statistical Manual of Mental Disorders 3rd Edition Revised (DSM-III-R) [29, 30] at examinations in 2000-2001, 2005-2006 and 2009-2010. This dementia

diagnosis was made according to components of the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog). A close informant interview was conducted using IQCode [31]. Symptom domains relevant for making a dementia diagnosis include: memory (short-term, long-term), aphasia (language disturbance), apraxia (inability to carry out motor activities despite intact function), agnosia (failure to identify or recognize objects despite intact sensory function), executive function (planning, organizing, abstract thinking) and personality changes (used in DSM-IIIR criteria for dementia, not in DSM-IV or DSM-V). Participants must have evidenced significant impairment in social or occupational functioning representing significant decline from a previous level of functioning. There was also a global rating of symptom status made by the interviewer (psychiatrist or psychiatric nurse) and information from close informants related to dementia symptoms. The Comprehensive Psychiatric Rating Scale (CPRS) [32], an extensive neuropsychiatric inventory, was used to rate psychiatric symptoms and signs at face-to-face examinations. The Mini-Mental Examination (MMSE) was used as an additional evaluation of global cognitive impairment, but is not considered diagnostic by itself. In addition, the Swedish Hospital Discharge Registry provided diagnostic information for individuals discharged from hospitals since 1978. Medical records were collected from hospitals and outpatient departments in Sweden's public health care system. Incident cases of dementia up to December 31, 2010 were also based on information from the Swedish Hospital Discharge Register (ICD-10: F00.1, F01.8, F01.9, F03.9, G30.9). Thus, dementia diagnoses were obtained for all study participants, since almost all people in Sweden receive health care from the community and have an equal chance of having a medical record. Dementia was diagnosed by neuropsychiatrists at consensus meetings based on all information sources available, e.g., neuropsychiatric examinations, medical records, and close informant interviews.

Anthropometric assessments

Anthropometric measurements were conducted in the morning when participants wore light clothing at each examination[33]. Body weight was recorded to the nearest 0.1 kg, and body height was measured to the nearest 0.5 cm. BMI was calculated as kg/m^2. Waist and hip circumferences were measured to the nearest 0.5 cm. Measures of each were conducted until there was agreement within 0.5 cm.

Blood measures

Blood samples were collected after a 12-hour fast, and plasma aliquots stored at −70°C. Regarding baseline adipokine measures, control standards and participant samples were tested in duplicate using High Molecular Weight (HMW) adiponectin and leptin ELISA assays (Linco Research, Inc, St. Louis, MO 63304) in the Clinical Chemistry Department at the University of Gothenburg.

Blood lipids including cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), and triglycerides, were measured at the certified Sahlgrenska Hospital Laboratory.

DNA was extracted from blood samples according to standard procedures. *APOE* (gene map locus 19q13.2) genotyping was performed by mini-sequencing as previously described in detail [34]. Genotypes were obtained for the two SNPs (rs7412 and rs429358), which are used to unambiguously define ε2, ε3, and ε4 alleles.

Lifestyle assessments and medical history

Level of education (completing six years compulsory education or less *vs* at least compulsory education); socioeconomic status (SES, working *vs* middle/upper class); alcohol consumption and cigarette smoking (ever *vs* never use); medication use; and medical history were queried at each examination. Diagnoses of myocardial infarction, stroke, cancer, and diabetes were self-reported as well as determined by clinical examinations (ECG and blood samples), case records, hospital discharge registry, national cancer registry, and national stroke registry. Systolic (SBP) and diastolic blood pressures (DBP) were measured while participants were sitting down and at rest for at least 5 minutes. Depressive symptoms were measured using the Montgomery–Åsberg depression rating scale (MADRS) [35].

Statistical analyses

Means and standard deviations were calculated for all continuous variables, and frequencies and percentages for categorical variables. BMI, WHR, leptin and adiponectin were used in analyses as continuous, and as traditional quartiled categorical variables. We considered baseline adiposity exposures at 2000 and 2005, and percent BMI change from 2000-2005 in association with dementia occurring between 2005 and 2010. Clinically relevant BMI change was categorized as +/- > 5%, and +/- >10%. We created combined anthropometric and adipokine categories as potentially better surrogates of adiposity-associated risk [36, 37]. We cross-tabulated leptin quartiles by the four traditional BMI (underweight, <20.00 kg/m^2; healthy, 20.00 - 24.99 kg/m^2; overweight, 25.00 - 29.99 kg/m^2; and obese ≥30.00 kg/m^2) categories. In other words, those with a low leptin and low BMI were compared to those with a high leptin and high BMI, versus

either alone. Similarly, leptin quartiles were cross-tabulated by WHR (central obesity: men >0.90 cm, women >0.85).

Multivariable logistic regression analyses were used to calculate odds ratios (OR) for developing dementia over different time periods. First, regression models estimated the odds of dementia over ten years (2000-2010) given adiposity exposures measured at baseline in 2000. Second, we estimated the association between baseline adiposity indicators measured in 2000 among those without dementia and subsequent dementia occurring during two five year periods, 2000-2005 and 2005-2010. To reiterate, prevalent dementia cases at baseline were excluded from all models. In models predicting dementia by adipokines, we adjusted for BMI if the correlation between adipokine and BMI did not exceed $r \geq 0.70$.

Selection of covariates originated from a pool of potentially biologically relevant variables: age; sex; education; socioeconomic status (SES); smoking; alcohol intake; depressive symptoms; diabetes; cancer; heart attack; stroke/transient ischemic attack; hypertension; blood triglyceride, cholesterol, HDL, LDL, and glucose levels; DBP; SBP; and APOEε4 genotype. All potential covariates were included in age-adjusted logistic regression models predicting dementia over the entire follow-up period. Age, sex, SES, smoking status (ever/never), diabetes (yes/no), alcohol intake (ever/never), depressive symptoms (MADRS score > 12), and presence of at least one APOEε4 allele were significant at $p \leq 0.05$ and included in multivariable models. Two-tailed tests were used with a significance level of $p \leq 0.05$. SPSS, version 20.0 (IBM Corporation, Armonk, New York, USA), was used to perform data analyses.

Results

Overall, 924 adults (224 men and 700 women) without dementia, participated in the baseline (year 2000) examination. PPSW and H70 were representative of the population base with regard to sex; marital status; income; community rent allowance for those who could not afford housing; rate of inpatient and outpatient care in psychiatric hospitals, clinics, and municipal outpatient departments; and rates of registration with the Temperance Board (national registry for alcohol abuse). Over ten years, 134 participants developed dementia.

The average age of the participants at baseline (n=924) was 74.0 years, and when stratified by sex, the average age of men was 70.0 years and for women, 75.3 years (Table 1). Compared to men, women were more likely to be underweight and had higher plasma levels of leptin and adiponectin. Approximately 25% of the study population had at least one APOEε4 allele (27.7% in men and 24.4% in women).

Multivariable logistic regression models were used to examine the relationship between continuous baseline adiposity indicators and subsequent dementias. No associations were found between BMI, WHR, leptin or adiponectin and dementia occurrence in the entire sample over the ten year follow up (Table 2; data not shown for adipokines).

To better understand the temporality of association between adiposity markers and dementia, we divided the ten year follow-up period into two five year dementia occurrence intervals - 2000-2005 and 2005-2010 (Table 2), as has been done previously [38]. When analyzed continuously, a higher baseline BMI lowered the

odds of dementia within five years. However, using traditional BMI categories, participants with an 'underweight' BMI (< 20 kg/m^2) had higher odds of developing dementia compared to participants with a 'healthy' BMI (reference category BMI 20.00-24.9 kg/m^2) (Table 2). This finding among underweight may have driven the protective association observed when BMI was modelled as a continuous variable. This association was driven by female participants (Table 2).

In women, we also found an association between leptin levels and odds of dementia within the first five years of follow up (2000-2005, Table 3). No associations were observed in men. Baseline leptin levels in the second quartile (18.66 - 30.52 ng/mL) were associated with lower odds of developing dementia compared to leptin levels in the first quartile (≤18.65 ng/mL, reference). No associations were found between serum levels of HMW adiponectin and dementia occurrence.

Considering only dementias occurring during 2005-2010, there were no associations with baseline BMI, WHR, leptin or adiponectin (Table 2). In addition, BMI change from 2000-2005 was not associated with dementias occurring from 2005-2010 (data not shown). Combinations of anthropometric BMI or WHR risk categories by leptin quartiles did not shed any additional light on these associations (data not shown).

Discussion

In an elderly Swedish sample of women and men, we observed that a low BMI (<20 kg/m2) was associated with over a 5-fold higher odds of developing dementia within five years in women, aged 70 years and older. Given published literature on mid-life obesity and later onset dementia, this may be evidence of an obesity paradox and/or reverse causality. However, without mid-life measures, we cannot be sure. In addition, the

odds of developing dementia were 70% lower in women aged 70 years and older who had intermediate serum leptin levels based on analysis of leptin quartiles. Thus, despite a robust correlation of r =0.71 between BMI and leptin in this sample, there is a suggestion that these adiposity indicators were differentially associated with development of dementia within 5 years of measurement in elderly women. Other studies in middle-aged and elderly women have suggested contradictory associations between anthropometric versus leptin levels and cognition or dementia [10, 39, 40].

Our analyses support a first-ever published report from the original Gothenburg Birth Cohort Study (H70) among those born 1901/02 [38]. Similar to the 2003 report, there was no association between higher BMI and dementia observed during the first 10 years of follow-up. In contrast to the 2003 report, the current analysis includes primarily those born 1930. Thus, with further follow-up, we will be able to observe a 30 year cohort comparison of the BMI-dementia association. In addition, we also chose to focus on all dementias, due to controversies and changes in the field regarding diagnoses of dementia subtypes without the use of neuroimaging or cerebrospinal fluid biomarkers [41].

Our study has many advantages. First, the population sample is part of a long-standing series of rich longitudinal birth cohort studies in Sweden beginning in 1968 (PPSW) and 1971 (the first H70 cohort) [25, 26], with consistent measures over time among unique birth cohorts. Second, there is long follow-up of a large sample of rigorously studied elderly, age 70 years and older, and adjustment for multiple potential confounders. Third, we measured blood levels of adipokines reflecting the metabolic activity of adipose tissue. Finally, we used the study design to our advantage, to estimate temporal (shorter versus longer term)

associations of adiposity indicators with dementia. Given the important role of temporality in understanding risk and protective factor-dementia associations, we see this as a definite strength of these studies.

As with any study design, there are limitations. First, while data from the Gothenburg Birth Cohort Studies have been published using this merged sample examined with identical methods by the same research group at the same time [42, 43], the study is unbalanced regarding sex and age. All men were aged 70 years at baseline, whereas women were aged 70 years and older. Thus, our observations regarding sex differences should be interpreted cautiously. Second, a small number of male participants reduced the power for analyzing associations in men given that dementia onset was monitored during a period of relatively low risk, notably the 8th decade of life [38]. Third, leptin and adiponectin measures were only measured at baseline, thus repeated measures and change in these important hormones over time cannot be considered. Fourth, other nutritional influencers of BMI and WHR, including estimates of energy intake and expenditure, are unavailable. Fifth, our leptin findings are rather conservative. While leptin has strong mechanistic actions in the brain, the use of this marker in the periphery as a reflection of the fat-brain axis remains unclear, especially at a life stage when there are ageing-related body composition changes. In addition, replication of our observations regarding leptin is essential. Finally, some may deem four and five year examination intervals to characterize date of dementia onset as unacceptable. However, given the insidious and often slowly progressive course of dementia onset and a population-based sample, we deem it highly acceptable for these types of analyses. Calculating odds ratios (OR), given this nuance, closely approximates the risk. We have shown this in a previous publication on adiposity measures and dementia [38].

While we found that the odds of developing dementia are higher in elderly women with low BMI within five years, this is not a new finding. The association between BMI and dementia appears to change over the life course. Some studies show that adults with a high midlife BMI or central obesity have a higher risk of late-life dementia [1]. Others have reported that weight loss or BMI decline is associated with dementia risk in elderly [44, 45]. Our data did not suggest associations of baseline BMI and dementias occurring between 2000-2010 nor dementias occurring between 2005 and 2010. Nor was BMI change from 2000-2005 related to dementias occurring between 2005-2010. This suggests temporal issues regarding the BMI-dementia association in this sample, however we cannot evaluate this historically since we do not have measures of BMI prior to 70 years. Thus, a lower BMI may be a preclinical marker for underlying dementia development within five years of a clinical diagnosis in women aged 70 years and older. These results should be interpreted with caution due to a small number of women in the lowest BMI category. The association of lower baseline BMI with dementia may result from a lengthier period of weight loss accompanying prodromal dementia prior to age 70 years, supporting BMI as a possible preclinical marker of dementia.

That low BMI may be a preclinical marker for dementia, is suggested by neuropathophysiological changes accompanying dementia. These changes can induce changes in body weight and adipose storage. For example, brain areas that control weight (i.e. mesial temporal cortex) are affected during the preclinical dementia phase; and adipose tissue loss may result from preclinical apathy, reduced olfactory function, difficulty with eating (e.g., aphasia), inadequate nutrition or prescribed medicines targeting dementia related symptoms e.g. depression or cognitive impairments [46].

Furthermore, we found that the odds of developing dementia in elderly women were lower among those with intermediate blood leptin levels. Postmenopausal women may have a greater risk of developing dementia than men, perhaps due to changes in leptin and brain function due to a fall in endogenous estrogen levels following menopause [47]. Estrogen and leptin have neuroprotective effects on cognition by regulating neurogenesis, hippocampal synaptic plasticity, and axonal growth [11]. However, the roles of adipokines are diverse, and often enigmatic. The adiposity-dementia association, remains to be elucidated, as this is by no means clear.

As higher levels of adiposity, commonly measured as anthropometric overweight and obesity, are associated with higher risk for cardiovascular disease (CVD) [48, 49], and CVD is a risk factor for dementia [50], we explored CVD variables as potential covariates. None were significantly associated with dementia in age-adjusted models. This null observation associating dementia with CVD risk in late-life concurs with other published reports [51]. In addition, adiponectin, known to be associated with CVD, was not associated with dementia.

The underlying neurodegenerative and vascular pathologies observed in dementia, and subsequent impairment of key fat-brain and gut-brain feedback loops [52], may be at the root of conflicting observations; and seemingly intertwined adiposity factors may be differentially associated with dementia when measured within five years. Our findings are supported by studies reporting that higher levels of leptin are prospectively associated with lower odds of dementia or mild-cognitive impairment in elderly [10, 53, 54]. Metabolic dysregulation may accompany or promote late-life alternations in leptin levels and dementias [55]. Atrophy of the posterior hypothalamus affects appetite and feeding behavior via disintegration of

network connections and effects on hormone synthesis [55, 56]. In addition, higher levels of leptin are observed to be neuroprotective [57].

Conclusion

Two highly correlated adiposity variables measured in late life do not associate similarly with late-onset dementia in women. Our analyses show a higher odds of dementia with a low BMI, and a lower odds of dementia with intermediate leptin levels when dementia occurs within 5 years of the adiposity measurement among women aged 70 years and older. Lower BMI and higher leptin may potentially characterize aspects of metabolic dysregulation associated with presence versus absence of prodromal dementia. However, both associations suggest a similar adiposity phenomenon, whether cast as lower BMI being risky or higher leptin levels being protective.

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Conflicts of Interest. All authors have no conflicts of interest.

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Figure 1. Flowchart of participant characteristics and number at baseline and in follow-up examinations

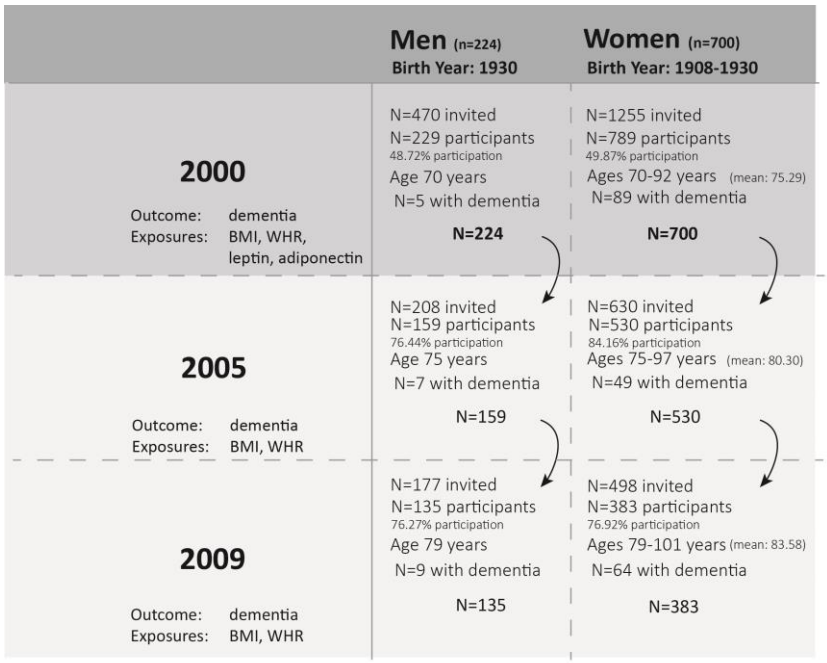

Table 1. Baseline characteristics of participants without dementia in the Gothenburg Birth Cohort Studies

Variable	**All** (n=924)	**Men** (n=224)	**Women** (n=700)
Age, years, mean ± SD	74.0 ± 5.3	70.0 ± 0.0	75.3 ± 5.5
Education <8 years, N (%)	544 (58.9)	125 (55.8)	419 (59.9)
Socioeconomic status (SES)			
working class, N (%)	351 (38.0)	57 (25.4)	294 (42.0)
middle or upper class, N (%)	300 (32.5)	100 (44.6)	200 (28.6)
Waist-hip ratio (WHR), mean ± SD	0.87 ± 0.083	0.95 ± 0.06	0.84 ± 0.07
Low WHR: men ≤ 0.90, women ≤ 0.85, N (%)	375 (40.6)	33 (14.7)	342 (48.9)
High WHR: men > 0.90, women > 0.85, N (%)	509 (55.1)	186 (83.0)	323 (46.1)
BMI, kg/m^2, mean ± SD	26.7 ± 4.2	29.9 ± 3.9	26.6 ± 4.3
≤20.00, N (%)	28 (3.0)	4 (1.8)	24 (3.4)
20.01 - 24.99, N (%)	290 (31.4)	66 (29.5)	224 (32.0)
25.00 - 29.99, N (%)	375 (40.6)	108 (48.2)	267 (38.1)
≥30.00, N (%)	180 (19.5)	45 (20.1)	135 (19.3)
Leptin (ng/mL), mean ± SD	31.6 ± 24.0	15.07 ± 10.5	37.28 ± 24.7
Q1 (ng/mL)	≤13.36	≤8.06	≤18.65
Q2 (ng/mL)	13.37 - 25.24	8.07 - 12.04	18.66 - 30.52
Q3 (ng/mL)	25.25 - 44.00	12.05 - 21.07	30.53 - 50.83
Q4 (ng/mL)	>44.00	>21.07	>50.83
Adiponectin (ng/mL), mean ± SD	6.10 ± 4.54	3.52 ± 2.34	6.97 ± 4.77
Q1 (ng/L)	≤3.11	≤1.97	≤3.76
Q2 (ng/L)	3.12 - 4.89	1.98 - 3.01	3.77 - 5.71
Q3 (ng/L)	4.90 - 7.84	3.02 - 4.57	5.72 – 8.90
Q4 (ng/L)	>7.84	>4.57	>8.90
Alcohol consumption			
g per week, mean ± SD	37.5 ± 66.9	72.2 ± 101.9	25.63 ± 44.4
Smoking, ever, N (%)	353 (38.2)	151 (67.4)	202 (28.9)
Serum levels (mmol/L)			
Triglycerides, mean ± SD	1.4 ± 0.7	1.41 ± 0.6	1.46 ± 0.8
Cholesterol, mean ± SD	5.9 ± 1.1	5.5 ± 0.9	6.1 ± 1.0
High density lipoprotein (HDL), mean ± SD	1.6 ± 0.4	1.3 ± 0.4	1.7 ± 0.4
Low density lipoprotein (LDL), mean ± SD	3.7 ± 0.9	3.6 ± 0.9	3.8 ± 0.9
Systolic blood pressure, mean ± SD	157.7 ± 22.5	155.1 ± 23.1	158.2 ± 22.3
Diabetes mellitus, N (%)	111 (12.0)	41 (18.2)	70 (9.9)
Depression,* N (%)	99 (10.7)	15 (6.7)	84 (12.0)
Presence of any Apoe ε4 allele,† N (%)	233 (25.2)	62 (27.7)	171 (24.4)

*Clinically relevant depressive symptom burden, MADRS score > 12. †APOEε4 allele: apolipoprotein epsilon 4 allele.

Table 2. Odds of developing dementia from 2000-2010, 2000-2005, and 2005-2010 by baseline BMI and WHR among participants without dementia. The Gothenburg Birth Cohort Studies.

	2000-2010			**2000-2005**			**2005-2010**		
	Total OR (95% CI)	Men OR (95% CI)	Women OR (95% CI)	Total OR (95% CI)	Men OR (95% CI)	Women OR (95% CI)	Total OR (95% CI)	Men OR (95% CI)	Women OR (95% CI)
Baseline BMI (kg/m²)									
Continuous	0.94 (0.86-1.02)	0.99 (0.85-1.10)	0.92 (0.83-1.01)	0.88 (0.79-0.97)*	0.89 (0.67-1.18)	0.87 (0.78-0.97)**	0.99 (0.89-1.11)	0.99 (0.83-1.21)	0.98 (0.86-1.12)
<20.0	2.94 (0.73-11.88)	NE†	4.59 (0.95-22.22)	4.21 (1.03-17.21)*	NE	5.34 (1.19-23.87)	1.12 (0.13-9.41)	NE	1.32 (0.14-11.45)
20.00 - 24.99 †	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
25.00 - 29.99	0.79 (0.39-1.56)	1.34 (0.34-5.24)	0.67 (0.29-1.50)	0.13 (0.25-1.19)	0.39 (0.04-3.37)	0.54 (0.24-1.27)	0.69 (0.28-1,74)	1.91 (0.33-11.26)	0.45 (0.14-1.43)
≥30.00	0.93 (0.39-2.22)	0.80 (0.13-5.10)	0.92 (0.34-2.51)	0.25 (0.19-1.54)	0.51 (0.04-6.94)	0.51 (0.16-1.66)	1.21 (0.41-3.57)	0.76 (0.06-9.29)	1.29 (0.38-4.40)
Baseline WHR (cm)									
Continuous	1.07 (0.69-1.65)	2.95 (0.92-9.42)	0.87 (0.54-1.39)	0.95 (0.59-1.51)	0.80 (0.17-3.80)	0.96 (0.59-1.57)	1.20 (0.65-2.24)	4.75 (1.03-21.78)	0.81 (0.42-1.55)
Low WHR†	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
High WHR	0.80 (0.42-1.52)	3.13 (0.37-26.52)	0.62 (0.30-1.28)	0.63 (0.32-1.27)	0.54 (0.05-5.45)	0.63 (0.31-1.32)	1.11 (0.47-2.65)	NE	0.77 (0.29-2.06)

Multivariable models included the following covariates: in 2000-2010, age, sex, socio-economic status (SES), ApoEε4 allele, and smoking; in 2000-2005, age, sex, depressive symptoms and SES; in 2005-2010, age, sex and smoking. †Reference category. Multivariable models were assessed for the complete cohort (total), and subsequent for both men and women in the cohort. Low WHR: men ≤ 0.90 cm, women ≤ 0.85; High WHR: men > 0.90 cm, women > 0.85. Number of incident dementias in 2000-2010, N=134 (men N=18 and women N=116); in 2000-2005, N=68 (men N=8 and women N=60); and in 2005-2010, N=66 (men N=10 and women N=56). * NE: not estimable due to small number. *P<0.05; ** P<0.001.

Table 3. Odds of developing dementia from 2000-2010, 2000-2005, and 2005-2010 by baseline leptin and adiponectin among participants without dementia. The Gothenburg Birth Cohort Studies.

			2000-2010			2000-2005			2005-2010		
			Total OR (95% CI)	Men OR (95% CI)	Women OR (95% CI)	Total OR (95% CI)	Men OR (95% CI)	Women OR (95% CI)	Total OR (95% CI)	Men OR (95% CI)	Women OR (95% CI)
Baseline leptin (ng/mL)											
Continuous			0.55 (0.23-1.30)	0.96 (0.18-5.16)	0.48 (0.17-1.31)	0.33 (0.11-0.99)*	0.42 (0.04-4.33)	0.36 (0.1-1.0)*	0.82 (0.23-2.89)	1.76 (0.17-18.70)	0.56 (0.12-2.56)
Quartiles											
	Men	Women									
Q1†	≤8.06	≤18.64	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Q2	8.07-12.04	18.65-30.52	1.15 (0.51-2.63)	0.30 (0.06-1.55)	1.87 (0.69-5.10)	2.62 (0.73-9.42)	1.91 (0.21-23.52)	0.32 (0.10-0.97)*	0.65 (0.22-1.89)	0.35 (0.05-2.65)	0.92 (0.25-3.36)
Q3	12.05-21.07	30.53-50.83	1.17(0.51-2.71)	0.56 (0.11-2.67)	0.63 (0.59-4.52)	3.47 (1.0-12.02)	1.65 (0.12-22.41)	0.82 (0.32-2.04)	0.37 (0.10-1.31)	0.29 (0.03-3.13)	0.35 (0.07-1.73)
Q4	>21.07	>50.83	0.33 (0.07-1.59)	0.44 (0.08-2.57)	0.79 (0.26-2.47)	0.66 (0.11-3.83)	NE	0.45 (0.13-1.13)	0.39 0.08-1.99)	0.69 (0.10-4.58)	0.62 (0.25-2.18)
Baseline adiponectin (ng/mL)											
Continuous			1.14 (0.38-3.40)	0.49 (0.07-3.45)	1.63 (0.42-6.33)	1.63 (0.32-8.31)	1.18 (0.06-25.13)	1.77 (0.26-12.22)	0.89 (0.22-3.54)	0.30 (0.03-3.29)	1.53 (0.25-9.30)
Quartiles											
	Men	Women									
Q1†	≤1.97	≤3.76	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Q2	1.98-3.01	3.78-5.71	0.39 (0.15-1.51)	0.19 (0.02-1.74)	0.49 (0.16-1.48)	0.43 (0.10-1.82)	1.22 (0.07-22.11)	0.29 (0.05-1.65)	0.36 (0.10-1.24)	NE	0.67 (0.16-2.73)
Q3	3.02-4.57	5.73-8.90	0.74 (0.31-1.07)	0.89 (0.21-3.83)	0.62 (0.22-1.77)	1.06 (0.33-3.43)	2.52 (0.19-34.24)	0.81 (0.21-3.13)	0.53 (0.18-1.61)	0.53 (0.09-2.91)	0.44 (0.09-2.03)
Q4	>4.57	>8.90	0.93 (0.42-2.08)	0.38 (0.06-2.27)	1.19 (0.47-3.03)	1.19 (0.38-3.77)	1.19 (0.07-21.63)	1.08 (0.31-3.76)	0.79 (0.28-2.21)	0.22 (0.02-2.23)	1.29 (0.36-4.56)

Multivariable models include in 2000-2010, age, sex, social economic status (SES), ApoEε4 allele, and smoking; in 2000-2005, age, sex, depressive symptoms and SES; in 2005-2010, age, sex and smoking. †Reference category. Multivariable models were assessed for the complete cohort (total), and subsequent for men and women. In adiponectin analyses BMI was included as covariate. NE: not estimable due to small number. Number of incident dementias in: 2000-2010, N=134 (men N=18 and women N=116), 2000-2005 N=68 (men N=8 and women N=60).