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Obesity and incidence of diabetes: Effect of absence of metabolic syndrome, insulin resistance, inflammation and fatty liver

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Short title: Metabolically Healthy Obesity and Incident Diabetes

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Abbreviations

BMI: body mass index; CIs: confidence intervals; CVD: cardiovascular disease; HDL-C: high-density lipoprotein cholesterol; HOMA-IR: homeostatic model assessment-Insulin resistance; HRs: hazard ratios; IR: insulin resistance; LDL-C: low-density lipoprotein cholesterol; MetS: metabolic syndrome; MHO: metabolically healthy obesity; NAFLD: non-alcoholic fatty liver disease; SD: standard deviation; T2DM: type 2 diabetes.

ABSTRACT

Background and aims: Obesity is frequently associated with non-alcoholic fatty liver disease (NAFLD), insulin resistance (IR), inflammation and metabolic syndrome (MetS) all of which increase risk of type 2 diabetes (T2DM). However, the role of these risk factors in mediating the effect of obesity remains unclear. We investigated the association between obesity and T2DM in the absence and presence of NAFLD, IR, inflammation and MetS components.

Methods: 29,836 obese people without diabetes were studied in a Korean health screening program. Obesity was defined by the appropriate ethnic-specific body mass index (BMI) threshold $\geq$25kg/m^2. Hazard ratios (HRs and 95% confidence Intervals, CIs) for incident T2DM were estimated for the group with none of hypertension, dyslipidemia, impaired fasting glucose, fatty liver, IR, or inflammation (n = 1,717), compared to the reference group, with one or more of these factors (n = 19,757).

Results: Mean (SD) age at baseline was 37 (7) years and 1,200 incident cases of diabetes occurred. Crude T2D incidence was 12.6 /10,000 person-years in the group without metabolic abnormality and was 143/10,000 person-years in the reference group. HR (95% CIs) for incident diabetes was 0.13 (0.06, 0.33) in the group without metabolic abnormality.

Conclusions: Obese subjects without components of the metabolic syndrome, IR, fatty liver and inflammation have an approximately 11 fold lower risk of incident type 2 diabetes than obese subjects who have these risk factors. These simple factors could be used to target limited resources at high risk obese subjects in the prevention of diabetes.

Keywords: Obesity; Non alcoholic fatty liver disease; Type 2 diabetes; Insulin resistance; Inflammation; Metabolic syndrome

1. Introduction

The prevalence of type 2 diabetes (T2DM) continues to increase across the world [1-3] and obesity is an important risk factor for T2DM. Non alcoholic fatty liver disease (NAFLD) and metabolic syndrome (MetS) are very common in obese individuals and also in subjects with T2DM) [4] and we have previously shown that approximately 90% of people who develop T2DM over ~5 years of follow up have one or more of obesity, insulin resistance and NAFLD [5]. Current population-based estimates of prevalence of NAFLD are approximately 30-40% in men and 15-20% in women [6], and in T2DM prevalence is as high as 70% [7]. The presence of NAFLD is associated with increased risk of T2DM in the majority of studies [5,8-17]. However, in these studies relative risk of T2DM varied markedly from a relatively small 64% increase [15], to a large 5.5 fold increase in risk [9]. This wide inter-study variation in risk of incident T2DM, suggests that variation in other risk factors associated with NAFLD, such as obesity, MetS, insulin resistance and inflammation, may be accounting for the marked differences in risk of T2DM between these studies. Consequently, it is important to know how obesity, with and without commonly associated risk factors such as NAFLD, inflammation, MetS and insulin resistance, influences risk of T2DM.

Metabolically healthy obesity (MHO) is a term that has been used to define a group of obese individuals who do not also have metabolic abnormalities although some studies have still shown that subjects with MHO remain at higher risk of T2DM and cardiovascular disease (CVD) than non-obese individuals [18-20]. Indeed, the variable risk of diabetes in MHO subjects, may be explained by the different definitions that have been used to define MHO. Previously, exclusion of MetS components, but not NAFLD, has been used to define MHO [21], and therefore it is not clear whether assessment of NAFLD status could contribute to a clinically

useful, pragmatic definition of MHO, that could be used to identify obese subjects who are at low risk of developing diabetes.

In a large, well phenotyped obese cohort, our aim was to investigate incidence and risk of T2DM in obese subjects with and without, fatty liver, inflammation, MetS components and insulin resistance.

2. Materials and Methods

The study population consisted of individuals who participated in a comprehensive health screening program, at least twice, at Kangbuk Samsung Hospital, Seoul and Suwon, Korea from 2007 to 2014 (n = 219,417). Among these subjects, we excluded subjects with missing body mass index (BMI) data n = 7, non obese subjects, n = 157,478 (normal weight n = 95,408, underweight n = 10,717, overweight n = 51,282). We also excluded subjects aged < 20 years (n = 54), and subjects with heart disease, or stroke, subjects taking medication for stroke or hyperlipidemia (n = 17,272), subjects with diabetes (n = 7,505), hypertension (n = 27,454), history of cancer (n = 3,599) or with relevant missing data (n = 83) (N.B some subjects were excluded for having more than one exclusion criterion).

Thus, we identified 29,836 obese subjects who were included in this analysis and the mean±SD [and median (IQR)] follow up period was 3.9±2.0 years, [3.8 (2.0-5.8)] years. The study was approved by the Institutional Review Board of Kangbuk Samsung Hospital and any requirement for informed consent was waived by the Board because de-identified information was retrieved retrospectively.

2.1. Measurements

As part of the health screening program, individuals completed self-administered

questionnaires, related to their medical and social history and medication usage. Individuals were asked about duration of education (years), regular exercise, smoking history (never, former, or current) and alcohol consumption (grams, g/week). Trained staff also collected anthropometric measurements and vital statistics. Body weight was measured in light clothing with no shoes to the nearest 0.1 kilogram using a digital scale. Height was measured to the nearest 0.1 centimeter. BMI was calculated as weight in kilograms divided by height in meters squared.

Blood samples were collected after at least 10-hours of fasting and samples were analyzed in the core clinical laboratory at the Kangbuk Samsung Hospital. The core clinical laboratory has been accredited and participates annually in inspections and surveys by the Korean Association of Quality Assurance for Clinical Laboratories. Serum levels of glucose, total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were measured using Bayer Reagent Packs (Bayer Diagnostics, Leverkusen, Germany) on an automated chemistry analyzer (Advia 1650 Autoanalyzer; Bayer Diagnostics, Leverkusen, Germany). Insulin was measured with an immunoradiometric assay (Biosource, Nivelle, Belgium) and insulin resistance was defined by a HOMA-IR≥2.5. MetS was defined according to the Joint Societies 2009 criteria for MetS [22]. We defined obesity in this Asian population by a BMI ≥ 25(kg/m^2). High sensitivity-C reactive protein (hsCRP) was analysed by particle-enhanced immunonephelometry with the BNIITM System (Dade Behring, Marburg, Germany) with a lower detection limit of 0.1 mg/L. A measurement of ≥1 mg/L was used to define subjects with inflammation. Gamma glutamyl transferase (GGT), aspartate amino transferase (AST), alanine amino transferase (ALT), concentrations were measured using Bayer Reagent Packs on an automated chemistry analyzer (Advia 1650 Autoanalyzer; Bayer Diagnostics, Leverkusen, Germany). Intra- and interassay coefficients of variation for all biochemical measurements were < 5%.

Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, self-report history of hypertension, or current use of antihypertensive medication. Weekly frequency of exercise was assessed using the validated Korean version of the International Physical Activity Questionnaire Short Form (IPAQ-SF) [23]. Abdominal ultrasonography (Logic Q700 MR; GE, Milwaukee, WI, USA) was undertaken by clinical radiologists using a 3.5MHz probe for all subjects at baseline and after five years. The following images were undertaken; i) sagittal view of the right lobe of the liver and right kidney, ii) transverse view of the left lateral segment of the liver and spleen and iii) transverse view of the liver for altered echo texture. Fatty infiltration of the liver (fatty liver) was identified if there was an increase in echogenicity of the liver compared with the echogenicity of the renal cortex where the diaphragm and intrahepatic vessels appeared normal [24]. Diabetes was defined as a self-reported history of diabetes, the use of glucose-lowering medications and/or HbA1c ≥6.5% or fasting glucose ≥ 126mg/d at baseline (to exclude people with prevalent diabetes), and at follow-up (to identify incident diabetes).

2.2. Statistical analyses

The statistical analysis was performed using STATA version 15.0 (StataCorp LP, College Station, TX, USA). Reported *p* values were two-tailed, and < 0.05 were considered statistically significant. The distribution of continuous variables was evaluated and transformations were conducted for nonparametric variables. Cox proportional hazards models were used to estimate Hazard Ratios (HRs and 95% confidence intervals) (and fully adjusted HRs, aHRs) for the association between sub-groups and incident diabetes at follow up. Three mutually exclusive obesity groups were generated:

Group A (reference group) (*n* = 19,757 (66.22%) = obese subjects with ≥1 component of MetS (i.e. dysglycaemia, low levels of HDL-C, or high levels of serum triglyceride

concentrations, or increased blood pressure [22]); or fatty liver (defined by presence of fatty liver on ultrasound), or IR (defined by HOMA-IR≥2.5), or inflammation (defined by hsCRP≥1mg/L).

Group B (*n* = 8,362 (28.03%) = obese subjects without features of the MetS [22], but with ≥1 of fatty liver, IR, or inflammation (defined as above).

Group C (*n* = 1,717 (5.75%) = obese subjects without features of the MetS [22], fatty liver, IR or inflammation (defined as above).

The proportional hazards model assumption was tested with a graphical analysis of the hazard of incident diabetes over time (see Supplementary Fig. 1). Models were adjusted for age, sex, center (Seoul or Suwon), year of screening exam, smoking status, alcohol intake, exercise, family history of diabetes and education level.

3. Results

The mean age ±SD (range) of the cohort was 37 ± 6 (range: 20-77) years. Table 1 describes the baseline characteristics of subjects who developed incident diabetes compared with characteristics of subjects remaining free from diabetes at follow up (mean±SD) 4±2 (range: 0.5-8) years of follow up. With 114,119 person-years of follow up, and 1200 incident cases of T2DM, the incidence rate was 1.1% (95% CIs 1.0, 1.1) per annum. Subjects who developed incident diabetes were older, had a higher prevalence of fatty liver and had a higher BMI, hsCRP and HOMA-IR, than subjects who did not develop diabetes during follow-up. Table 2 (men) and Table 3 (women) show the baseline characteristics of the cohort in the three sub-groups of obesity according to the presence or absence of metabolic abnormalities as described in the Methods.

Since fatty liver often co-exists with T2DM [4], we investigated the association between fatty liver and incident T2DM. Adjusting for age, sex, center, year of screening exam, smoking status, alcohol intake, regular exercise, family history of diabetes and education level, BMI ≥25kg/m^2; all MetS factors; IR; and inflammation, the aHR (95% CIs) for the association between fatty liver and incident T2DM was 2.03 (1.73, 2.38) for men, and 3.09 (2.04, 4.67) for women.

Next, we investigated the numbers of incident cases of diabetes, incidence of diabetes per 10,000 patient years, and age-adjusted and fully adjusted HRs for incident diabetes in obese men and women combined (Table 4). Compared to the reference group (*n* = 19,757), (crude incidence rate for diabetes = 143.0 cases/10,000 person-years), in the obese group without MetS components, crude incidence rate for diabetes = 28.8 cases/10,000 person-years) and aHR (95% CIs) for incident diabetes was 0.25 (0.20, 0.31). In the obese group without MetS components, fatty liver or inflammation, crude incidence rate for diabetes = 12.6 cases/10,000 person-years) and aHR (95% CIs) for incident diabetes was 0.13 (0.06, 0.33).

4. Discussion

Our novel results show that in an obese Korean cohort, the incidence of type 2 diabetes is approximately 1.1% per annum and that there are marked differences in T2DM incidence within the cohort, depending on the presence or absence of metabolic abnormalities. Incidence of T2DM was ~90% lower among obese people who do not have any other MetS components, or evidence of IR, inflammation and fatty liver, than among the group with one or more of these metabolic abnormalities. The overall incidence of T2DM in our study is similar to that described in many cohorts from different regions around the world [1,25-29].

Current population-based prevalence of NAFLD is approximately 30-40% in men and 15-20% in women [6] and is even higher in people with T2DM, occurring in up to 70% of this group of patients [7]. Recent evidence shows that liver fat, as a manifestation of NAFLD, is a risk factor for both T2DM and CVD [5,30,31]. Given that liver fat is very common in patients with obesity [32], and can be diagnosed with ultrasound, identification of fatty liver provides a potentially useful strategy for finding subjects at increased risk of diabetes in obese subjects.

Obesity is a risk factor for increased all cause mortality [33-35] and a recent meta-analysis investigating whether MHO is ever a benign condition, suggested that obese persons are at increased risk of cardiovascular events, even in the absence of metabolic abnormalities [36]. These findings led the authors of the meta-analysis to conclude that there is no healthy pattern of increased weight. However many of the studies included in the meta-analysis adjusted for different metabolic risk factors [37-39], and the summary results of the meta-analysis were presented as crude hazard ratios. These data emphasise that further research is needed to test whether obesity is ever a metabolically benign condition, having adjusted for a comprehensive range of risk factors for metabolic and vascular disease. The optimum BMI associated with metabolic health is not clear and may vary by ethnic group and sex. A recent large meta-analysis showed that the associations of both overweight and obesity with higher all-cause mortality were broadly consistent across 10,625,411 participants from different ethnic groups in Asia, Australia and New Zealand, Europe, and North America (data from 239 prospective studies) across four continents [35]. However, that said, a recent study of 12.8 million Korean adults, aged 18-99 years, suggested that the BMI which predicted the lowest mortality increased with age and was lower in women than men [40]. The change in optimum BMI with age was also more profound in women than in men and sex and age-specific optimums for BMI were generally higher than for the current normal range (BMI of 18.5-24.9kg/m^2) (except for women < 50 years). Taken together, these data highlight the notion that BMI is an imprecise measure

of risk of ill health, and associations between BMI and ill health are likely to differ according to age, sex and the presence of other risk factors such as those studied herein. In keeping with the data we have presented, we suggest that in order to improve the clinical utility of BMI to assess risk of incident disease in obese subjects, it is important to consider the co-existing presence of fatty liver, IR and inflammation besides more traditional risk factors. Assessment of these easily measured risk factors may improve the prognostic value of BMI as an indicator of future risk of T2DM and importantly, allow limited resources available for diabetes prevention to be targetted at higher risk obese sub-groups.

Recently, the issue of whether MHO exists as a phenomenon, has been discussed in an editorial [33] based on the work of Yi et al [40], with the authors of the editorial concluding that MHO is common among the obese population and constitutes a unique subset of protective characteristics that reduce metabolic and cardiovascular risk factors despite the presence of excessive fat mass. However, it was acknowledged that the protective factors that grant a healthier profile to individuals with MHO are poorly understood and are still being elucidated. Numerous possible mechanisms underlying the explanation for MHO have been suggested, including adipose tissue distribution and an absence of inflammation. However, the prognostic value of MHO remains controversial [41-43] and the lack of a standard definition for metabolic health and obesity (as well as the dynamic properties of MHO) may have contributed to contrasting results regarding the prognostic value of MHO [44]. Whilst our manuscript was under review a meta-analysis of three studies with 132,667 subjects including 8675 MHO subjects without fatty liver, and 7218 MHO subjects with fatty liver, suggested that that the MHO phenotype, with or without fatty liver, presents a risk of the development of type 2 diabetes [45]. However, our data emphasise that if a term such as MHO is to be used, it should be defined by including subjects with obesity, only after exclusion of inflammation, IR and fatty liver, as well as exclusion of easily measured components of the MetS (dysglycaemia,

atherogenic dyslipidaemia – low levels of HDL-C and high levels of serum triglyceride concentrations, and increased blood pressure). Whilst exclusion of inflammation, IR, fatty liver and easily measured components of the MetS did not completely abolish the risk of diabetes associated with obesity; exclusion of these factors did markedly attenuate the risk of diabetes over ~4 years of follow up.

The strengths and limitations of our study should be considered. We have studied a large number of obese individuals (n = 29,836) with ~4 years of follow up. There were a substantial number (n = 1,200), incident cases of diabetes at follow up. As an oral glucose tolerance test was not undertaken to identify prevalent or incident diabetes, it is possible that some misclassification bias occurred. However, any such bias would not be expected to be differential, so would attenuate the strength of the observed associations, and would bias associations towards the null. We have also assessed the presence of fatty liver using abdominal ultrasonography at baseline. Whilst the sensitivity of ultrasound for detecting fatty liver is limited to identification of ~>25% fat infiltration [24], and the detection of liver fat can be affected by severe obesity, in our predominantly single ethnic group population, there were very few severely obese subjects. Although we acknowledge that it is possible that subjects with low levels of liver fat compatible with a diagnosis of NAFLD would not have been identified by ultrasound, any misclassification bias would attenuate the strength of the associations we have observed. Additionally, another important limitation is that it was not possible to assess the effect of waist circumference (a key component of the MetS) in these subjects. However, despite widespread evidence that waist circumference is a better indicator of future risk, waist circumference is rarely measured in clinical practice and BMI remains the more frequently used simple measure for assessing obesity. Given that BMI is the much more frequently used measure, it is therefore clinically relevant to ascertain what factors added to obesity contribute markedly to increasing risk of T2DM, in order to determine what factors have to be excluded

to define MHO. In this cohort, waist circumference was only available on a proportion of subjects, and therefore we considered it more appropriate to use the BMI threshold ≥25kg/m^2 as well as the other recognized features of the MetS to define the presence or absence of the syndrome. Finally, HbA1c was not measured using a method standardized to the Diabetes Control and Complications Trial and approved by the National Glycohemoglobin Standardization Program.

5. Conclusion

Our results add to existing evidence by showing that obese subjects who do not have increased blood pressure, dyslipidaemia, impaired fasting glucose, IR, fatty liver and inflammation are at very low risk of incident diabetes at ~4 year follow up. We suggest that measuring these simple easily measured risk factors in obese individuals would be useful to assess risk of T2DM in clinical practice. Although further work is necessary to test the durability of our findings over a longer period of follow up, we suggest that measurement, and exclusion of these risk factors in clinical practice, may help better targeting of limited resources for diabetes prevention to obese people at highest risk of developing diabetes.

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Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Authors' contributions

K.S and C.D.B. contributed to the hypothesis. K.S. wrote the methods and contributed to discussion. M.L analyzed the data. J.H. J.K. H.K. and S.W. contributed to the discussion. C.D.B. wrote the introduction, results and discussion, K.S. is the guarantor for the article.

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446 **Tables**

Table 1

Baseline characteristics of the whole cohort according to incident DM

Characteristics	No DM	Incident DM	*p* value
Number (%)	28,636 (96.0)	1,200 (4.0)	
Age (years)*	36±6	39±6	<0.001
Male, *n* (%)	23,052 (80.5)	973 (81.1)	0.617
Systolic BP (mmHg)*	115±10	117±10	<0.001
Diastolic BP (mmHg)*	74±7	75±7	<0.001
Glucose (mg/dl)*	95±8	106±10	<0.001
Total cholesterol (mg/dl)*	200±32	206±33	<0.001
LDL-C (mg/dl)*	124±29	128±29	<0.001
HDL-C (mg/dl)*	49±11	46±10	<0.001
Triglycerides (mg/dl)†	128 (92-181)	158 (115-221)	<0.001
ALT (IU/L)†	27 (19-40)	36 (24-55)	<0.001
AST (IU/L)†	23 (19-29)	27 (22-35)	<0.001
GGT (IU/L)†	30 (19-49)	42 (27-69)	<0.001
hsCRP†(mg/l)†	0.07 (0.04-0.13)	0.09 (0.05-0.2)	<0.001
HOMA-IR†	1.56 (1.09-2.17)	2.25 (1.58-3.16)	<0.001
Smoking, *n* (%)			<0.001
Current smoker	10,357 (36.2)	505 (42.1)	
Never/former smoker	17,258 (60.3)	663 (55.3)	
Unknown	1,021 (3.6)	32 (2.7)	
Alcohol intake, *n* (%)			0.065
<20g/day	21,180 (74.0)	868 (72.3)	

20g/day	5,558 (19.4)	263 (21.9)	
Unknown	1,898 (6.6)	69 (5.8)	
Regular exercise, *n* (%)[§]			0.319
<1 times per week	14,834 (51.8)	595 (49.6)	
≥1 times per week	13,359 (46.7)	585 (48.8)	
Unknown	443 (1.6)	20 (1.7)	
Family history of DM, *n* (%)			<0.001
No	23,837 (83.24)	892 (74.33)	
Yes	4,666 (16.30)	296 (24.67)	
Unknown	133 (0.46)	12 (1.00)	
High education level, *n* (%)			<0.001
≤High school	1,589 (5.6)	54 (4.5)	
≥College graduate	12,081 (42.2)	406 (33.8)	
Unknown	14,966 (52.3)	740 (61.7)	
Seoul center, *n* (%)	14,758 (51.5)	615 (51.3)	0.846
BMI (kg/m^2)	27±2	28±2	<0.001
Fatty liver, *n* (%)			<0.001
No	12,697 (44.4)	276 (23.0)	
Yes	15,910 (55.6)	923 (77.0)	
MetS, *n* (%)	8,377 (29.3)	744 (62.0)	<0.001
Inflammation (hsCRP >1mg/L), *n* (%)	9,454 (33.0)	540 (45.0)	<0.001

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; DM, diabetes; GGT, gamma-glutamyl transferase; HDL-C, high-density lipoprotein-cholesterol; HOMA-IR, homeostatic model assessment-Insulin resistance; hs CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol.

Data are *mean (standard deviation), †median (interquartile range).

§ ≥1 time per week.

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Table 2

Baseline characteristics according to obesity type (men)

	All	obese(A)	Obese, without MetS components (B)	Obese, without MetS components, fatty liver or inflammation (C)	*p* value
Number (%)	24,025	16,441 (68.43)	6,376 (26.54)	1,208 (5.03)	
Age (years)*	36±6	37±6	36±6	35±6	<0.001
Systolic BP (mmHg)*	117±9	118±10	114±8	112±8	<0.001
Diastolic BP (mmHg)*	75±7	76±7	73±6	70±7	<0.001
Glucose (mg/dl)*	96±8	98±8	91±6	91±5	<0.001
Total cholesterol (mg/dl)*	202±32	205±33	197±30	193±29	<0.001
LDL-C (mg/dl)*	126±29	127±30	124±28	123±28	<0.001
HDL-C (mg/dl)*	48±10	46±10	52±9	56±11	<0.001
Triglycerides (mg/dl)†	138 (100-192)	168 (124-219)	103 (81-124)	90 (70-112)	<0.001
ALT (IU/L)†	30 (22-43)	32 (23-46)	27 (20-39)	22 (17-30)	<0.001
AST (IU/L)†	24 (20-30)	25 (21-31)	24 (20-28)	21 (18-25)	<0.001
GGT (IU/L)†	35 (24-55)	39 (26-61)	29 (21-44)	25 (18-36)	<0.001
hsCRP(mg/l)†	0.07 (0.04-0.13)	0.07 (0.04-0.13)	0.07 (0.04-0.14)	0.03 (0.02-0.05)	<0.001

HOMA-IR†	1.65 (1.13-2.35)	1.95 (1.37-2.76)	1.40 (0.99-1.97)	1.19 (0.81-1.61)	<0.001
Smoking, *n* (%)					<0.001
Current smoker	10,582 (44.05)	7,621 (46.35)	2,515 (39.44)	446 (36.92)	
Never/former smoker	12,829 (53.40)	8,401 (51.1)	3,725 (58.42)	703 (58.2)	
Unknown	614 (2.56)	419 (2.55)	136 (2.13)	59 (4.88)	
Alcohol intake, *n* (%)					<0.001
<20g/day	19,931 (82.96)	11,714 (71.25)	4,885 (76.62)	800 (66.23)	
20g/day	3,110 (12.94)	4,070 (24.76)	1,233 (19.34)	339 (28.06)	
Unknown	984 (4.10)	657 (4)	258 (4.05)	69 (5.71)	
Regular exercise, *n* (%)§					0.136
<1 times per week	11,872 (49.42)	8,321 (50.61)	3,024 (47.43)	527 (43.63)	
≥1 times per week	11,835 (49.26)	7,902 (48.06)	3,272 (51.32)	661 (54.72)	
Unknown	318 (1.32)	218 (1.33)	80 (1.25)	20 (1.66)	
Family history of DM, *n* (%)					0.007
No	20,129 (83.78)	13,631 (82.91)	5,474 (85.85)	1,024 (84.77)	
Yes	3,792 (15.78)	2,732 (16.62)	877 (13.75)	183 (15.15)	
Unknown	104 (0.43)	78 (0.47)	25 (0.39)	1 (0.08)	

High education level, *n* (%)					<0.001
≤High school	851 (3.54)	608 (3.7)	178 (2.79)	65 (5.38)	
≥College graduate	10,752 (44.75)	7,070 (43)	2,813 (44.12)	869 (71.94)	
Unknown	12,422 (51.70)	8,763 (53.3)	3,385 (53.09)	274 (22.68)	
Seoul center, *n* (%)	11,413 (47.5)	8,196 (49.85)	2,751 (43.15)	466 (38.58)	<0.001
BMI (kg/m^2)	27 ± 2	27 ± 2	27 ± 2	26 ± 1	<0.001
Fatty liver, *n* (%)					<0.001
No	9,318 (38.78)	5,356 (32.6)	2,754 (43.24)	1,208 (100)	
Yes	14,688 (61.14)	11,073 (67.4)	3,615 (56.76)	-	
Unknown	19 (0.08)	12 (0.07)	7 (0.11)	-	
MetS, *n* (%)	7,828 (32.58)	7,828 (47.61)	-	-	<0.001
Inflammation (hsCRP >1mg/L), *n* (%)	7,750 (32.26)	5,571 (33.88)	2,179 (34.18)	-	<0.001

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; DM, diabetes; GGT, gamma-glutamyl transferase; HDL-C, high-density lipoprotein-cholesterol; HOMA-IR, homeostatic model assessment-Insulin resistance; hs CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol.

Data are *mean (standard deviation), †median (interquartile range).

§ ≥1 time per week.

Table 3

Baseline characteristics according to obesity type (women)

	All	obese(A)	Obese, without MetS components (B)	Obese, without MetS components, fatty liver or inflammation (C)	*p* value
Number (%)	5,811	3,316 (57.06)	1,986 (34.18)	509 (8.76)	
Age (years)*	38±7	38±7	37±7	37±6	<0.001
Systolic BP (mmHg)*	110±11	112±11	108±9	105±9	<0.001
Diastolic BP (mmHg)*	69±8	71±8	68±7	66±7	<0.001
Glucose (mg/dl)*	94±8	96±9	90±6	90±6	<0.001
Total cholesterol (mg/dl)*	195±33	195±36	196±30	189±28	<0.001
LDL-C (mg/dl)*	118±29	120±30	115±28	113±25	<0.001
HDL-C (mg/dl)*	55±12	50±11	62±10	64±10	<0.001
Triglycerides (mg/dl)†	98 (73-137)	120 (87-169)	82 (64-104)	73 (56-92)	<0.001
ALT (IU/L)†	17 (13-23)	18 (14-25)	16 (13-22)	14 (11-18)	<0.001
AST (IU/L)†	19 (16-23)	19 (17-24)	19 (17-23)	17 (15-20)	<0.001
GGT (IU/L)†	15 (11-22)	17 (12-25)	14 (11-20)	13 (11-17)	<0.001
hsCRP (mg/l)†	0.08 (0.04-0.16)	0.09 (0.05-0.18)	0.08 (0.04-0.17)	0.03 (0.02-0.05)	<0.001

HOMA-IR†	1.65 (1.13-2.35)	1.95 (1.37-2.76)	1.40 (0.99-1.97)	1.19 (0.81-1.61)	<0.001
Smoking, *n* (%)					<0.001
Current smoker	280 (4.82)	173 (5.22)	93 (4.68)	14 (2.75)	
Never/former smoker	5,092 (87.63)	2,891 (87.18)	1,769 (89.07)	432 (84.87)	
Unknown	439 (7.55)	252 (7.6)	124 (6.24)	63 (12.38)	
Alcohol intake, *n* (%)					<0.001
<20g/day	4,649 (80.0)	2,679 (80.79)	1,620 (81.57)	350 (68.76)	
20g/day	179 (3.08)	92 (2.77)	57 (2.87)	30 (5.89)	
Unknown	983 (16.92)	545 (16.44)	309 (15.56)	129 (25.34)	
Regular exercise, *n* (%)§					<0.001
<1 times per week	3,557 (61.21)	2,021 (60.95)	1,201 (60.47)	335 (65.82)	
≥1 times per week	2,109 (36.29)	1,206 (36.37)	742 (37.36)	161 (31.63)	
Unknown	145 (2.50)	89 (2.68)	43 (2.17)	13 (2.55)	
Family history of DM, *n* (%)					<0.001
No	4,600 (79.16)	2,574 (77.62)	1,620 (81.57)	406 (79.76)	
Yes	1,170 (20.13)	717 (21.62)	351 (17.67)	102 (20.04)	
Unknown	41 (0.71)	25 (0.75)	15 (0.76)	1 (0.2)	

High education level, *n* (%)					<0.001
≤High school	792 (13.63)	480 (14.48)	204 (10.27)	108 (21.22)	
≥College graduate	1,735 (29.86)	885 (26.69)	559 (28.15)	291 (57.17)	
Unknown	3,284 (56.51)	1,951 (58.84)	1,223 (61.58)	110 (21.61)	
Seoul center, *n* (%)	3,050 (52.49)	1,810 (54.58)	1,009 (50.81)	231 (45.38)	<0.001
BMI (kg/m^2)	27±2	27±2	27±2	26±1	<0.001
Fatty liver, *n* (%)					<0.001
No	3,655 (62.90)	1,778 (53.62)	1368 (68.88)	509 (100)	
Yes	2,145 (36.91)	1,534 (46.26)	611 (30.77)	-	
Unknown	11 (0.19)	4 (0.12)	7 (0.35)	-	
MetS, *n* (%)	1,293 (22.25)	1,293 (38.99)	-	-	<0.001
Inflammation (hsCRP >1mg/L), *n* (%)	2,244 (38.62)	1,430 (43.12)	814 (40.99)	-	<0.001

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; DM, diabetes; GGT, gamma-glutamyl transferase; HDL-C, high-density lipoprotein-cholesterol; HOMA-IR, homeostatic model assessment-Insulin resistance; hs CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol.

Data are *mean (standard deviation), †median (interquartile range).

§ ≥1 time per week.

Table 4

Numbers of incident DM, incident DM rates and hazard ratios (HRs) for all incident DM in obese subjects

Obese groups	Number	Median (IQR) f/up(Days)	Person-years	Number of events	Incident DM (10,000person-year)	Model 1Age-adjusted HRs (95% CI)*	Model 2Multivariate HRs (95% CI)*
All	29,836						
A	19,757	1,408 (735-2,154)	76,870.8	1,099	143.0	1 (reference)	1 (reference)
B	8,362	1,418 (741-2,143)	33,276.9	96	28.8	0.25 (0.20-0.31)	0.25 (0.20-0.31)
C	1,717	743 (641-1,082)	3,971.2	5	12.6	0.16 (0.07-0.38)	0.13 (0.06-0.33)
p for trend						<0.001	<0.001
Men	24,025						
A	16,441	1,414 (735-2,157)	64,325.9	896	139.3	1 (reference)	1 (reference)
B	6,376	1,415 (739-2,141)	25,366.9	73	28.8	0.26 (0.20-0.33)	0.25 (0.20-0.33)
C	1,208	735 (634-1,034)	2,735.3	4	14.6	0.20 (0.07-0.52)	0.16 (0.06-0.44)
p for trend						<0.001	<0.001
Women	5,811						
A	3,316	1,383 (735-2,128)	1,2544.9	203	161.8	1 (reference)	1 (reference)

B	1,986	1,429 (743-2,151)	7,910.0	23	29.1	0.22 (0.14-0.34)	0.22 (0.14-0.35)
C	509	770 (655-1,203)	1,235.9	1	8.1	0.09 (0.01-0.61)	0.07 (0.01-0.51)
p for trend						<0.001	<0.001

Group A (reference group) (*n* = 19,757 (66.22%) = obese subjects with ≥1 component of MetS (i.e. dysglycaemia, low levels of HDL-C, high levels of serum triglyceride concentrations, or increased blood pressure [22]); or fatty liver (defined by presence of fatty liver on ultrasound), or IR (defined by HOMA-IR≥2.5), or inflammation (defined by hsCRP≥1mg/L).

Group B (*n* = 8,362 (28.03%) = obese subjects without features of the MetS [22], but with ≥1 of fatty liver, IR, or inflammation (defined as above).

Group C (*n* = 1,717 (5.75%) = obese subjects without features of the MetS [22], fatty liver, IR or inflammation (defined as above).

*Adjustments: Model 1 = Age, Model 2 Age, sex, center, year of screening exam, smoking status, alcohol intake, regular exercise, Family history of DM and education level.

Median interquartile range (IQR) follow up (F/U) (days).

Supplementary figure 1. Graphical analysis to test proportional hazards assumption for t hree obesity groups and risk of incident diabetes over time