BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-021768
Article Type:	Research
Date Submitted by the Author:	26-Jan-2018
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Keywords:	type 2 diabetes, body mass index, young onset diabetes, aging

Association of body mass index and age with incident diabetes in Chinese adults

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Running head: Effect of BMI and age on incident diabetes

Key terms: type 2 diabetes, body mass index, age, young-onset diabetes

Conflict of interest:

The authors declare no conflicts of interest.

Financial support:

The authors thank the field investigators for their contribution and the participants for their cooperation. This work is supported by grants from the National Key Research and Development Program of China (No.2016YFC1304801), the Natural Science Foundation of Nantong (HS2014036), the six talent peaks project in Jiangsu Province (WSN-098), the open research project of Shanghai Key Laboratory of Diabetes Mellitus (SHKLD-KF-1303).

Authors' contributions:

YC, XZ, SC and XL participated in study concept and design. YC, XZ, XW, XW, and YZ did the data collection. YC, BC, JY, ZT, TY, XZ, YG participated in the analysis and interpretation of the data, and drafted the manuscript. XL, SC and YC revised the manuscript and approved the final version of the manuscript. All authors approved the final version of the manuscript.

Data sharing statement:

No additional data sharing available.

Abstract

Objective Type 2 diabetes mellitus is increasing in young adults and greater adiposity is considered as a major risk factor. However, whether the heterogeneity of the association exited among young, middle, and old adults is little known. We investigated the association of BMI with incidence of diabetes in wide range of age groups (20-30, 30-40, 40-50, 50-60, 60-70, ≥70), and modifying effect of younger age was further explored.

Design A retrospective cohort study using a healthy screening program data.

Setting A total of 211,833 adult Chinese aged more than 20 years old, who were free of diabetes at baseline, were resident in 32 sites from 11 cities in China (Shanghai, Beijing, Nanjing, Suzhou, Shenzhen, Changzhou, Chengdu, Guangzhou, Hefei, Wuhan, Nantong).

Primary and secondary outcome measures Fasting plasma glucose level was measured and information of history of diabetes was collected at each visit. Diagnosis of incident diabetes was made according to 1999 WHO criteria. Patients were censored at the date of diagnosis of diabetes or the final visit, whichever came first.

Results In a median follow-up of 3.1 years, 4174 of 211,833 participants developed diabetes, with an age-adjusted incidence rate of 7.35 per 1000 persons. The risk of incident diabetes increased by dose-responsive manner of baseline BMI values, with 23% increased risk of incident diabetes by each kg/m^2 increase of BMI (95%CI: 1.22, 1.24). Across all age groups (20-30, 30-40, 40-50, 50-60, 60-70, ≥70) respectively, the linear association between BMI and risk of incident diabetes always existed, and a

stronger association of BMI and incident diabetes was shown in younger age group (age × BMI interaction, $P< 0.0001$).

Conclusions An increased BMI is also independently associated with a higher risk of developing diabetes in young adults and effect of BMI on incident diabetes was accentuated in younger age adults.

Key terms: type 2 diabetes, body mass index, age, young-onset diabetes

Strengths and limitations of this study:

1. The large sample size allows analysis of the interaction of age and BMI on incident diabetes.
2. Our study was comprised of young, middle, and old-aged apparently healthy adults, while participants in many other cohorts tended to be older.
3. The data was collected under standardized conditions and followed according to uniform procedures by trained staff. Laboratory methods also were carefully standardized with rigorous internal and external quality controls.
4. We only measured body weight and height at baseline, which could not address fat distribution and weigh change.

Type 2 diabetes is worldwide epidemic. The IDF estimates that about 415 million people worldwide had type 2 diabetes mellitus in 2015. This number is expected to rise to 642 million by 2040, with 140.2 million of affected people living in Asia [1]. Although diabetes has traditionally been thought of as a disease that affects elderly people, the prevalence of type 2 diabetes in young adults is increasing. The national surveys in China reported that 7.09% individuals had developed diabetes younger than 40 years in 2011, while it was less than 1% two decades ago [2]. Those younger diabetic patients would have poorer prognosis; risk of cardiovascular disease and microvascular complications was greater increased [3, 4]. The reasons for the declining age at onset of type 2 diabetes are complicated; it was speculated the increasing prevalence of obesity in young-aged individuals might partly contribute to the epidemic of diabetes in young people [5].

Greater adiposity is a major risk factor for development of type 2 diabetes. A meta-analysis combining 18 prospective cohort studies reported that the overall RR of diabetes for obese persons compared to those with normal weight was 7.19 (95% CI: 5.74, 9.00) and for overweight was 2.99 (95% CI: 2.42, 3.72) [6]. Obesity and diabetes are so related that was deemed as “diabesity” [7]. Of note, they are all age-related [8, 9]. Younger age itself is a protective factor of incident diabetes, with per 10 years decrease of age, the risk of developing diabetes decrease by 50%-70% [10]. However, obesity prevalent in young seemed to weaken the protective effect of age on diabetes. The NCD Risk Factor Collaboration pooled 128·9 million children, adolescents, and adults to assess worldwide trends in body-mass index, underweight,

overweight, and obesity from 1975 to 2016 and found that the mean BMI and obesity prevalence in adolescents and young adults is rising in past decades, and the trend is still continuing [11]. However, heterogeneous and differences effect of BMI on obesity-related disease between young adults and the elder remained unconsistent. It was found that the risk of mortality by per unit increase of BMI is greater in younger than in older people [12]. However, the modified effect of age on the association between BMI and kidney disease seems the opposite [13]. The heterogeneity of the association for diabetes in young, middle, and old adults has rarely explored. Asia Pacific Cohort Studies Collaboration pooled twenty-seven cohorts from Asia, New Zealand and Australia found that the association between BMI and risk of diabetes was stronger in participants aged less than 60 years old compared with 60-69 age group and more than 70 age group [14]. Of note, the conclusion was derived from older adults whom aged more than 40 years old. Whether it can generalize to young adults, which age group was rarely pained attention for risk of developing diabetes in the past but currently increased diabetes were occurred, is unknown. Therefore, in the present study, we investigated the association of BMI and risk of incident diabetes in a large retrospective cohort ranging from 20 to 99 years old, and further whether the heterogeneity of the association existed in young adults compared with older adults was investigated.

METHODS

Study design and participants

Data were extracted from a computerized database established by Rich Healthcare Group, China which includes all medical records for the participants who receive the health check from 2010 to 2016. The present analysis initially included all study participants aged equal to or more than 20 years old with at least two visits between 2010 to 2016 (n=685277). Participants were excluded at baseline if they had no available weight and height measurements (n=103946), no available information for gender (n=1), extreme BMI values (<15 kg/m^2 or >55 kg/m^2) (n=152), or no available fasting plasma glucose value (n=31370). We further excluded participants of visit interval less than 2 years (n=324233), participants diagnosed of diabetes at baseline (2997 participants diagnosed by self-reported and 4115 diagnosed by fasting plasma glucose ≥7.0 mmol/L), and participants with status of diabetes undefined at follow up (n=6630). Finally, a total of 211833 participants (116123 male and 95710 female) were included in the analysis. Cohort entry was defined as the date of the initial visit.

This study has been approved by the Rich Healthcare Group Review Board. And the information was retrieved retrospectively.

In each visit to the health check center, participants were requested to complete a detailed questionnaire assessing demographic, lifestyle, medical history and family history of chronic disease. Height, weight, and blood pressure are measured by trained staffs. Body weight was measured in light clothing with no shoes to the nearest 0.1 kg. Height was measured to the nearest 0.1cm. Body mass index was derived from weight

in kilograms divided by height in meters squared. Blood pressure was measured by standard mercury sphygmomanometers.

Fasting venous blood samples were collected after at least 10-h fast at each visit. Serum triglyceride (TG), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), and high density lipoprotein cholesterol (HDL-C), were measured on the autoanalyser (Beckman 5800). Plasma glucose levels were measured by glucose oxidase method on an autoanalyser (Beckman 5800).

Ascertainment of incident diabetes

Diagnosis of incident diabetes was made according to 1999 WHO criteria, with fasting plasma glucose of ≥ 7.00 mmol/L or self-reported diabetes during the follow-up period. Patients were censored at the date of diagnosis of diabetes or the final visit, whichever came first.

Statistical analysis

Statistical analyses were performed on SAS 9.3 (SAS Institute, Cary, NC). A two-sided *P* value less than 0.05 was considered as statistical significance. Data from descriptive analyses were reported as mean (SD), or median (IQR), or proportions. Participants were stratified into six baseline age groups with 10-year increments starting from 20-30 years old to over 70 years old. Linear regression models were performed to assess the relationship of BMI, metabolic parameters, lifestyles, and family history of diabetes with age. Diabetes incidence was calculated in each and

total age groups, and age-standardized diabetes incidence was adjusted to the Chinese population in 2010 [15].

Cox proportional hazard regression models were performed to estimate BMI-adjusted and multivariable-adjusted hazard ratios (95% confidence intervals) of age with incident diabetes, and age-adjusted and multivariable-adjusted hazard ratios (95% confidence intervals) of BMI with incident diabetes. Analyses of BMI used predefined standard categories according to Chinese criteria of obesity [16]: underweight (<18.5kg/m^2), normal weight (18.5-<24.0 kg/m^2), overweight (24.0-<28.0 kg/m^2), and obesity (≥28.0 kg/m^2). The normal BMI group (18.5-<24.0 kg/m^2) was chosen as the referent category. Covariates in the multivariable models included age, sex, smoking status, drinking status, family history of diabetes. The association of BMI with incident diabetes influenced by age was further investigated. Hazard ratios (HRs) of incident diabetes were calculated respectively in each age group by Cox proportional hazard regression models with BMI of 18.5-<24.0 kg/m^2 as the reference category. Since the associations of BMI with risk of incident diabetes were approximately linear, the HRs and corresponding 95%CI for incident diabetes across all age groups were estimated for per kg/m^2 increase of BMI value. The modification effect was assessed for interaction of age and BMI in the Cox model.

In consideration of the baseline confounding factors including smoking status, and family history of diabetes were considered related to diabetes in young adult, subgroup analyses were further performed respectively HR of smoking status, and family history of diabetes on the risk of diabetes. And interaction of BMI*current

smoker, age*family history of diabetes were assessed in Cox model.

RESULTS

211,833 participants (116123 male and 95710 female) without diabetes at baseline were recruited. The mean age was 42.1 years old (SD 12.6), ranging from 20 to 99 years old. The mean BMI value was 23.2 kg/m^2 (SD 3.3). Baseline clinical and biochemical characteristics of participants stratified by age and sex are presented in Table 1. BMI, total serum cholesterol, triglyceride, and LDL-C, fasting plasma glucose, systolic blood pressure, and diastolic blood pressure were gradually increased with age increase respectively in men and women.

During a median of 3.1 year follow-up (660,191 person-years), 4174 of 211,833 participants developed diabetes. The incidence of diabetes was 7.35 per 1000 person-year with age-standardization (Table 2). The risk of incident diabetes was increased by dose-responsive manner of baseline age and BMI values (Table 2). With per 10 years increase of age, the HR of developing diabetes increased by 88% (95%CI: 1.85, 1.92). Taken participants aged 20-30 years old as reference, BMI-adjusted HR for incident diabetes was 1.64 (95%CI: 1.29-2.09) in participants aged 30-40 years old, 3.83 (95%CI: 3.03, 4.86) in participants aged 40-50 years old, 8.39 (95%CI: 6.64, 10.59) in participants aged 50-60 years old, 11.77 (95%CI: 9.30, 14.89) in participants aged 60-70 years old, and 17.55 (95%CI: 13.79, 22.33) in participants aged ≥70 years old. Taken participants with BMI of 18.5-<24.0 kg/m^2 as reference, age-adjusted HR for incident diabetes was 0.39 (95%CI: 0.27-0.56) in participants with BMI of <18.5 kg/m^2, 2.51 (95%CI: 2.33, 2.70) with BMI of 24.0-27.9 kg/m^2, and 5.58 (95%CI: 5.13, 6.07) with BMI of ≥28.0 kg/m^2. Further adjustment for sex,

smoking status, drinking status, and family history of diabetes did not alter the trend appreciably.

Sex-adjusted HRs (95%CI) of BMI for risk of incident diabetes was shown in Figure 1 and Supplementary Table 1. Taken participants with BMI of 18.5-<24.0 kg/m^2 as reference, age-adjusted HR for incident diabetes for overweight and obesity were higher at younger ages than older ages. The linear association between BMI and risk of incident diabetes existed in participants across all age groups. When BMI was analyzed as a continuous variable, sex-adjusted HR of developing diabetes was 1.23 (95%CI: 1.22, 1.24) for each kg/m^2 increase of BMI. A stronger association of BMI and incident diabetes was shown in younger age group (Table 3). The risk of incident diabetes was increased by 35% (95%CI: 1.29, 1.40) for each kg/m^2 increase of BMI in 20-30 years old group, 31% (95%CI: 1.29, 1.33) in 30-40 years old group, 27% (95%CI: 1.25, 1.29) in 40-50 years old group, 18% (95%CI: 1.17, 1.20) in 50-60 years old group, 13% (95%CI: 1.11, 1.15) in 60-70 years old group, and 11% (95%CI: 1.08, 1.14) in greater than 70 years old group. The descending trend by age was not altered by further adjustment of smoking status, drinking status, family history of diabetes. Obviously, age significantly modified the association of BMI and risk of incident diabetes (age × BMI interaction, $P< 0.0001$).

Current smokers were at a decreased risk of incident diabetes (HR: 0.79; 95%CI: 0.74, 0.84), and participants with family history of diabetes were at an increased risk of incident diabetes (HR: 1.68; 95%CI:1.38-2.03). The multiplicative interactions of BMI × smoking status (P for interaction=0.25), age × family history of diabetes (P for

interaction=0.71) for the risk of incident diabetes were not detected (Supplementary table 2).

DISCUSSION

In the present cohort, an age-standardized diabetes incidence of 7.35 per 1000 person-year during 2010-2016 was detected. We demonstrated a linear association between baseline BMI and risk of developing diabetes, with increased each kg/m^2 of BMI associated with 23% (95%CI: 1.22, 1.24) higher risk of incident diabetes. The risk of incident diabetes was increased by 35% (95%CI: 1.29, 1.40) for each kg/m^2 increase of BMI in 20-30 years old group, 31% (95%CI: 1.29, 1.33) in 30-40 years old group, and slightly lower in 40-50 years old group, 50-60 years old group, 60-70 years old group, and more than 70 years old group, with HR of 1.27 (95%CI: 1.25, 1.29), 1.18 (95%CI: 1.17, 1.20), 1.13 (95%CI: 1.11, 1.15), 1.11 (95%CI: 1.08, 1.14), respectively. Further analyses showed that age had a modifying effect on the association. Effect of BMI on incident diabetes was stronger in young adults. Subgroup analyses showed that the interactions of BMI × smoking status and age × family history of diabetes for the risk of incident diabetes were not detected.

Our study reported an age-standardized diabetes incidence of 7.35 per 1000 person-year during 2010-2016. With lifestyle changes, prevalence of type 2 diabetes has increased rapidly in the past decades in China. Data from national surveys showed that the prevalence of diabetes was 0.9% in 1980 [18], 2.5% in 1994 [19], 9.7% in 2007 [20], and 10.9% in 2013 [21]. However, the incidence of diabetes appears to have stabilized and there have been small declines from 2007 to 2014 [22], which is unconsistent with the prevalence trend. As from our large sample cohort, cases of diabetes increased by 7.35 per 1000 person-year between 2010 and 2016. All diabetes

diagnoses was based on self-reported diabetes combined with fasting glucose level equal to or more than 7.0 mmol/L. Regarding to the high intake of carbohydrate, Chinese is characteristic of impaired post load glucose regulation. The definition lacking of 2 h postprandial plasma glucose assessment might underestimate the true incidence of diabetes. However, 2h postprandial plasma glucose assessed by an oral glucose-tolerance test is not suitable for large sample surveys.

Obesity is the major risk factor for diabetes development. Hartemink N et al. conducted a meta-analyses with a dose-response relationship between body mass index and type 2 diabetes detected. It was shown that, with per kg/m^2 increase of BMI, the risk of diabetes increased by 18% (95% CI: 1.16-1.20), accounting for the heterogeneity of studies [23]. The etiological effect of BMI was mostly derived from European population, Chinese individuals tend to have a higher diabetes risk, and increased risk in other diabetes risk factors with per unit increase of BMI have been reported [24, 25]. In the present study, age-adjusted HR for incident diabetes was 2.51 (95%CI: 2.33, 2.70) in overweight individuals with BMI of 24.0-27.9 kg/m^2, and 5.58 (95%CI: 5.13, 6.07) in obese individuals with BMI of ≥28.0 kg/m^2, compared with normal weight individuals with BMI of 18.5-<24.0 kg/m^2. Our HR of risk of diabetes incidence with per kg/m^2 increase of BMI was 1.23 (95% CI: 1.22-1.24), which was slightly higher than previous reported [23]. Moreover, it was interesting to find that HR was significantly higher in earlier adulthood aged less than 40 years old.

Young age itself is a remarkable protective factor for developing diabetes. Whilst most of the increase in the prevalence of T2DM has been seen in the middle-aged and

elderly, there is strong evidence that it is becoming more common among young adults. Increasing prevalence of obesity in young individuals has been speculated to partly explain the increasing prevalence of diabetes in young adults. However, available data on diabetes in young are rare. Recent studies have shown the association between BMI and its outcomes varied in younger adults vs old adults. The global BMI mortality collaboration including 239 prospective studies in four continents found that risk of mortality with per units increase of BMI was greater in younger than older people [12], however, the modified effect of age on the association between BMI and kidney disease seems the opposite [13].The heterogeneity of age on the association of obesity and type 2 diabetes has been assessed in only a few studies and the results were unconsistent. Data from the Third National Health and Nutrition Examination Survey showed that BMI was strongly associated with increased relative risk of metabolic disorders including type 2 diabetes and cardiovascular diseases; Furthermore, the association between BMI and cardiovascular disease and hypertension was attenuated with age increased. However, the modifying effect of age on the association between BMI and type 2 diabetes was not detected [26]. Meta-analysis data from Japan, Australia and New Zealand, respectively demonstrated a stronger association between BMI and risk of diabetes in subjects aged less than 60 years as compared with those aged over 70 years [27]. However, included individuals were most middle and elderly aged. The limited sample size and age range might contribute to the disparity. Avoiding these factors, we found a generally consistent linear association between BMI and incident diabetes that

weakened by increasing age. BMI had a much greater risk on incident diabetes in earlier adulthood than in later adulthood, which was consistent with the findings from meta analysis conducted by Ni Mhurchu C et al [27], and extending the finding to adults less than 40 years old.

The mechanism of heterogeneity of BMI effect between earlier adulthood vs later adulthood is unclear. Young onset obesity adulthood are reported to have chronically increased levels of circulating free fatty acids and adipokines, which reduce insulin sensitivity and might contribute to increased reactive oxygen species and impaired insulin secretion [28, 29]. Furthermore, young onset obesity patients might have an early life exposure to maternal undernutrition or over-nutrition, which are associated with an increased risk of type 2 diabetes [30, 31]. And young onset obesity individuals tend to have a detrimental lifestyle, which might also contribute to development of adiposity, insulin resistance, hyperglycaemia, and other cardiovascular risk factors in young people [32, 33]. Therefore, obese youth were led to lose the relative protection of youth.

Smoking is a concern in analysis of BMI and diabetes because it is associated with decreased body weight and an increased risk of diabetes [34]. In our study, smoking status was statistically adjusted. And interaction of BMI*smoking status on the risk of incident diabetes was explored, and no statistical significance was found. Previous studies have reported type 2 diabetes in youth usually had positive family history of diabetes [35]. Similar in our study, family history of diabetes is an independent risk factor for type 2 diabetes. However, no interaction of age*family

history of diabetes had been detected.

Addition to the large sample size, the major strenghth of our study is that our sample was comprised of young, middle, and old-aged apparently healthy adults, while participants in many other cohorts tended to be older. And the data was collected under standardized conditions and followed according to uniform procedures by trained staff. Laboratory methods also were carefully standardized with rigorous internal and external quality controls. Some limitations also existed in our present study. We did not distinguish between type 1 and type 2 diabetes in the present study. However, because type 2 diabetes accounts for about 95% of all diabetes, our findings are likely more representative of type 2 diabetes [36]. And we only measured body weight and height at baseline, which could not address fat distribution and weigh change.

In summary, we demonstrated BMI is independently associated with increased risk of incident diabetes not only in later adults but also in earlier adults, and importantly extend existing knowledge to show BMI had much greater effect on incident diabetes in younger aged adults. This novel observation might partly explain the emerging epidemic of young-onset diabetes is driven by overweight and obesity in China. Strategically, it is crucial to prevent diabetes by controlling the overweight and obesity, particularly in younger adults.

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Table 1
Baseline characteristics of participants free of diabetes according to age groups

	Age group, y						P for trend
	20 to <30	30 to <40	40 to <50	50 to <60	60 to <70	⩾70	
Male							
Participants, n	15833	45049	23729	17460	9673	4379	
BMI, kg/m^2	23.0 (3.6)	24.1 (3.4)	24.6 (3.0)	24.7 (2.9)	24.7 (2.9)	24.2 (3.1)	< 0.0001
Current smoker, %	19.3	21.7	37.7	53.9	43.2	23.6	< 0.0001
Current drinker, %	1.0	1.7	4.8	6.7	6.8	3.1	< 0.0001
Fasting plasma glucose, mmol/L	4.86 (0.51)	4.86 (0.59)	4.99 (0.63)	5.14 (0.67)	5.21 (0.68)	5.26 (0.68)	< 0.0001
Systolic blood pressure, mmHg	122 (13)	120 (13)	121 (15)	125 (17)	130 (18)	139 (19)	< 0.0001
Diastolic blood pressure, mmHg	73 (9)	75 (10)	78 (11)	80 (11)	80 (11)	79 (11)	< 0.0001
Total cholesterol, mmol/L	4.32 (0.81)	4.64 (0.86)	4.87 (0.88)	4.95 (0.89)	4.95 (0.89)	4.89 (0.88)	< 0.0001
Triglyceride, mmol/L	0.99 (0.70, 1.40)	1.22 (0.86, 1.80)	1.45 (1.00, 2.15)	1.50 (1.02, 2.19)	1.40 (1.00, 2.00)	1.27 (0.92, 1.78)	< 0.0001
LDL-C, mmol/L	2.55 (0.60)	2.72 (0.66)	2.85 (0.67)	2.89 (0.68)	2.90 (0.69)	2.84 (0.66)	< 0.0001
HDL-C, mmol/L	1.32 (0.24)	1.28 (0.27)	1.28 (0.28)	1.29 (0.30)	1.29 (0.29)	1.32 (0.29)	0.11
Family history of diabetes, %	0.61	1.59	2.14	1.43	0.65	0.14	0.01
Female							
Participants, n	12800	37927	21685	12546	7861	2891	
BMI, kg/m^2	20.6 (2.7)	21.4 (2.9)	22.5 (2.9)	23.4 (2.9)	23.8 (3.1)	24.0 (3.4)	< 0.0001
Current smoker, %	0.12	0.13	0.14	0.04	0.32	0.15	0.43
Current drinker, %	0.12	0.11	0.20	0.13	0.13	0.15	0.70
Fasting plasma glucose, mmol/L	4.73 (0.50)	4.74 (0.55)	4.86 (0.57)	5.00 (0.61)	5.12 (0.63)	5.19 (0.69)	< 0.0001
Systolic blood pressure, mmHg	110 (12)	109 (12)	113 (15)	122 (17)	130 (18)	141 (20)	< 0.0001
Diastolic blood pressure, mmHg	69 (9)	69 (9)	71 (10)	76 (11)	77 (11)	77 (12)	< 0.0001

Total cholesterol, mmol/L	4.34 (0.78)	4.44 (0.79)	4.64 (0.81)	5.14 (0.93)	5.46 (0.94)	5.50 (0.96)	< 0.0001
Triglyceride, mmol/L	0.71 (0.55, 0.95)	0.78 (0.59, 1.06)	0.86 (0.63, 1.20)	1.10 (0.80, 1.58)	1.36 (1.00, 1.92)	1.47 (1.09, 2.02)	< 0.0001
LDL-C, mmol/L	2.47 (0.59)	2.54 (0.60)	2.69 (0.62)	3.03 (0.71)	3.21 (0.74)	3.20 (0.73)	< 0.0001
HDL-C, mmol/L	1.51 (0.30)	1.46 (0.31)	1.46 (0.30)	1.47 (0.32)	1.47 (0.32)	1.48 (0.32)	0.05
Family history of diabetes, %	1.72	2.82	4.08	3.00	1.77	0.62	0.45

Data are mean (SD), or median (IQR), or proportions.

Table 2

Association between age and body mass index with risk of incident diabetes in Chinese adults

	N0. of participants	N0. of events	Incidence rate (per 1000 persons per year)	Hazard Ratios	
Age, y				Body mass index -adjusted	Multivariable-adjusted + body mass index
20 to <30	28633	75	0.93	Ref.	Ref.
30 to <40	82976	546	2.18	1.64 (1.29, 2.09)	2.07 (1.24, 3.47)
40 to <50	45414	789	5.45	3.83 (3.03, 4.86)	4.83 (2.90, 8.03)
50 to <60	30006	1224	12.50	8.39 (6.64, 10.59)	12.26 (7.42, 20.27)
60 to <70	17534	976	17.61	11.77 (9.30, 14.89)	15.50 (9.34, 25.70)
⩾70	7270	564	22.39	17.55 (13.79, 22.33)	21.98 (13.14, 36.77)
P for trend	-	-	-	< 0.0001	< 0.0001
Crude rate	211833	4174	6.17	-	-
Standardized rate[†]	211833	4174	7.35	-	-
Body mass index, kg/m^2				Age-adjusted	Multivariable-adjusted
<18.5	12081	31	0.82	0.39 (0.27, 0.56)	0.46 (0.24, 0.90)
18.5-<24.0	116812	1073	2.72	Ref.	Ref.
24.0-<28.0	64774	1936	9.44	2.51 (2.33, 2.70)	2.36 (2.04, 2.73)
⩾28.0	18166	1134	21.00	5.58 (5.13, 6.07)	5.22 (4.44, 6.13)
P for trend				< 0.0001	< 0.0001

[†]The incidence rate was standardized to the population of mainland China in 2010.

Multivariable-adjusted model adjusted for age, sex, smoking status, drinking status, family history of diabetes.

Table 3

Association of per kg/m^2 increase of body mass index and incident diabetes, by baseline age group

	HR	
Age, y	Sex-adjusted	Multivariable-adjusted
20 to <30	1.35 (1.29, 1.40)	1.39 (1.27, 1.52)
30 to <40	1.31 (1.29, 1.33)	1.30 (1.26, 1.34)
40 to <50	1.27 (1.25, 1.29)	1.27 (1.23, 1.32)
50 to <60	1.18 (1.17, 1.20)	1.17 (1.13, 1.21)
60 to <70	1.13 (1.11, 1.15)	1.14 (1.10, 1.19)
⩾70	1.11 (1.08, 1.14)	1.12 (1.07, 1.17)
Age × BMI interaction, P	< 0.0001	< 0.0001

Multivariable-adjusted model adjusted for sex, smoking status, drinking status, family history of diabetes.

Figure legends

Figure 1. Association of body mass index with risk of incident diabetes, by baseline age group. A BMI of 18.5 to 23.9 kg/m^2 was defined as the referent category.

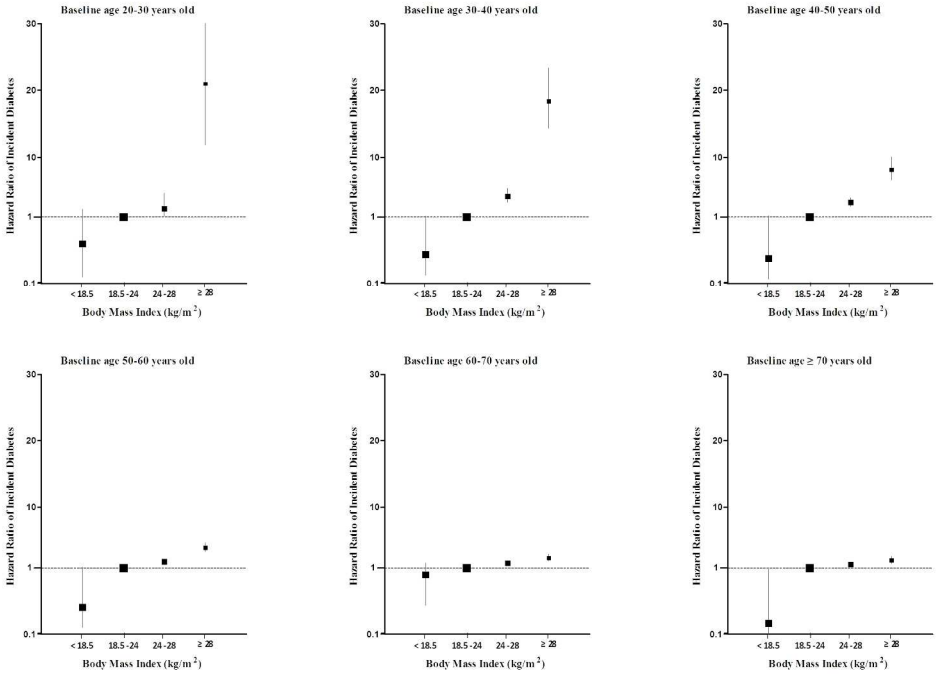

Figure 1. Association of body mass index with risk of incident diabetes, by baseline age group. A BMI of 18.5 to 23.9 kg/m2 was defined as the referent category.

266x189mm (300 x 300 DPI)

Supplemental table 1

Sex-adjusted HRs of incident diabetes with increasing body mass index, by baseline age groups.

	Body mass index, kg/m^2			
	<18.5	18.5-<24.0	24.0-<28.0	≥28
Age, y				
20 to <30	0.64 (0.19, 2.15)	Ref.	2.22 (1.08, 4.57)	21.01 (11.92, 37.04)
30 to <40	0.50 (0.22, 1.14)	Ref.	4.10 (3.19, 5.28)	18.35 (14.36, 23.44)
40 to <50	0.44 (0.16, 1.19)	Ref.	3.19 (2.64, 3.86)	8.21 (6.68, 10.08)
50 to <60	0.46 (0.19, 1.11)	Ref.	1.92 (1.67, 2.20)	4.00 (3.41, 4.69)
60 to <70	0.91 (0.49, 1.72)	Ref.	1.71 (1.47, 1.98)	2.48 (2.06, 2.99)
≥70	0.24 (0.08, 0.76)	Ref.	1.53 (1.27, 1.84)	2.12 (1.67, 2.68)

Supplemental table 2

Interaction of BMI × smoking status and age × family history of diabetes on the risk of incident diabetes.

	HR	
	Unadjusted	Multivariable-adjusted
Risk of per increase of BMI		
Current smoker	1.84 (1.69-2.00)	1.97 (1.80-2.15)
Non-smoker	2.16 (1.76-2.64)	2.34 (1.86-2.93)
BMI × smoking status interaction, P	0.10	0.25
Risk of family history of diabetes		
Total	1.98 (1.70-2.31)	1.68 (1.38-2.03)
20 to <30	2.13 (0.52-8.67)	4.38 (0.82-23.39)
30 to <40	3.06 (2.23-4.21)	2.81 (1.86-4.24)
40 to <50	2.10 (1.59-2.79)	1.81 (1.25-2.64)
50 to <60	1.90 (1.43-2.52)	1.80 (1.27-2.56)
60 to <70	2.04 (1.36-3.06)	1.44 (0.85-2.42)
≥70	1.35 (0.43-4.20)	0.78 (0.19-3.22)
Age × family history of diabetes interaction, P	0.45	0.71

Multivariable-adjusted model adjusted for age, sex, smoking status, drinking status, family history of diabetes, except the strata variable.

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BMJ Open

Association of body mass index and age with incident diabetes in Chinese adults: a population-based cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-021768.R1
Article Type:	Research
Date Submitted by the Author:	03-May-2018
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Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Diabetes and endocrinology, Epidemiology
Keywords:	type 2 diabetes, body mass index, young onset diabetes, aging

Association of body mass index and age with incident diabetes in Chinese adults: a population-based cohort study

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Running head: Effect of BMI and age on incident diabetes

Key terms: type 2 diabetes, body mass index, age, young-onset diabetes

Conflict of interest:

The authors declare no conflicts of interest.

Financial support:

The authors thank the field investigators for their contribution and the participants for their cooperation. This work is supported by grants from the National Key Research and Development Program of China (No.2016YFC1304801), the Natural Science Foundation of Nantong (HS2014036), Science and technology project of Nantong City (MS32016021).

Authors' contributions:

YC, XZ, JY, SC, ZW and XL participated in study concept and design. YC, XZ, XW, XW, and YZ did the data collection. YC, JY, BC, TY, XZ, YG participated in the analysis and interpretation of the data, and drafted the manuscript. XL, SC, ZW and YC revised the manuscript and approved the final version of the manuscript. All authors approved the final version of the manuscript.

Data sharing statement:

Extra data can be accessed via the Dryad data repository at http://datadryad.org/ with the doi: 10.5061/dryad.ft8750v

Abstract

Objective. Type 2 diabetes mellitus is increasing in young adults, and greater adiposity is considered a major risk factor. However, whether there is an association between obesity and diabetes and how this might be impacted by age is not clear. Therefore, we investigated the association between body mass index (BMI) and diabetes across a wide range of age groups (20-30, 30-40, 40-50, 50-60, 60-70, ≥70 years old).

Design. We performed a retrospective cohort study using healthy screening program data.

Setting. A total of 211,833 adult Chinese persons > 20-years-old across 32 sites and 11 cities in China (Shanghai, Beijing, Nanjing, Suzhou, Shenzhen, Changzhou, Chengdu, Guangzhou, Hefei, Wuhan, Nantong) were selected for the study; these persons were free of diabetes at baseline.

Primary and secondary outcome measures. Fasting plasma glucose levels were measured and information regarding the history of diabetes was collected at each visit. Diabetes was diagnosed as fasting plasma glucose ⩾ 7.00 mmol/L and/or self-reported diabetes. Patients were censored at the date of diagnosis or the final visit, whichever came first.

Results. With a median follow-up of 3.1 years, 4,174 of the 211,833 participants developed diabetes, with an age-adjusted incidence rate of 7.35 per 1,000 persons. The risk of incident diabetes increased proportionally with increasing baseline BMI values, with a 23% increased risk of incident diabetes with each kg/m^2 increase in BMI (95%CI: 1.22, 1.24). Across all age groups, there was a linear association between BMI and the risk of incident diabetes, although there was a stronger association between BMI and incident diabetes in the younger age groups (age × BMI interaction, $P < 0.0001$).

Conclusions. An increased BMI is also independently associated with a higher risk of developing diabetes in young adults and the effects of BMI on incident diabetes were accentuated in younger adults.

Key terms: type 2 diabetes, body mass index, age, young-onset diabetes

Strengths and limitations of this study:

1. The large sample size allows analysis of the interaction of age and BMI on incident diabetes.
2. Our study was comprised of young, middle, and old-aged apparently healthy adults, while participants in many other cohorts tended to be older.
3. The data was collected under standardized conditions and followed according to uniform procedures by trained staff. Laboratory methods also were carefully standardized with rigorous internal and external quality controls.
4. We only measured body weight and height at baseline, which could not address fat distribution and weigh change.

Type 2 diabetes is global epidemic. The International Diabetes Foundation (IDF) estimates that about 415 million people worldwide had type 2 diabetes mellitus in 2015. This number is expected to rise to 642 million by 2040, with 140.2 million of the affected people living in Asia [1]. Although diabetes has traditionally been thought of as a disease that affects elderly people, the prevalence of type 2 diabetes in young adults is increasing. National surveys in China report that 7.09% of the individuals that had developed diabetes were younger than 40 years in 2011, while this percentage was less than 1% two decades ago [2]. Younger diabetic patients tend to have a poorer prognosis, associated with an increased risk of cardiovascular disease and microvascular complications [3, 4]. The reasons for the declining age at the onset of type 2 diabetes are poorly understood and complicated. However, it has been speculated that the increasing prevalence of obesity in younger individuals may contribute to the epidemic of diabetes in young people [5].

Greater adiposity is a major risk factor for the development of type 2 diabetes. A meta-analysis combining 18 prospective cohort studies reported that the relative risk (RR) of diabetes for obese persons compared to those with normal weight was 7.19 (95% CI: 5.74, 9.00) and compared to overweight individuals was 2.99 (95% CI: 2.42, 3.72) [6]. Obesity and diabetes are so interconnected that the term “diabesity” has been coined [7]. However, there also seems to be an important relationship with age [8, 9]. Younger age itself is a protective factor for incident diabetes; for every 10 years younger a person is, the risk of developing diabetes decreases by 50%-70% [10]. However, the increasing prevalence of obesity in young individuals seems to

weaken the protective effects of age, in regards to diabetes incidence. The NCD Risk Factor Collaboration pooled 128·9 million children, adolescents, and adults to assess worldwide trends in body-mass index, looking at underweight, overweight, and obese individuals from 1975 to 2016 and found that the mean BMI and obesity prevalence in adolescents and young adults has risen in past decades, and the trend is still continuing [11]. However, the relationship between age, BMI, and diabetes incidence remains unclear. The risk of mortality per unit increase in BMI is greater in younger than in older people [12]. However, the effect of age on the association between BMI and kidney disease is the opposite [13]. The heterogeneity of the association between diabetes and age has been seldom explored. The Asia Pacific Cohort Studies Collaboration pooled twenty-seven cohorts from Asia, New Zealand, and Australia found that the association between BMI and the risk of diabetes was stronger in participants under 60 compared with individuals between 60-69 years of age, while the association was lowest in patients > 70-years-old [14]. However, these conclusions were based on an older population where most adults were older than 40-years-old. Whether these findings can be extrapolated to younger adults is unclear, despite the increasing risk of type 2 diabetes in younger individuals. Therefore, in the present study, we investigated the association between BMI and the risk of incident diabetes in a large retrospective cohort of individuals ranging from 20 to 99-years-old.

METHODS

Study design and participants

Data were extracted from a computerized database established by the Rich Healthcare Group in China, which includes all medical records for participants who received a health check from 2010 to 2016. The present analysis initially included all study participants that were at least 20-years-old with at least two visits between 2010 and 2016 (n=685,277). Participants were excluded at baseline if they had no available weight and height measurements (n=103,946), no available information on gender (n=1), extreme BMI values (<15 kg/m^2 or >55 kg/m^2) (n=152), or no available fasting plasma glucose value (n=31,370). We further excluded participants with visit intervals less than 2 years (n=324,233), participants diagnosed with diabetes at baseline (2,997 participants diagnosed by self-report and 4,115 diagnosed by a fasting plasma glucose ≥7.0 mmol/L), and participants with undefined diabetes status at follow up (n=6,630). Finally, a total of 211,833 participants (116,123 male and 95,710 female) were included in the analysis. Cohort entry was defined as the date of the initial visit. Compared with individuals excluded from the present analyses, those included in the analyses were with similar age (42.1 vs 41.9 years old) and similar BMI (23.2 vs 23.3 kg/m2), and with a relatively higher proportion of males (54.8 vs 52.1%).

This study was approved by the Rich Healthcare Group Review Board, and the information was retrieved retrospectively.

In each visit to the health check center, participants were requested to complete a

detailed questionnaire assessing demographic, lifestyle, medical history, and family history of chronic disease. Height, weight, and blood pressure were measured by trained staff. Body weight was measured in light clothing with no shoes to the nearest 0.1 kg. Height was measured to the nearest 0.1 cm. Body mass index was derived from weight in kilograms divided by height in meters squared. Blood pressure was measured by standard mercury sphygmomanometers.

Fasting venous blood samples were collected after at least a 10-h fast at each visit. Serum triglyceride (TG), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), and high density lipoprotein cholesterol (HDL-C), were measured on an autoanalyser (Beckman 5800). Plasma glucose levels were measured by the glucose oxidase method on an autoanalyser (Beckman 5800).

Ascertainment of incident diabetes

Diagnosis of incident diabetes was defined as fasting plasma glucose of $\geqslant$ 7.00 mmol/L and/or self-reported diabetes during the follow-up period. Patients were censored at the date of diagnosis of diabetes or the final visit, whichever came first.

Statistical analysis

Statistical analyses were performed on SAS 9.3 (SAS Institute, Cary, NC). A two-sided *P* value less than 0.05 was considered statistically significant. Data from descriptive analyses were reported as mean (SD), or median (IQR), or proportions. Participants were stratified into six baseline age groups with 10-year increments

starting from 20-30-years-old to over 70-years-old. Linear regression models were performed to assess the relationship between BMI, metabolic parameters, lifestyles, and family history of diabetes with age. Diabetes incidence was calculated in each and in the total of all age groups, and age-standardized diabetes incidence was adjusted to the Chinese population in 2010 [15].

Cox proportional hazard regression models were performed to estimate BMI-adjusted and multivariable-adjusted hazard ratios (95% confidence intervals) of age with incident diabetes and age-adjusted and multivariable-adjusted hazard ratios (95% confidence intervals) of BMI with incident diabetes. Analyses of BMI used predefined standard categories according to the Chinese criteria of obesity [16]: underweight (<18.5kg/m^2), normal weight (18.5-<24.0 kg/m^2), overweight (24.0-<28.0 kg/m^2), and obese (≥28.0 kg/m^2). The normal BMI group (18.5-<24.0 kg/m^2) was chosen as the referent category. Covariates in the multivariable models included age, sex, smoking status, drinking status, and family history of diabetes. The association between BMI and incident diabetes, as influenced by age, was further investigated. Hazard ratios (HRs) of incident diabetes were calculated respectively in each age group by Cox proportional hazard regression models with a BMI of 18.5-<24.0 kg/m^2 as the reference category. Since the association between BMI and incident diabetes were approximately linear, the HRs and corresponding 95% CI for incident diabetes across all age groups were estimated for per kg/m^2 increase in BMI value. The modification effect was assessed for the interaction of age and BMI in the Cox model.

In consideration of the baseline, confounding factors including smoking status, and family history of diabetes, related to diabetes in young adults, subgroup analyses were further performed respective to the HR of smoking status and family history of diabetes, in regards to the overall risk of diabetes. The interaction of BMI*current smoker, age*family history of diabetes was assessed in the Cox model.

Patient and Public involvement

Given the retrospective nature of the study, no patients were involved in any aspect of the study.

RESULTS

211,833 participants (116,123 male and 95,710 female) without diabetes at baseline were recruited. The mean age was 42.1-years-old (SD 12.6), ranging from 20 to 99-years-old. The mean BMI value was 23.2 kg/m^2 (SD 3.3). Baseline clinical and biochemical characteristics of participants were stratified by age and sex, BMI and sex, are presented in Table 1 and Supplementary Table 1. Total serum cholesterol, triglyceride, LDL-C, fasting plasma glucose, systolic blood pressure, and diastolic blood pressure gradually increased with age and BMI in both men and women.

During a median of 3.1 year follow-up (660,191 person-years), 4,174 of 211,833 participants developed diabetes. The incidence of diabetes was 7.35 per 1,000 person-year with age-standardization (Table 2). The risk of incident diabetes increased proportionally with age and BMI values (Table 2). For every 10 years of increasing age, the hazard ratio (HR) of developing diabetes increased by 88% (95% CI: 1.85, 1.92). Using participants ages 20-30-years-old as the reference, the BMI-adjusted HR for incident diabetes was 1.64 (95% CI: 1.29-2.09) in participants ages 30-40-years-old, 3.83 (95% CI: 3.03, 4.86) in participants ages 40-50-years-old, 8.39 (95% CI: 6.64, 10.59) in participants ages 50-60-years-old, 11.77 (95% CI: 9.30, 14.89) in participants ages 60-70-years-old, and 17.55 (95% CI: 13.79, 22.33) in participants ≥ 70-years-old. Using participants with a BMI of 18.5-<24.0 kg/m^2 as reference, the age-adjusted HR for incident diabetes was 0.39 (95% CI: 0.27-0.56) in participants with a BMI of <18.5 kg/m^2, 2.51 (95% CI: 2.33, 2.70) with a BMI of 24.0-27.9 kg/m^2, and 5.58 (95% CI: 5.13, 6.07) with a BMI of ≥28.0 kg/m^2. Further adjustment for sex,

smoking status, drinking status, and family history of diabetes did not alter the trend appreciably.

Sex-adjusted HRs (95% CI) of BMI for risk of incident diabetes are shown in Figure 1 and Supplementary Table 2. Using participants with a BMI of 18.5-<24.0 kg/m^2 as the reference, the age-adjusted HR for incident diabetes in overweight and obese individuals was higher at younger ages than older ages. The linear association between BMI and risk of incident diabetes was present in participants across all age groups. When BMI was analyzed as a continuous variable, the sex-adjusted HR of developing diabetes was 1.23 (95% CI: 1.22, 1.24) for each kg/m^2 increase in BMI. A stronger association between BMI and incident diabetes was shown in the youngest age group (Table 3). The risk of incident diabetes was increased by 35% (95% CI: 1.29, 1.40) for each kg/m^2 increase of BMI in the 20-30-year-old group, 31% (95% CI: 1.29, 1.33) in the 30-40-year-old group, 27% (95% CI: 1.25, 1.29) in the 40-50-year-old group, 18% (95% CI: 1.17, 1.20) in the 50-60-year-old group, 13% (95% CI: 1.11, 1.15) in the 60-70-year-old group, and 11% (95% CI: 1.08, 1.14) in the greater than 70-years-old group. The descending trend by age remained separately in men and women, and was not altered by further adjustment for smoking status, drinking status, and family history of diabetes. Obviously, age significantly modified the association between BMI and the risk of incident diabetes (age × BMI interaction, $P < 0.0001$).

Current smokers were at a decreased risk of incident diabetes (HR: 0.79; 95%CI: 0.74, 0.84), and participants with a family history of diabetes were at an increased risk of incident diabetes (HR: 1.68; 95%CI: 1.38-2.03). The multiplicative interactions of

BMI × smoking status (*P* for interaction=0.25) and age × family history of diabetes (*P* for interaction=0.71) in regards to the risk of incident diabetes were not significant (Supplementary table 3).

DISCUSSION

In the present cohort, an age-standardized diabetes incidence of 7.35 per 1,000 person-year during 2010-2016 was detected. We demonstrated a linear association between baseline BMI and the risk of developing diabetes, which increased with each kg/m^2 of BMI, associated with 23% (95% CI: 1.22, 1.24) higher risk of incident diabetes. The risk of incident diabetes was increased by 35% (95% CI: 1.29, 1.40) for each kg/m^2 increase of BMI in the 20-30-year-old group and 31% (95% CI: 1.29, 1.33) in the 30-40-year-old group. However, the risk of incident diabetes was slightly lower in the 40-50, 50-60, and 60-70-year-old group: 1.27 (95% CI: 1.25, 1.29), 1.18 (95% CI: 1.17, 1.20), and 1.13 (95% CI: 1.11, 1.15), respectively. Again, the HR of incident diabetes was the lowest in the 70-year-old group at 1.11 (95% CI: 1.08, 1.14). Further analyses showed that age had a modifying effect on this association. Overall, the effect of BMI on incident diabetes was stronger in younger adults. Subgroup analyses showed that the interactions between BMI and smoking status or age and family history of diabetes, in regards to the risk of incident diabetes, were not significant.

Our study reported an age-standardized diabetes incidence of 7.35 per 1,000 person-year during 2010-2016. With lifestyle changes, the prevalence of type 2 diabetes has increased rapidly in the past decades in China. Data from national surveys show that the prevalence of diabetes was 0.9% in 1980 [17], 2.5% in 1994 [18], 9.7% in 2007 [19], and 10.9% in 2013 [20]. However, the incidence of diabetes appears to have stabilized and there have been small declines from 2007 to 2014 [21],

which is not consistent with the prevalence trend. Based on our large sample cohort, the incidence of diabetes increased by 7.35 per 1,000 person-years between 2010 and 2016. All diabetes diagnoses were based on a self-reported diagnosis of diabetes and/or a fasting glucose level equal to or greater than 7.0 mmol/L. As such, we could have missed some cases of type 2 diabetes. The Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) and Asia (DECODA) studies show that fasting glucose alone only detected about 68% of new diabetic patients in Europe [22] and 55% of new diabetic patients in Asia [23]. And national surveys have reported 46.6% of Chinese with undiagnosed diabetes had isolated increased 2-h plasma glucose after an oral glucose tolerance test. Therefore, the true estimated incidence of diabetes should be higher than the data from this study. However, oral glucose tolerance tests are not applicable for large sample survey due to its complexity to operate.

Obesity is the major risk factor for diabetes development. Hartemink N et al. conducted a meta-analyses that detected a dose-response relationship between body mass index and type 2 diabetes. It was shown that per kg/m^2 increase in BMI, the risk of diabetes increased by 18% (95% CI: 1.16-1.20), accounting for the heterogeneity among studies [24]. The etiological effects of BMI have mostly been extrapolated from the European population, while Chinese individuals tend to have a higher incidence of diabetes and related risk factors per unit increase in BMI [25, 26]. In the present study, the age-adjusted HR for incident diabetes was 2.51 (95% CI: 2.33, 2.70) in overweight individuals with a BMI of 24.0-27.9 kg/m^2, and 5.58 (95% CI:

5.13, 6.07) in obese individuals with a BMI of ≥28.0 kg/m^2, compared with normal weight individuals with a BMI of 18.5-<24.0 kg/m^2. Our HR of diabetes incidence per kg/m^2 increase in BMI was 1.23 (95% CI: 1.22-1.24), which was slightly higher than previously reported [24]. Moreover, it was interesting to find that the HR was significantly higher in younger adults less than 40-years-old.

Young age itself is a remarkable protective factor for developing diabetes. While most of the increase in the prevalence of T2DM has been seen in the middle-aged and elderly, there is strong evidence that it is becoming more common among young adults. The increasing prevalence of obesity in young individuals has been speculated to at least partly explain the increasing prevalence of diabetes in young adults. However, the available data on diabetes in younger populations is limited. Recent studies have shown the association between BMI and its outcomes more significantly varied in younger versus older adults. The global BMI mortality collaboration, including 239 prospective studies in four continents, found that the risk of mortality per unit increase in BMI was greater in younger than in older people [12]. However, the effect of age on the association between BMI and kidney disease appears to be the opposite [13].The heterogeneity of age on the association of obesity and type 2 diabetes has been assessed in only a few studies with inconsistent results. Data from the Third National Health and Nutrition Examination Survey showed that BMI was strongly associated with an increased relative risk of developing a metabolic disorder, including type 2 diabetes and cardiovascular diseases. Furthermore, the association between BMI and cardiovascular disease and hypertension was reduced with

increasing age. However, any modifying effects of age on the association between BMI and type 2 diabetes were not detected [27]. Meta-analysis data from Japan, Australia, and New Zealand, demonstrated a stronger association between BMI and the risk of diabetes in subjects younger than 60-years-old compared to people older than 70-years-old [28]. However, most of the persons included in this study were older than 40-years-old. The limited sample size and age range might contribute to this disparity. Avoiding these factors, we found a generally consistent linear association between BMI and incident diabetes that weakened with advancing age. BMI had a much greater risk on incident diabetes in earlier adulthood than in later adulthood, which was consistent with the findings from a meta-analysis conducted by Ni Mhurchu C et al [28], which extends this finding to adults younger than 40-years-old.

The mechanism(s) responsible for the heterogeneity of BMI effect in regards to age are unclear. Young onset obesity has been reported to have more genetic predisposition to metabolic disorders, and resulted in chronically increased levels of circulating free fatty acids and adipokines, which reduced insulin sensitivity and might contribute to increased reactive oxygen species and impaired insulin secretion [29, 30]. Furthermore, young onset obesity patients might have an early life exposure to maternal undernutrition or over-nutrition, which is associated with an increased risk of type 2 diabetes [31, 32]. And individuals with young onset obesity tend to have a detrimental/inactive lifestyle, which might also contribute to the development of adiposity, insulin resistance, hyperglycaemia, and other cardiovascular risk factors

[33, 34]. Therefore, obese youth lose the protective effects of a young age in regards to diabetes risk. On the other side, weight constitutes of fat and muscle. The decrease in body weight by increasing age can be explained by the process of sarcopenia with significant decreases in muscle mass combined with slightly increases in fat mass [35]. An additional process associated with aging is fat redistribution. Subcutaneous fat which was considered as metabolic protective is redistributed to visceral fat that pose greater metabolic risk as visceral adiposity is more strongly linked with many conditions. However, these age-related changes in BMI should theoretically increase the diabetes risk associated with BMI, rather weaken the association between BMI and diabetes.

Smoking is a concern in the analysis of BMI-diabetes associations, because smoking is associated with decreased body weight and an increased risk of diabetes [36]. In our study, smoking status was statistically adjusted. The interaction between BMI and smoking status on the risk of incident diabetes was explored, and no statistically significant associations were found. Previous studies have reported that the risk of type 2 diabetes in youth is usually increased in persons with a family history of diabetes [37]. Similarly, we found that a family history of diabetes is an independent risk factor for type 2 diabetes. However, no interaction between age and family history of diabetes were detected.

In addition to the large sample size, the major strength of our study is that our sample was comprised of young, middle, and old-aged apparently healthy adults, while participants in many other cohorts tended to be older. Furthermore, the data

were collected under standardized conditions, and the study followed uniform procedures performed by trained staff. Laboratory methods were also carefully standardized with rigorous internal and external quality controls. Some limitations also existed in our present study. One limitation of our study is that our analysis was not performed on a representative sample of the population, which limits the generalizability of this study; however, data come from sites in China and age range is wide. The results of the current study will have wide applicability for the population in China. We did not distinguish between type 1 and type 2 diabetes in the present study. However, because type 2 diabetes accounts for about 95% of all diabetes cases, our findings are likely more representative of type 2 diabetes [38]. In addition, we only measured body weight and height at baseline, which did not evaluated fat distribution and weight changes. Finally, even though we adjusted for an extensive set of confounding factors, residual confounding due to the measurement error in the assessment of confounding factors, unmeasured factors such as physical activity, and dietary factors, cannot be excluded.

In summary, we demonstrated BMI is independently associated with an increased risk of incident diabetes not only in older adults but also in younger adults. This information extends our existing knowledge to show BMI has a much greater effect on the incidence of diabetes in younger adults. This novel observation likely helps to explain the emerging epidemic of young-onset diabetes, suggesting that it is driven by weight gain and obesity in China. Strategically, it is crucial to prevent diabetes by controlling risk factors, such as weight gain or excessive weight,

particularly in younger adults.

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Table 1

Baseline characteristics of participants free of diabetes according to age groups

	Age group, y						P for trend
	20 to <30	30 to <40	40 to <50	50 to <60	60 to <70	⩾70	
Male							
Participants, n	15833	45049	23729	17460	9673	4379	
BMI, kg/m^2	23.0 (3.6)	24.1 (3.4)	24.6 (3.0)	24.7 (2.9)	24.7 (2.9)	24.2 (3.1)	< 0.0001
Current smoker, %	19.3	21.7	37.7	53.9	43.2	23.6	< 0.0001
Current drinker, %	1.0	1.7	4.8	6.7	6.8	3.1	< 0.0001
Fasting plasma glucose, mmol/L	4.86 (0.51)	4.86 (0.59)	4.99 (0.63)	5.14 (0.67)	5.21 (0.68)	5.26 (0.68)	< 0.0001
Systolic blood pressure, mmHg	122 (13)	120 (13)	121 (15)	125 (17)	130 (18)	139 (19)	< 0.0001
Diastolic blood pressure, mmHg	73 (9)	75 (10)	78 (11)	80 (11)	80 (11)	79 (11)	< 0.0001
Total cholesterol, mmol/L	4.32 (0.81)	4.64 (0.86)	4.87 (0.88)	4.95 (0.89)	4.95 (0.89)	4.89 (0.88)	< 0.0001
Triglyceride, mmol/L	0.99 (0.70, 1.40)	1.22 (0.86, 1.80)	1.45 (1.00, 2.15)	1.50 (1.02, 2.19)	1.40 (1.00, 2.00)	1.27 (0.92, 1.78)	< 0.0001
LDL-C, mmol/L	2.55 (0.60)	2.72 (0.66)	2.85 (0.67)	2.89 (0.68)	2.90 (0.69)	2.84 (0.66)	< 0.0001
HDL-C, mmol/L	1.32 (0.24)	1.28 (0.27)	1.28 (0.28)	1.29 (0.30)	1.29 (0.29)	1.32 (0.29)	0.11
Family history of diabetes, %	0.61	1.59	2.14	1.43	0.65	0.14	0.01
Female							
Participants, n	12800	37927	21685	12546	7861	2891	
BMI, kg/m^2	20.6 (2.7)	21.4 (2.9)	22.5 (2.9)	23.4 (2.9)	23.8 (3.1)	24.0 (3.4)	< 0.0001
Current smoker, %	0.12	0.13	0.14	0.04	0.32	0.15	0.43
Current drinker, %	0.12	0.11	0.20	0.13	0.13	0.15	0.70
Fasting plasma glucose, mmol/L	4.73 (0.50)	4.74 (0.55)	4.86 (0.57)	5.00 (0.61)	5.12 (0.63)	5.19 (0.69)	< 0.0001
Systolic blood pressure, mmHg	110 (12)	109 (12)	113 (15)	122 (17)	130 (18)	141 (20)	< 0.0001
Diastolic blood pressure, mmHg	69 (9)	69 (9)	71 (10)	76 (11)	77 (11)	77 (12)	< 0.0001
Total cholesterol, mmol/L	4.34 (0.78)	4.44 (0.79)	4.64 (0.81)	5.14 (0.93)	5.46 (0.94)	5.50 (0.96)	< 0.0001
Triglyceride, mmol/L	0.71 (0.55, 0.95)	0.78 (0.59, 1.06)	0.86 (0.63, 1.20)	1.10 (0.80, 1.58)	1.36 (1.00, 1.92)	1.47 (1.09, 2.02)	< 0.0001
LDL-C, mmol/L	2.47 (0.59)	2.54 (0.60)	2.69 (0.62)	3.03 (0.71)	3.21 (0.74)	3.20 (0.73)	< 0.0001
HDL-C, mmol/L	1.51 (0.30)	1.46 (0.31)	1.46 (0.30)	1.47 (0.32)	1.47 (0.32)	1.48 (0.32)	0.05
Family history of diabetes, %	1.72	2.82	4.08	3.00	1.77	0.62	0.45

Data are mean (SD), or median (IQR), or proportions.

Table 2

Association between age and body mass index with risk of incident diabetes in Chinese adults

	N0. of participants	N0. of events	Incidence rate (per 1000 persons per year)	Hazard Ratios	
Age, y				Body mass index - adjusted	Multivariable-adjusted + body mass index
20 to <30	28633	75	0.93	Ref.	Ref.
30 to <40	82976	546	2.18	1.64 (1.29, 2.09)	2.07 (1.24, 3.47)
40 to <50	45414	789	5.45	3.83 (3.03, 4.86)	4.83 (2.90, 8.03)
50 to <60	30006	1224	12.50	8.39 (6.64, 10.59)	12.26 (7.42, 20.27)
60 to <70	17534	976	17.61	11.77 (9.30, 14.89)	15.50 (9.34, 25.70)
⩾70	7270	564	22.39	17.55 (13.79, 22.33)	21.98 (13.14, 36.77)
P for trend	-	-	-	< 0.0001	< 0.0001
Crude rate	211833	4174	6.17	-	-
Standardized rate[†]	211833	4174	7.35	-	-
Body mass index, kg/m^2				Age-adjusted	Multivariable-adjusted
<18.5	12081	31	0.82	0.39 (0.27, 0.56)	0.46 (0.24, 0.90)
18.5-<24.0	116812	1073	2.72	Ref.	Ref.
24.0-<28.0	64774	1936	9.44	2.51 (2.33, 2.70)	2.36 (2.04, 2.73)
⩾28.0	18166	1134	21.00	5.58 (5.13, 6.07)	5.22 (4.44, 6.13)
P for trend				< 0.0001	< 0.0001

[†]The incidence rate was standardized to the population of mainland China in 2010.

Multivariable-adjusted model adjusted for age, sex, smoking status, drinking status, family history of diabetes.

Table 3

Association of per kg/m^2 increase of body mass index and incident diabetes, by baseline age group

	HR	
Age, y	Sex-adjusted	Multivariable-adjusted
20 to <30	1.35 (1.29, 1.40)	1.39 (1.27, 1.52)
30 to <40	1.31 (1.29, 1.33)	1.30 (1.26, 1.34)
40 to <50	1.27 (1.25, 1.29)	1.27 (1.23, 1.32)
50 to <60	1.18 (1.17, 1.20)	1.17 (1.13, 1.21)
60 to <70	1.13 (1.11, 1.15)	1.14 (1.10, 1.19)
≥70	1.11 (1.08, 1.14)	1.12 (1.07, 1.17)
Age × BMI interaction, P	< 0.0001	< 0.0001
Male		
Age, y	Non-adjusted	Multivariable-adjusted
20 to <30	1.37 (1.31, 1.44)	1.41 (1.29, 1.55)
30 to <40	1.31 (1.29, 1.34)	1.30 (1.26, 1.35)
40 to <50	1.26 (1.23, 1.28)	1.25 (1.20, 1.30)
50 to <60	1.18 (1.16, 1.21)	1.17 (1.13, 1.21)
60 to <70	1.14 (1.11, 1.17)	1.17 (1.11, 1.23)
≥70	1.13 (1.09, 1.17)	1.16 (1.10, 1.24)
Age × BMI interaction, P	< 0.0001	0.0004
Female		
Age, y	Non-adjusted	Multivariable-adjusted
20 to <30	1.29 (1.19, 1.40)	1.31 (1.21, 1.43)
30 to <40	1.30 (1.26, 1.34)	1.30 (1.26, 1.35)
40 to <50	1.31 (1.26, 1.35)	1.29 (1.24, 1.34)
50 to <60	1.19 (1.15, 1.22)	1.18 (1.15, 1.21)
60 to <70	1.12 (1.09, 1.15)	1.12 (1.08, 1.16)
≥70	1.09 (1.05, 1.13)	1.09 (1.05, 1.14)
Age × BMI interaction, P	< 0.0001	< 0.0001

Multivariable-adjusted model adjusted for sex, smoking status, drinking status, family history of diabetes.

Figure legends

Figure 1. Association of body mass index with risk of incident diabetes, by baseline age group. A BMI of 18.5 to 23.9 kg/m^2 was defined as the referent category.

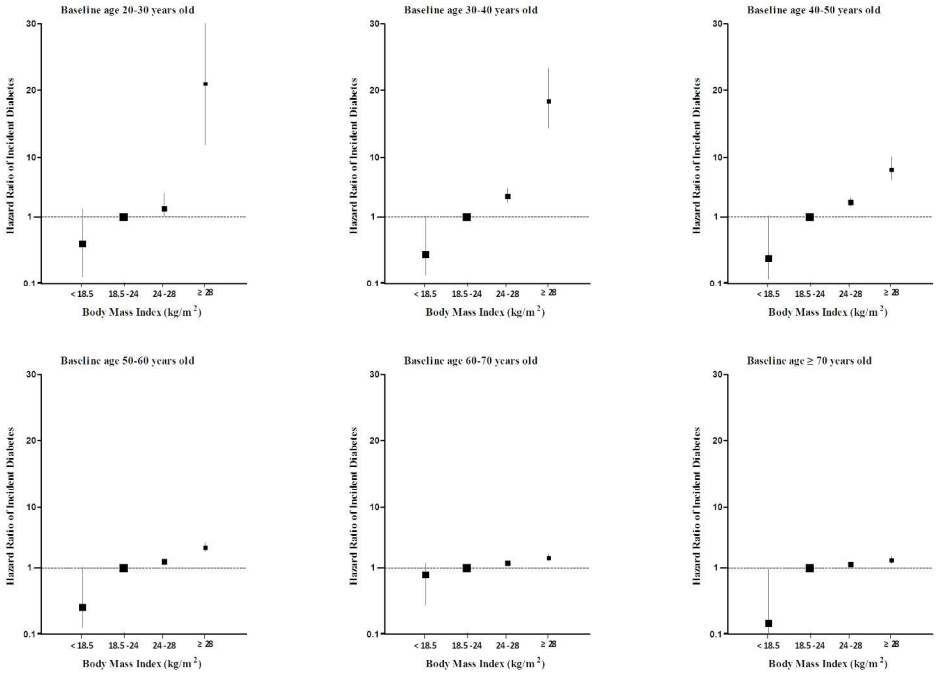

Figure 1. Association of body mass index with risk of incident diabetes, by baseline age group. A BMI of 18.5 to 23.9 kg/m2 was defined as the referent category.

266x189mm (300 x 300 DPI)

Supplemental table 1

Baseline characteristics of participants free of diabetes according to BMI groups

	Body mass index, kg/m^2				P for trend
	<18.5	18.5-<24.0	24.0-<28.0	≥28	
Male					
Participants, n	3429	52741	46159	13793	
BMI, kg/m^2	17.6 (0.7)	21.8 (1.5)	25.7 (1.1)	29.9 (1.9)	< 0.0001
Age, y	36.6 (12.5)	40.9 (12.9)	44.2 (12.8)	42.9 (12.5)	< 0.0001
Current smoker, %	28.8	28.5	32.1	35.8	< 0.0001
Current drinker, %	1.7	2.8	3.8	4.7	< 0.0001
Fasting plasma glucose, mmol/L	4.76 (0.56)	4.89 (0.60)	5.04 (0.63)	5.15 (0.67)	< 0.0001
Systolic blood pressure, mmHg	115 (14)	120 (15)	125 (15)	130 (16)	< 0.0001
Diastolic blood pressure, mmHg	72 (10)	74 (10)	78 (11)	82 (11)	< 0.0001
Total cholesterol, mmol/L	4.26 (0.80)	4.58 (0.86)	4.85 (0.89)	4.97 (0.89)	< 0.0001
Triglyceride, mmol/L	0.81 (0.62, 1.05)	1.07 (0.77, 1.51)	1.50 (1.05, 2.17)	1.81 (1.30, 2.59)	< 0.0001
LDL-C, mmol/L	2.47 (0.62)	2.71 (0.65)	2.85 (0.67)	2.91 (0.68)	< 0.0001
HDL-C, mmol/L	1.44 (0.30)	1.33 (0.28)	1.25 (0.27)	1.22 (0.27)	< 0.0001
Family history of diabetes, %	0.79	1.24	1.52	1.85	< 0.0001
Female					
Participants, n	8652	64070	18614	4373	
BMI, kg/m^2	17.6 (0.7)	21.2 (1.5)	25.5 (1.1)	30.1 (2.1)	< 0.0001
Age, y	34.9 (9.2)	40.6 (11.5)	47.7 (13.1)	48.5 (13.9)	< 0.0001
Current smoker, %	0.05	0.14	0.17	0.01	0.80
Current drinker, %	0.10	0.15	0.10	0.21	0.008
Fasting plasma glucose, mmol/L	4.65 (0.55)	4.80 (0.56)	5.02 (0.60)	5.16 (0.64)	< 0.0001

Systolic blood pressure, mmHg	108 (13)	112 (15)	122 (18)	129 (18)	< 0.0001
Diastolic blood pressure, mmHg	68 (9)	70 (10)	75 (11)	79 (12)	< 0.0001
Total cholesterol, mmol/L	4.43 (0.81)	4.62 (0.89)	4.92 (0.94)	5.03 (0.97)	< 0.0001
Triglyceride, mmol/L	0.70 (0.55, 0.90)	0.81 (0.60, 1.12)	1.16 (0.82, 1.67)	1.43 (1.03, 2.00)	< 0.0001
LDL-C, mmol/L	2.52 (0.61)	2.70 (0.68)	2.91 (0.71)	2.97 (0.72)	< 0.0001
HDL-C, mmol/L	1.59 (0.33)	1.49 (0.31)	1.39 (0.28)	1.34 (0.26)	< 0.0001
Family history of diabetes, %	1.86	2.82	3.14	3.50	< 0.0001

Data are mean (SD), or median (IQR), or proportions.

Supplemental table 2

Sex-adjusted HRs of incident diabetes with increasing body mass index, by baseline age groups.

	Body mass index, kg/m^2			
	<18.5	18.5-<24.0	24.0-<28.0	≥28
Age, y				
20 to <30	0.56 (0.18, 1.76)	0.77 (0.48, 1.22)	1.43 (0.79, 2.61)	13.06 (8.98, 19.00)
30 to <40	0.51 (0.22, 1.15)	Ref.	4.06 (3.18, 5.18)	18.03 (14.28, 22.78)
40 to <50	1.35 (0.50, 3.65)	3.21 (2.50,4.12)	11.07 (8.86, 13.82)	28.83 (22.82, 36.42)
50 to <60	5.05 (2.06, 12.41)	11.16 (8.91,13.99)	22.40 (18.10, 27.72)	47.17 (37.55, 59.24)
60 to <70	18.25 (9.52, 34.97)	19.93 (15.85,25.06)	33.35 (26.87, 41.39)	48.51 (38.01, 61.92)
≥70	7.90 (2.50, 24.91)	32.19 (25.23,41.08)	48.14 (38.19, 60.69)	68.30 (51.99, 89.73)

Supplemental table 3

Interaction of BMI × smoking status and age × family history of diabetes on the risk of incident diabetes.

	HR	
	Unadjusted	Multivariable-adjusted
Risk of per increase of BMI		
Current smoker	1.84 (1.69-2.00)	1.97 (1.80-2.15)
Non-smoker	2.16 (1.76-2.64)	2.34 (1.86-2.93)
BMI × smoking status interaction, P	0.10	0.25
Risk of family history of diabetes		
Total	1.98 (1.70-2.31)	1.68 (1.38-2.03)
20 to <30	2.13 (0.52-8.67)	4.38 (0.82-23.39)
30 to <40	3.06 (2.23-4.21)	2.81 (1.86-4.24)
40 to <50	2.10 (1.59-2.79)	1.81 (1.25-2.64)
50 to <60	1.90 (1.43-2.52)	1.80 (1.27-2.56)
60 to <70	2.04 (1.36-3.06)	1.44 (0.85-2.42)
≥70	1.35 (0.43-4.20)	0.78 (0.19-3.22)
Age × family history of diabetes interaction, P	0.45	0.71

Multivariable-adjusted model adjusted for age, sex, smoking status, drinking status, family history of diabetes, except the strata variable.

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	(1.1) Abstract, paragraph 2 (1.2) Abstract, paragraph 3 (1.3) Abstract, paragraph 5
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			Introduction, paragraphs 1-2
Objectives	3	State specific objectives, including any prespecified hypotheses			Introduction, paragraph 2
Methods					
Study Design	4	Present key elements of study design early in the paper			Methods, paragraph 1
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection			Methods, paragraph 1
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods		RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If	(6.1.) Methods, paragraph 1

		of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	(6.2) NA (6.3) Methods, paragraph 1
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.			Methods, paragraph 3-5
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group			Methods, paragraph 3-5
Bias	9	Describe any efforts to address potential sources of bias			Methods, paragraph 7-8
Study size	10	Explain how the study size was arrived at			Methods, paragraph 1
Quantitative	11	Explain how quantitative			Methods, paragraph 7

variables		variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* – If applicable, explain how loss to follow-up was addressed *Case-control study* – If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* – If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			(a) Methods, paragraph 6-8 (b) Methods, paragraph 7-8 (c) Methods, paragraph 1 (d) Methods, paragraph 1 (e) Methods, paragraph 8
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	(12.1) Methods, paragraph 1 (12.2) Methods, paragraph 1
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more	

				databases. The methods of linkage and methods of linkage quality evaluation should be provided.	
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	(13.1) Results, paragraphs 1
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)			(a) Results, paragraph 1-2, Table 1, S1 Table (b) Table 1 (c) Results, paragraph 2
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			Results, paragraph 2 Table 2
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-			(16.a) Results, paragraph 2

		adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			Table 2 (16.b)Results, paragraph 3 Tables 3 Figure 1 (16.c) Results, paragraph 3
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses			Results, paragraph 4 S2 Table
Discussion					
Key results	18	Summarise key results with reference to study objectives			Discussion, paragraph 1-6
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Discussion, paragraph 7
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			Discussion, paragraph 8
Generalisability	21	Discuss the generalisability (external validity) of the study results			Discussion, paragraph 8
Other information					

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based			

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The Reporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.