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Risk of type 2 diabetes according to the cumulative exposure to metabolic syndrome or obesity: A nationwide population-based study

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ABSTRACT

Aims/Introduction: We investigated the risk of incident type 2 diabetes according to the cumulative exposure to obesity or metabolic syndrome (MetS) during annual or biennial health examinations.

Materials and Methods: The Korean National Health Insurance Service datasets from 2002 to 2017 were used for this retrospective longitudinal study. The risk for type 2 diabetes was analyzed according to the cumulative exposure to obesity and MetS among individuals who underwent four health examinations from 2009 to 2012 or 2013 (n = 2,851,745).

Results: During examinations, 28.56 and 17.86% of the total participants showed fluctuations in metabolic health state and obesity, respectively. During a mean 5.01 years of follow up, 98,950 new type 2 diabetes cases developed. The risk for type 2 diabetes increased with the increase in exposure to MetS (hazard ratio [HR] 2.92, 95% confidence interval [CI] 2.86–2.99; HR 4.96, 95% CI 4.85–5.08; HR 7.46, 95% CI 7.30–7.63; HR 12.24, 95% CI 12.00–12.49 in groups with number of exposures one to four, respectively) and obesity (HR 1.60, 95% CI 1.56–1.65; HR 1.87, 95% CI 1.81–1.92; HR 2.25, 95% CI 2.19–2.31; HR 3.46, 95% CI 3.41–3.51 in groups with number of exposures one to four, respectively), showing a more detrimental effect of cumulative exposure to MetS, when compared with the exposure to obesity.

Conclusions: Metabolic health and obesity fluctuated within a relatively short period of 4–5 years. Although the impact was much greater for MetS than for obesity, the cumulative duration of both obesity and MetS was associated with an increased risk of type 2 diabetes in a dose-response manner. Therefore, continuously maintaining metabolic health and normal weight is crucial to prevent incident type 2 diabetes.

INTRODUCTION

Although body mass index (BMI) has been widely used to define obesity because of its practicality, it has a definite limitation – it cannot discriminate between lean and fat mass[1–3]. Therefore, there have been studies about the unique body size phenotypes, such as metabolically healthy obese (MHO) and metabolically unhealthy normal-weight phenotypes, showing a non-linear relationship between BMI and adverse outcomes[3–10]. However, the status of metabolic health and obesity is not constant[11–16]. Soriguer *et al.*[11] reported that 41.9% of MHO individuals became metabolically unhealthy during the 6-year follow up, suggesting that MHO is a dynamic concept. An analysis of the Nurses' Health Study showed that 84% of the MHO women converted to unhealthy phenotypes after 20 years[12]. The risk assessment based on an MHO phenotype at a single time point is prone to underestimating its cardiometabolic risk; being MHO at baseline does not confer a reduced risk of diabetes or cardiovascular diseases (CVDs) if these individuals become metabolically unhealthy over time[12,17].

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Therefore, the trajectory of the metabolically unhealthy status rather than the presence of metabolic syndrome (MetS) at a specific time might provide more information on the risk of cardiometabolic diseases, including type 2 diabetes.

Growing evidence emphasizes the effect of the exposure duration to a metabolically unhealthy status or obesity on the cardiometabolic disorders incidence[17,18]. In the Multi-Ethnic Study of Atherosclerosis, there was a dose–response relationship between the duration of MetS and CVDs, with an odds ratio (OR) of 1.42 (95% confidence interval [CI] 1.07–1.89) for every additional visit with MetS after transition from MHO at baseline[17]. Mongraw-Chaffin *et al.*[18] showed that the total obesity duration by number of visits was associated with greater odds of incident MetS. Although the co-presence of both metabolic abnormality and obesity has been reported to be associated with >10-fold increased risk of diabetes compared with the metabolically healthy normal-weight phenotype[19], no study has compared the effects of the cumulative exposure with a metabolic abnormality versus obesity on the incidence of type 2 diabetes.

To establish preventive strategies for incident type 2 diabetes, we determined the proportion of individuals who maintained their metabolic heath status and bodyweight over time, and compared the relative risk of type 2 diabetes according to the cumulative exposure to a metabolic abnormality, defined as MetS, or obesity during annual or biennial health examinations. Finally, we examined the relative risk of type 2 diabetes according to the exposure frequency to specific metabolic risk factors, such as hypertension, dyslipidemia, abdominal obesity (assessed by waist circumference [WC]), and general obesity (measured using the BMI).

METHODS

Data sources

We used the Korean National Health Insurance Service (NHIS) datasets of claims and preventive health examinations from January 2002 to December 2017. The NHIS covers all Korean residents as a single-payer organization. Its users are recommended to undergo standardized health examinations at least every 2 years. These examination results are entered into the dataset of preventive health examinations, which includes >10 million Koreans. Previous reports have described details on this database[20,21].

The institutional review board of Korea University approved this study (2019GR0089). An informed consent exemption was granted by the institutional review board, because the NHIS provided the researchers with anonymous, de-identified information.

Study cohort, outcomes and follow up

In this retrospective longitudinal study, we included individuals aged ≥20 years at baseline who satisfied both of the following: (i) they underwent at least one health examination between 2012 and 2013; and (ii) had three additional examinations between 2009 and baseline. The time point of the last examination between 2012 and 2013 was considered as baseline. Among these, we excluded the individuals who had a history of total or partial pancreatectomy; those with missing data for at least one variable; and those who had, at or before baseline, at least one prescription for antidiabetic medication or claims under the International Classification of Diseases, 10th Revision (ICD-10) codes E10–14, fasting plasma glucose (FPG) ≥126 mg/dL or CVDs (myocardial infarction, stroke or heart failure that required hospitalization; Figure 1).

The end-point was newly diagnosed type 2 diabetes, defined as a recording of at least one claim per year for the prescription of antidiabetic medication under the ICD-10 codes E11–14 or a FPG level ≥126 mg/dL, according to a previous report[20]. Those who had claims under the ICD-10 code E10 were excluded to rule out type 1 diabetes. The study population was followed up from baseline until the date of death, development of type 2 diabetes or 31 December 2017, whichever came first.

Measurements and definitions

Questionnaires were used to obtain information on the current smoking, alcohol consumption, regular exercise and family history of diabetes. The definitions of heavy alcohol consumption, regular exercise and a low-income level are presented in Table S1. BMI was calculated from the bodyweight in kilograms divided by the height in meters squared (kg/m^2). The FPG and lipid profiles were measured using venous samples obtained after an overnight fast. These examinations were carried out only at hospitals certified by the NHIS.

Exposures to MetS and obesity

Obesity was defined as BMI ≥25 kg/m^2 according to the obesity guidelines for the Korean population[22]. MetS was determined according to the harmonized International Diabetes Federation criteria[23], using the cut-offs for abdominal obesity from the Korean Society for the Study of Obesity (WC ≥90 cm in men, ≥85 cm in women)[24]. All individuals were assessed for the presence of MetS and obesity during all four health examinations, and were considered exposed to these conditions if they satisfied the criteria of MetS or obesity at a certain examination. They were categorized into five groups according to the number of exposures to MetS or obesity (0–4).

Statistical analysis

The baseline characteristics of the study population were analyzed according to the five groups stratified by the number of exposures to MetS or obesity. Continuous variables with normal distributions are expressed as the mean ± standard deviation, whereas those with non-normal distributions are presented as the median and interquartile range. Frequencies and percentages are used to express categorical data.

The incidence rate of type 2 diabetes was derived from the number of incident cases divided by the total follow-up duration (person-years). The cumulative incidence rates of type 2 diabetes according to the number of exposures to MetS or

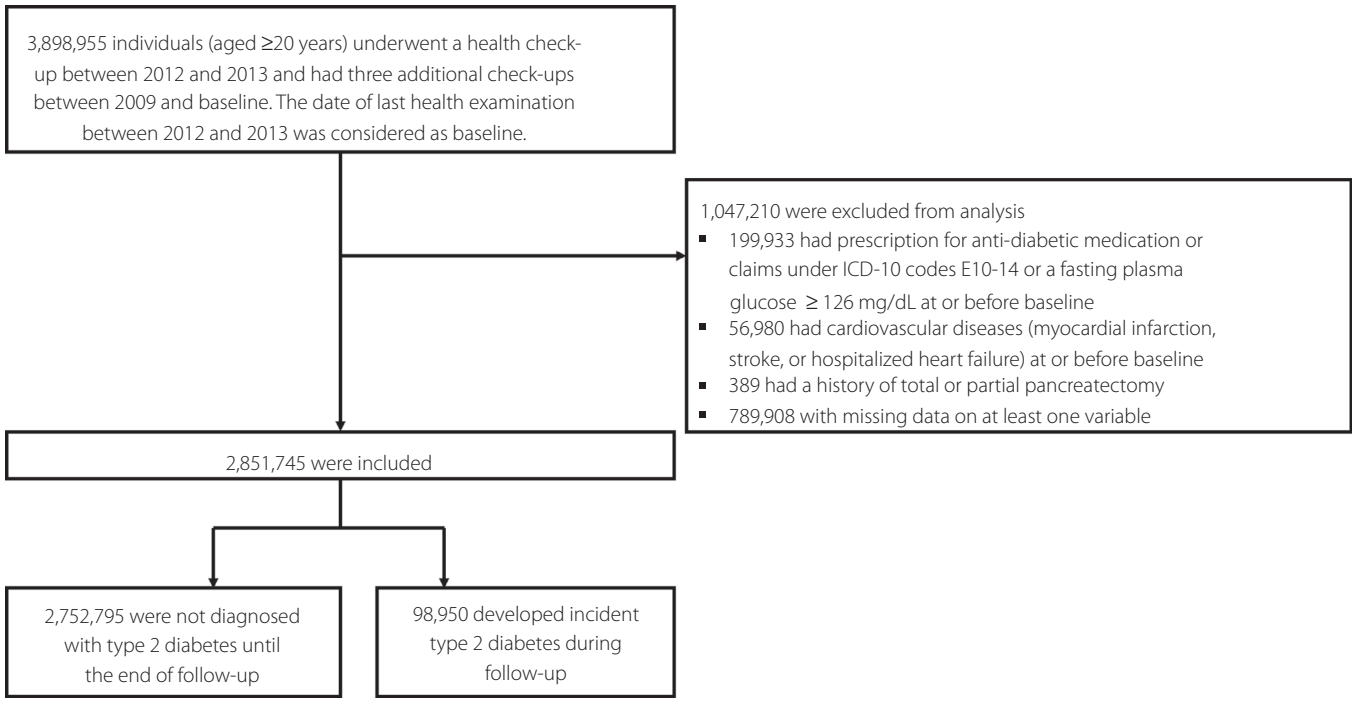

Figure 1 | Enrollment, exclusions and follow up.

obesity were compared using the Kaplan-Meier curves; the differences among the groups were evaluated using the log–rank test. A multivariate Cox regression analysis was carried out to calculate the hazard ratios (HRs) and 95% CIs for the outcome incidence rates according to the number of exposures to MetS or obesity: unadjusted in model 1, adjusted for age and sex in model 2, and additionally for smoking history, alcohol consumption, regular exercise, family history of diabetes and mean FPG during the four health examinations in model 3. This analysis was carried out in the total population of both sex and also separately by sex.

The participants were categorized into five groups according to the number of exposures to each MetS component (blood pressure [BP] ≥130/85 mmHg or antihypertensive medication use; triglyceride ≥150 mg/dL or lipid-lowering medication use; high-density lipoprotein cholesterol <40 mg/dL in men and <50 mg/dL in women or lipid-lowering medication use; WC ≥90 cm in men and ≥85 cm in women). The glucose criterion among the MetS components was excluded for this analysis, as the end-point was type 2 diabetes. Cox regression analyses were applied to derive the HRs (95% CIs) for the outcome incidence according to the number of exposures to each MetS component. The regression models were adjusted for the same potential confounders used in the previous analysis.

The HRs (95% CIs) for type 2 diabetes incidence rate in participants with at least one exposure to MetS were compared with those in participants with no exposure to MetS (reference) in subgroups classified by age (<65 vs ≥65 years), sex, regular exercise and presence of obesity. The stratified analysis and interaction testing were carried out to assess the potential effect modification by the factors determining the subgroups. The HRs (95% CIs) for the outcome incidence in participants with at least one exposure versus those with no exposure to obesity were also estimated in subgroups stratified by age (<65 vs ≥65 years), sex, regular exercise and the presence of MetS. The regression models were adjusted for age, sex, smoking history, alcohol consumption, regular exercise, family history of diabetes and mean FPG during the four examinations.

The individuals were classified into four groups according to the presence of at least one exposure to MetS and obesity (never exposed to MetS and obesity; no exposure to MetS, but at least one exposure to obesity; at least one exposure to MetS, but no exposure to obesity; and at least one exposure to both MetS and obesity). Cox regression analysis was carried out to estimate the HRs (95% CIs) for type 2 diabetes incidence according to these four groups. The individuals with no exposure to MetS and obesity were used as a reference. The regression models were adjusted for the same potential confounders used in the previous analysis.

We also carried out sensitivity analyses after excluding the following patients: (i) those with impaired fasting glucose (FPG ≥100 mg/dL) from the first to last examinations; and (ii) those with any malignancy (ICD-10 codes C00-C97) at or before baseline. SAS software (version 9.3; SAS Institute, Cary, NC, USA) was used for the statistical analyses. Two-sided *P*-values <0.05 were considered significant.

Table 1 | Baseline characteristics of participants according to the number of exposures to metabolic syndrome or obesity

Metabolic syndrome	No. exposures					*P*-value	*P* for trend
	0 (*n* = 1,875,845)	1 (*n* = 416,758)	2 (*n* = 232,376)	3 (*n* = 165,335)	4 (*n* = 161,431)		
Age (years)	41.24 ± 10.09	44.70 ± 10.18	46.04 ± 10.24	46.98 ± 10.13	48.60 ± 9.98	<0.001	<0.001
Men, *n* (%)	1,257,546 (67.04)	332,353 (79.75)	188,561 (81.14)	134,962 (81.63)	127,563 (79.02)	<0.001	<0.001
Current smoker, *n* (%)	562,956 (30.01)	156,421 (37.53)	89,124 (38.35)	63,721 (38.54)	60,026 (37.18)	<0.001	<0.001
Heavy alcohol consumption, *n* (%)	132,460 (7.06)	44,503 (10.68)	27,227 (11.72)	20,817 (12.59)	20,639 (12.79)	<0.001	<0.001
Regular exercise, *n* (%)	399,858 (21.32)	93,446 (22.42)	51,889 (22.33)	36,592 (22.13)	35,995(22.30)	<0.001	<0.001
Low-income level, *n* (%)	311,930 (16.63)	75,086 (18.02)	43,694 (18.80)	31,461 (19.03)	37,295 (23.10)	<0.001	<0.001
Family history of diabetes, *n* (%)	198,650 (10.59)	49,486 (11.87)	29,332 (12.62)	22,239 (13.45)	22,691 (14.06)	<0.001	<0.001
Bodyweight (kg)	63.96 ± 10.54	70.98 ± 11.03	73.87 ± 11.72	76.14 ± 12.29	77.56 ± 13.25	<0.001	<0.001
Body mass index (kg/m^2)	22.75 ± 2.69	24.93 ± 2.78	25.90 ± 2.91	26.64 ± 3.05	27.27 ± 3.26	<0.001	<0.001
Waist circumference (cm)	77.54 ± 7.81	83.92 ± 7.31	86.49 ± 7.45	88.42 ± 7.67	89.97 ± 8.25	<0.001	<0.001
Systolic BP (mmHg)	117.80 ± 12.32	125.00 ± 12.51	127.62 ± 12.68	129.54 ± 12.94	131.21 ± 13.64	<0.001	<0.001
Diastolic BP (mmHg)	74.24 ± 8.75	78.83 ± 8.88	80.54 ± 9.08	81.82 ± 9.36	82.88 ± 9.85	<0.001	<0.001
Fasting plasma glucose (mg/dL)	91.15 ± 11.34	97.18 ± 14.85	100.36 ± 17.47	103.76 ± 21.15	108.91 ± 27.53	<0.001	<0.001
Total cholesterol (mg/dL)	190.81 ± 32.6	201.73 ± 35.07	205.15 ± 36.16	206.88 ± 37.08	207.69 ± 38.61	<0.001	<0.001
Triglyceride (mg/dL)	93.45 (93.38–93.51)	144.55 (144.32–144.79)	168.96 (168.59–169.33)	187.73 (187.25–188.22)	201.04 (200.49–201.59)	<0.001	<0.001
HDL-C (mg/dL)	58.11 ± 14.55	50.75 ± 13.99	48.41 ± 13.75	46.93 ± 13.44	46.58 ± 13.95	<0.001	<0.001
LDL-C (mg/dL)	111.86 ± 31.95	119.64 ± 36.48	120.77 ± 38.82	120.69 ± 41.08	119.29 ± 43.01	<0.001	<0.001
ALT (U/L)	19.21 (19.20–19.23)	25.23 (25.19–25.27)	28.02 (27.96–28.08)	30.16 (30.08–30.24)	31.60 (31.51–31.68)	<0.001	<0.001
AST (U/L)	22.09 (22.08–22.10)	24.67 (24.64–24.69)	25.84 (25.80–25.88)	26.79 (26.74–26.84)	27.67 (27.62–27.72)	<0.001	<0.001
GGT (U/L)	23.43 (23.41–23.46)	34.52 (34.45–34.60)	39.93 (39.81–40.05)	44.20 (44.05–44.36)	47.40 (47.23–47.57)	<0.001	<0.001
Obesity	No. exposures					*P*-value	*P* for trend
	0 (*n* = 1,698,706)	1 (*n* = 189,514)	2 (*n* = 147,723)	3 (*n* = 172,147)	4 (*n* = 643,655)		
Age (years)	42.55 ± 10.57	43.09 ± 10.53	43.10 ± 10.42	43.33 ± 10.32	43.54 ± 9.85	<0.001	<0.001
Men, *n* (%)	1,101,044 (64.82)	143,901 (75.93)	116,329 (78.75)	138,054 (80.20)	541,657 (84.15)	<0.001	<0.001
Current smoker, *n* (%)	511,921 (30.14)	62,622 (33.04)	50,566 (34.23)	60,596 (35.20)	246,543 (38.30)	<0.001	<0.001
Heavy alcohol consumption, *n* (%)	118,389 (6.97)	17,411 (9.19)	14,552 (9.85)	17,816 (10.35)	77,478 (12.04)	<0.001	<0.001
Regular exercise, *n* (%)	342,668 (20.17)	44,022 (23.23)	35,583 (24.09)	42,208 (24.52)	153,299 (23.82)	<0.001	<0.001
Low-income level, *n* (%)	294,745 (17.35)	34,370 (18.14)	26,705 (18.08)	31,679 (18.40)	111,967 (17.40)	<0.001	<0.001
Family history of diabetes, *n* (%)	176,993 (10.42)	21,916 (11.56)	17,533 (11.87)	20,895 (12.14)	85,061 (13.22)	<0.001	<0.001
Bodyweight (kg)	61.00 ± 8.60	69.65 ± 7.81	71.71 ± 7.79	73.58 ± 8.10	80.43 ± 10.01	<0.001	<0.001
Body mass index (kg/m^2)	21.82 ± 1.89	24.60 ± 1.19	25.19 ± 1.10	25.79 ± 1.30	27.98 ± 2.20	<0.001	<0.001
Waist circumference (cm)	76.01 ± 6.94	82.40 ± 5.78	83.81 ± 5.54	85.20 ± 5.64	89.92 ± 6.73	<0.001	<0.001
Systolic BP (mmHg)	118.46 ± 13.01	122.21 ± 12.78	123.07 ± 12.63	123.86 ± 12.65	126.52 ± 12.90	<0.001	<0.001
Diastolic BP (mmHg)	74.60 ± 9.09	76.99 ± 9.05	77.59 ± 9.00	78.11 ± 8.99	80.05 ± 9.31	<0.001	<0.001
Fasting plasma glucose (mg/dL)	92.64 ± 13.52	94.91 ± 14.96	95.56 ± 15.72	96.32 ± 16.59	98.65 ± 18.72	<0.001	<0.001
Total cholesterol (mg/dL)	191.06 ± 33.40	198.51 ± 34.95	199.70 ± 34.77	200.61 ± 34.94	203.85 ± 35.26	<0.001	<0.001
Triglyceride (mg/dL)	98.58 (98.50–98.67)	122.17 (121.85–122.49)	127.03 (126.65–127.40)	132.23 (131.87–132.59)	151.65 (151.44–151.86)	<0.001	<0.001
HDL-C (mg/dL)	57.66 ± 15.04	53.52 ± 14.38	52.58 ± 14.37	51.73 ± 13.80	49.61 ± 13.72	<0.001	<0.001

Table 1 (*Continued*)

Obesity	No. exposures					*P*-value	*P* for trend
	0 (n = 1,698,706)	1 (n = 189,514)	2 (n = 147,723)	3 (n = 172,147)	4 (n = 643,655)		
LDL-C (mg/dL)	111.03 ± 33.22	117.53 ± 35.00	118.73 ± 35.07	119.39 ± 35.62	121.17 ± 36.84	<0.001	<0.001
ALT (U/L)	18.66 (18.64–18.67)	23.07 (23.01–23.12)	24.26 (24.20–24.33)	25.51 (25.45–25.58)	30.07 (30.03–30.11)	<0.001	<0.001
AST (U/L)	22.05 (22.04–22.06)	23.62 (23.58–23.65)	24.01 (23.97–24.05)	24.45 (24.41–24.49)	26.26 (26.23–26.28)	<0.001	<0.001
GGT (U/L)	23.48 (23.45–23.50)	29.71 (29.61–29.80)	31.69 (31.58–31.80)	33.61 (33.50–33.72)	40.32 (40.25–40.39)	<0.001	<0.001

Values are presented as number (%), mean ± standard deviation or median (interquartile range). ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; GGT, gamma-glutamyl transferase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

RESULTS

Baseline characteristics

The study population consisted of a total of 2,851,745 participants (Figure 1). During 14,299,943.82 person-years of follow up (mean 5.01 ± 0.75 years), there were 98,950 incident type 2 diabetes cases. The baseline characteristics are summarized according to the number of exposures to MetS and obesity (Table 1). Among the 2,851,745 participants, 1,875,845 (65.78%) had maintained a metabolically healthy status, whereas 161,431 (5.66%) had consistently shown a metabolically unhealthy phenotype throughout the four examinations. The remaining 814,469 (28.56%) had been intermittently exposed to MetS at a frequency of one to three times. With respect to obesity, 1,698,706 (59.57%) and 643,655 (22.57%) individuals had continued to be non-obese and obese, respectively. The remaining 509,384 (17.86%) had intermittently shown the obese phenotype from one to three times during the four annual or biennial examinations. The participants with a greater number of exposures to MetS or obesity were more likely to be older and heavy alcohol consumers, and had a trend of increasing baseline BMI, WC, systolic BP, diastolic BP, FPG, total cholesterol, triglycerides, alanine aminotransferase, aspartate aminotransferase and gamma-glutamyl transferase, and decreasing high-density lipoprotein cholesterol levels. Furthermore, those with a greater number of exposures to MetS or obesity had a higher proportion of a family history of diabetes. The participants with a greater number of exposures to obesity were more likely to be men and current smokers, and had higher low-density lipoprotein cholesterol, whereas those with a greater number of exposures to MetS had a higher proportion of a low-income level.

Number of exposures to MetS or obesity and incident type 2 diabetes

The cumulative incidence of type 2 diabetes showed a sequential increase as the number of exposures to MetS or obesity advanced (Figure 2). As presented in Table 2, the risk of type 2 diabetes increased in the groups with a higher number of exposures to MetS (HR 2.92, 95% CI 2.86–2.99; HR 4.96, 95% CI 4.85–5.08; HR 7.46, 95% CI 7.30–7.63; HR 12.24, 95% CI 12.00–12.49 in groups with number of exposures one to four, respectively) and obesity (HR 1.60, 95% CI 1.56–1.65; HR 1.87, 95% CI 1.81–1.92; HR 2.25, 95% CI 2.19–2.31; HR 3.46, 95% CI 3.41–3.51 in groups with number of exposures one to four, respectively). Separate analyses by sex showed consistent results (Tables S2;S3), exhibiting a stronger positive association of cumulative number of exposures to MetS or obesity with incident type 2 diabetes risk in women than in men (P for interaction <0.001).

Number of exposures to each MetS component and incident type 2 diabetes

The HRs (95% CIs) for type 2 diabetes were calculated according to the number of exposures to each MetS component (Figure 3; Table S4). The risk of type 2 diabetes increased as the

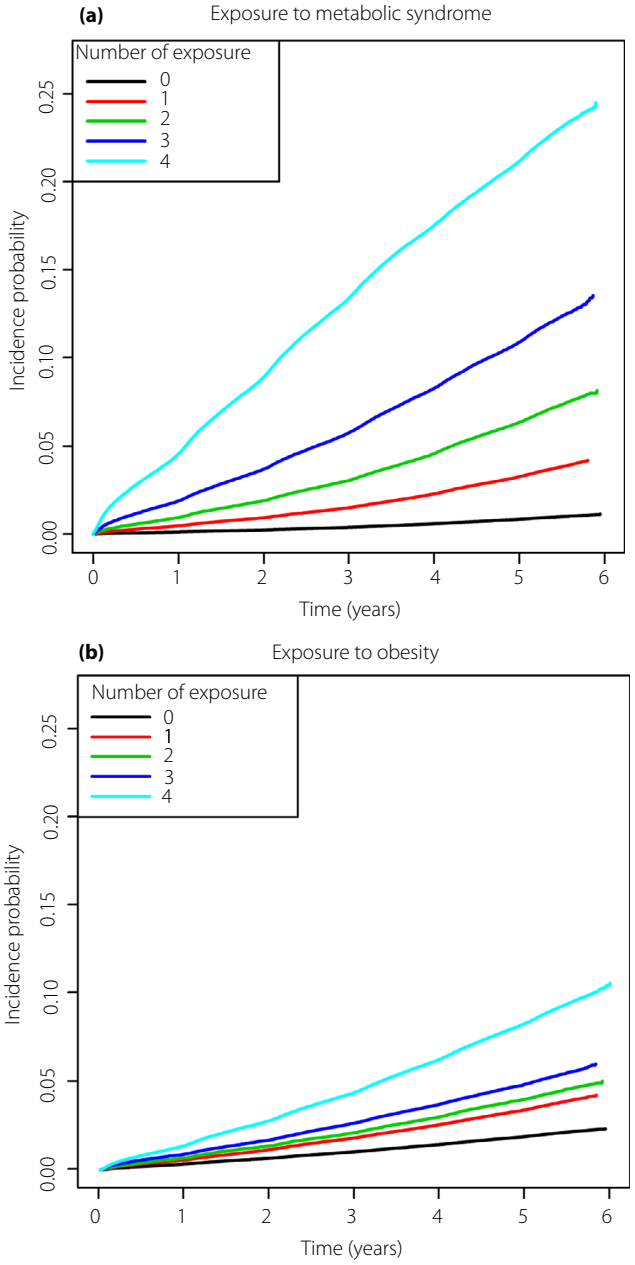

Figure 2 | Cumulative incidence of type 2 diabetes according to the number of exposures to (a) metabolic syndrome or (b) obesity.

number of exposures to components of BP, triglyceride, high-density lipoprotein cholesterol and abdominal obesity (defined by WC) advanced. Among these, the triglyceride criterion showed the most prominent association, whereas the extent of association of the BP component was modest in model 3.

Subgroup analysis

The HRs (95% CIs) for type 2 diabetes in the participants with at least one exposure to MetS or obesity were analyzed in subgroups stratified by age, sex, regular exercise and the presence of obesity or MetS, respectively, and compared with those of the participants with no exposure to these conditions (Figure 4). The participants with at least one exposure to MetS had a higher risk for type 2 diabetes in all subgroups compared with those without exposure. However, the association was more prominent in participants aged <65 years, women and individuals not exercising regularly (P for interaction <0.001). No effect modification was observed according to the presence of obesity. Although those with at least one exposure to obesity had an increased risk for type 2 diabetes compared with those without exposure in all subgroups, a more prominent association was observed in participants aged <65 years, women, individuals not exercising regularly and individuals without MetS (P for interaction <0.001).

Combined exposures to MetS and obesity, and incident type 2 diabetes

The HRs (95% CIs) for type 2 diabetes were calculated in four groups created based on the presence of at least one exposure to MetS and obesity (Figure 5). When the group never exposed to MetS or obesity was set as a reference, the HRs for type 2 diabetes increased sequentially for the group exposed only to obesity (HR 1.74, 95% CI 1.68–1.79), that exposed only to MetS (HR 4.63, 95% CI 4.51–4.74), and that exposed to both obesity and MetS (HR 7.90, 95% CI 7.73–8.07).

Sensitivity analyses

The results were consistent when the participants with an impaired fasting glucose (FPG ≥100 mg/dL) from the first through the last examinations were excluded (Table S5), with higher HRs according to the number of exposures to obesity compared with the original analysis. The analysis after excluding patients with any malignancy at or before baseline also showed consistent results (Table S6).

DISCUSSION

This large-scale longitudinal study including 2,851,745 participants with four annual or biennial examinations showed that the cumulative exposure to both obesity and MetS is associated with type 2 diabetes incidence in a dose–response manner. The influence of the cumulative exposure to MetS on the incidence of type 2 diabetes was much more detrimental, compared with the exposure to obesity. The increasing exposure to the individual components of MetS was associated with a sequential increase in the type 2 diabetes risk.

In the present study, the metabolic health status changed in 28.56% of the participants, whereas 17.86% showed fluctuations in the obesity status during the four examinations. There have been reports on the transition of the metabolic health and obesity status[12–14,16,25,26]. In the recent Framingham Heart Study, the changes in obesity sub-phenotypes determined by the presence of obesity and metabolic abnormality were noticed in

Table 2 | Hazard ratios and 95% confidence intervals for the incidence of type 2 diabetes according to the number of exposures to metabolic syndrome or obesity

No. exposures	Events (*n*)	Follow-up duration (person-years)	Incidence rate (per 1,000 person-years)	Model 1	Model 2	Model 3
Metabolic syndrome						
0 (*n* = 1,875,845)	16,310	9,545,893.58	1.71	1(Ref.)	1(Ref.)	1(Ref.)
1 (*n* = 416,758)	14,188	2,089,464.12	6.79	3.99 (3.90–4.08)	3.63 (3.55–3.71)	2.92 (2.86–2.99)
2 (*n* = 232,376)	15,279	1,145,990.00	13.33	7.84 (7.67–8.02)	6.88 (6.73–7.04)	4.96 (4.85–5.08)
3 (*n* = 165,335)	18,543	795,224.25	23.32	13.75 (13.46–14.04)	11.78 (11.53–12.04)	7.46 (7.30–7.63)
4 (*n* = 161,431)	34,630	723,371.88	47.87	28.44 (27.91–28.97)	23.32 (22.87–23.77)	12.24 (12.00–12.49)
P for trend				<0.001	<0.001	<0.001
Obesity						
0 (*n* = 1,698,706)	29,983	8,600,474.36	3.49	1(Ref.)	1(Ref.)	1(Ref.)
1 (*n* = 189,514)	6,032	948,366.50	6.36	1.83 (1.78–1.88)	1.78 (1.74–1.83)	1.60 (1.56–1.65)
2 (*n* = 147,723)	5,524	736,937.33	7.50	2.16 (2.10–2.22)	2.11 (2.05–2.17)	1.87 (1.81–1.92)
3 (*n* = 172,147)	7,768	855,208.85	9.08	2.61 (2.55–2.68)	2.54 (2.47–2.60)	2.25 (2.19–2.31)
4 (*n* = 643,655)	49,643	3,158,956.78	15.72	4.52 (4.46–4.59)	4.40 (4.33–4.46)	3.46 (3.41–3.51)
P for trend				<0.001	<0.001	<0.001

Model 1: unadjusted. Model 2: adjusted for age and sex. Model 3: adjusted for age, sex, smoking history, alcohol consumption, regular exercise, family history of diabetes, and mean fasting plasma glucose level during the four health examinations. Ref., reference.

>25% of the participants within 4 years, almost consistent with the present finding[13]. In that study, the probability of MHO becoming metabolically unhealthy obesity was 43% in women and 46% in men, suggesting that MHO is the phenotype most susceptible to change over time[13]. Not accounting for changes in the metabolic health and obesity status over time might have contributed to the controversy over the clinical significance of the MHO.

Only a limited number of studies have reflected the fluctuation of the metabolic health and obesity status over time by exploring the relationship between the metabolic health and obesity status, and the clinical outcomes, including type 2 diabetes. Although Echouffo-Tcheugui *et al.*[13] tried to account for the cumulative effect of the dynamic changes in the metabolic health and obesity status by developing a scoring system, this system only reflected the combined effect of the metabolic health and obesity status, and could not calculate the cumulative duration of MetS and obesity individually. To the best of our knowledge, the present study is the first to show the dose–response effect of the cumulative exposure to MetS and obesity on the incidence of type 2 diabetes, respectively. In the present study, the risk of type 2 diabetes increased with the increased exposure to MetS, and this effect was much greater than that observed for the exposure to obesity. Several studies had similar conclusions, that metabolic unhealthiness was a stronger predictor of incident type 2 diabetes than obesity[4,27,28]. Navarro-Gonzalez *et al.*[27] showed that among the MHO participants, only individuals who progressed to an unhealthier status over time had a greater risk of diabetes. Liu *et al.*[4] reported that for participants with the same number of metabolic abnormalities, the risk for diabetes did not increase along with the BMI category, but it showed an increasing trend along with the metabolic abnormalities for the same BMI categories. Similarly, in the present study, those who were ever exposed to MetS had an increased risk for type 2 diabetes, regardless of the presence of obesity at baseline. All these results suggest that the metabolic unhealthiness is a more important determinant for diabetes incidence than obesity. Similarly, with regard to CVDs, Kouvari *et al.*[29] reported that, when both obesity and metabolic status were included in the mediation analysis, an independent effect on a 10-year CVD event was retained only for the metabolic status, but not for obesity.

However, other evidence supports the notion that the continuous exposure to obesity can increase the risk of type 2 diabetes or CVDs[12,30,31]. Arnlov *et al.*[30] reported that overweight and obese men without MetS had an increased risk for diabetes after 20 years, and the Nurses' Health Study showed that obesity remains a risk factor for CVD, even when metabolic health is maintained during long periods of time[12]. In the present study, the participants who were exposed only to obesity, but not to MetS, showed a modest increase in the HR for type 2 diabetes. Furthermore, a significant dose–response relationship was found between the frequency of exposure to obesity and type 2 diabetes incidence. Interestingly, the present study

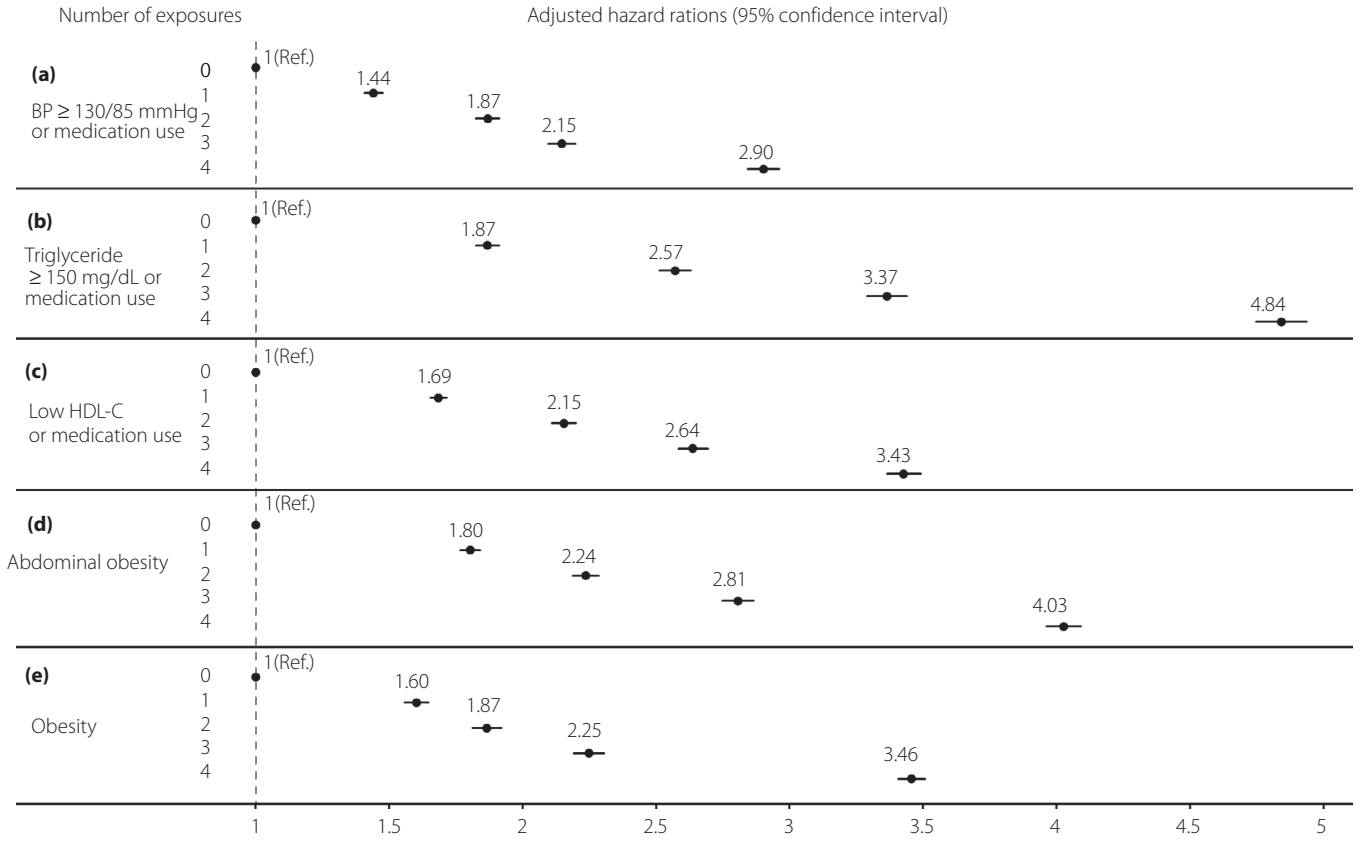

Figure 3 | Hazard ratios and 95% confidence intervals for the incidence of type 2 diabetes according to the number of exposures to obesity or metabolic syndrome components. (a) Blood pressure ≥130/85 mmHg or medication use. (b) Triglyceride level ≥150 mg/dL or medication use. (c) High-density lipoprotein cholesterol <40 mg/dL in men and <50 mg/dL in women or medication use. (d) Abdominal obesity. (e) Obesity. Cut-off values for abdominal obesity: waist circumference: ≥90 cm in men, ≥85 cm in women according to the Korean Society for the Study of Obesity. Adjusted for age, sex, smoking history, alcohol consumption, regular exercise, family history of diabetes and mean fasting plasma glucose level during the four health examinations. BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; Ref., reference.

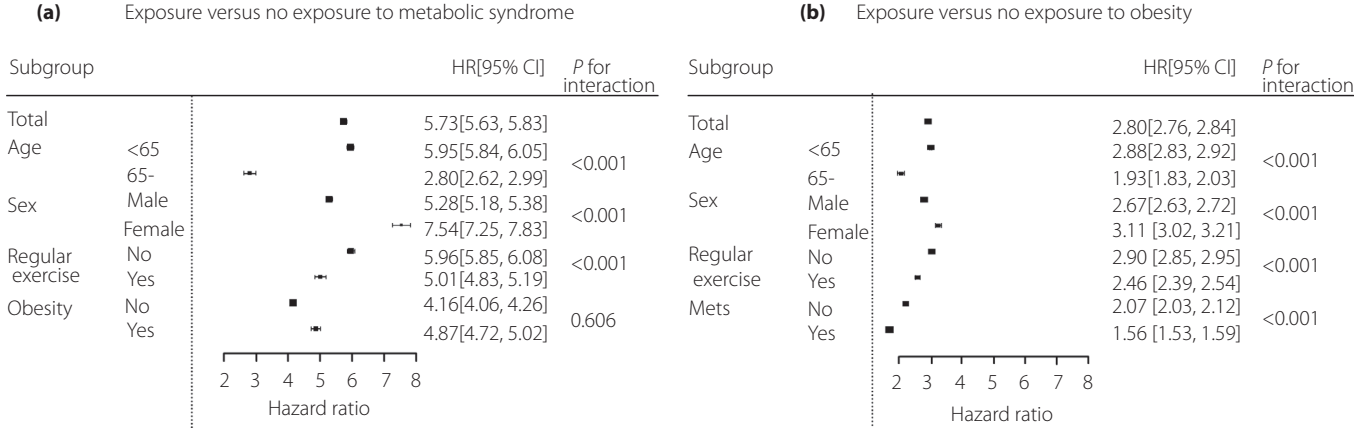

Figure 4 | Adjusted hazard ratios (HR) and 95% confidence intervals (CI) for the incidence of type 2 diabetes in participants with exposure versus no exposure to (a) metabolic syndrome or (b) obesity in subgroups. Adjusted for age, sex, smoking history, alcohol consumption, regular exercise, family history of diabetes and mean fasting plasma glucose level during the four health examinations. MetS, metabolic syndrome.

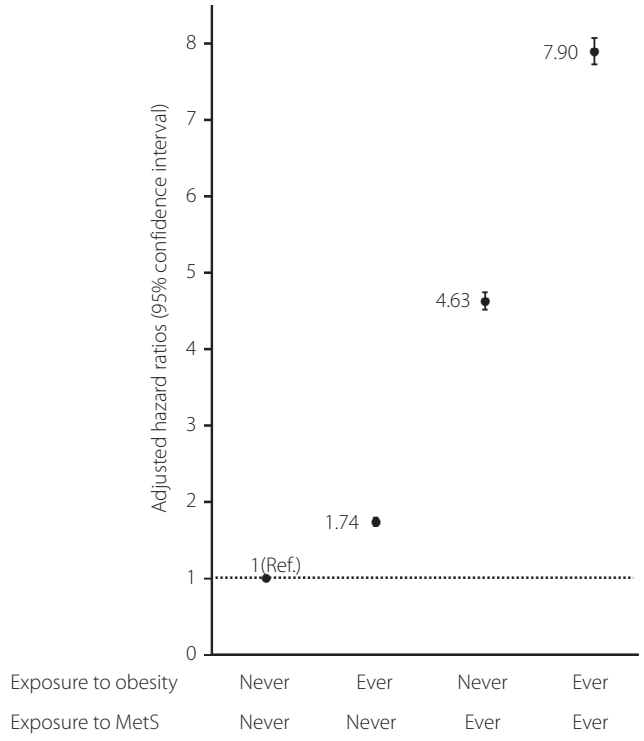

Figure 5 | Adjusted hazard ratios and 95% confidence intervals for the incidence of type 2 diabetes according to the presence or absence of at least one exposure to metabolic syndrome and obesity. Adjusted for age, sex, smoking history, alcohol consumption, regular exercise, family history of diabetes and mean fasting plasma glucose level during the four health examinations. MetS, metabolic syndrome; Ref., reference.

showed a more prominent association between the exposure to obesity and the risk of type 2 diabetes in the individuals without baseline MetS, suggesting that the exposure to obesity has an additional role as a risk factor for type 2 diabetes in a metabolically healthy condition. In the Women's Health Initiative, over the 6-year follow up, metabolically healthy women with a greater baseline BMI showed a tendency toward metabolic deterioration, and those with a lower baseline BMI, toward metabolic improvement[26]. In 2,748 participants of the Multi-Ethnic Study of Atherosclerosis without baseline MetS, the duration of obesity was positively associated with incident MetS[18]. Camhi *et al.*[32] showed that the obesity duration was higher in participants with a transient MHO phenotype than in those with a stable MHO phenotype. In this respect, the cumulative obesity exposure can lead to the development of MetS and cardiometabolic disorders, including type 2 diabetes. Therefore, continuous weight control in obese individuals, as well as the management of metabolic risk factors, is warranted for the prevention of type 2 diabetes.

In the subgroup analysis, the association between the exposure to MetS or obesity and the risk for type 2 diabetes was more prominent in individuals aged <65 years, women and individuals not exercising regularly. When separate analyses by sex were applied, a stronger positive association between the cumulative number of exposures to MetS or obesity and type 2 diabetes risk was observed in women than in men. Caleyachetty *et al.*[33] reported a similar result; MHO individuals aged <65 years and MHO women had a stronger positive association with CVDs during a mean follow-up period of 5.4 years, suggesting possible vulnerability of these subgroups. The more prominent association between obesity exposure and type 2 diabetes risk in women might arise from the dependency of BMI on sex as a measure to reflect fat mass. For the same BMI, women have been reported to have greater amounts of fat mass than men throughout their entire adult life[34–36]. Furthermore, previous meta-analyses have shown that the CVD risk conferred by the MetS is higher in women than men[37], and varied distribution of central adiposity, lipid profiles, hormones, platelet biology and biochemistry have been proposed as possible explanations[37]. In respect to a more prominent association in individuals aged <65 years, from a statistical point of view, in an older population, more individuals might be at risk for type 2 diabetes incidence in general, possibly attenuating the excess effect of exposures to MetS or obesity.

The limitations of the present study should be considered. First, because of the retrospective nature, the clarification of causal relationships is inevitably limited. However, to minimize the possible reverse causality effect, individuals with prescriptions for antidiabetes medications or claims under diabetes codes at or before baseline were excluded, and the number of exposures to obesity or MetS was assessed before the baseline. Furthermore, the sensitivity analysis excluding individuals with impaired fasting glucose showed consistent results. Second, considering that the mean BMI of the participants who were continuously obese during the four examinations was 27.98 kg/m^2, the present results might not be generalizable to individuals with more severe obesity. Third, the possibility of missing early type 2 diabetes incidence cannot be fully excluded, because data about oral glucose tolerance tests and glycated hemoglobin were unavailable to diagnose incident type 2 diabetes.

In this large, population-based study, we observed that the metabolic health and obesity status might fluctuate within a relatively short period (4–5 years). Furthermore, the cumulative exposure to both MetS and obesity was associated with an increased risk of incident type 2 diabetes in a graded dose–response manner, and the exposure to MetS had a much greater impact than the exposure to obesity. It would be warranted to minimize the exposure to MetS and obesity through constantly maintaining metabolic health and normal weight for the prevention of type 2 diabetes.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Definitions of covariates.

Table S2 | Hazard ratios and 95% confidence intervals for the incidence of type 2 diabetes according to the number of exposures to metabolic syndrome or obesity, subgroup analysis including only male participants.

Table S3 | Hazard ratios and 95% confidence intervals for the incidence of type 2 diabetes according to the number of exposures to metabolic syndrome or obesity, subgroup analysis including only female participants.

Table S4 | Hazard ratios and 95% confidence intervals for the incidence of type 2 diabetes according to the number of exposures to obesity or metabolic syndrome components.

Table S5 | Hazard ratios and 95% confidence intervals for the incidence of type 2 diabetes according to the number of exposures to metabolic syndrome or obesity, sensitivity analysis after excluding patients with impaired fasting glucose (fasting glucose ≥100 mg/dL) from the first to last health examinations.

Table S6 | Hazard ratios and 95% confidence intervals for the incidence of type 2 diabetes according to the number of exposures to metabolic syndrome or obesity, sensitivity analysis after excluding patients with any malignancy at or before baseline.