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Association of pre-diabetes with the risks of adverse health outcomes and complex multimorbidity: evidence from population-based studies in the NIS and UK Biobank

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ABSTRACTS

Introduction This study aimed to examine the risk of common diseases among people with pre-diabetes and explored the relationship between pre-diabetes and multimorbidity (in this case, two or more comorbid diseases).

Methods An observational multicohort study using data from the UK Biobank database and the National Inpatient Sample (NIS) database (2016–2018) was conducted. We analysed 461 535 participants and 17 548 442 patients aged 18 years or older from both databases, of whom 14.0% and 0.7% were diagnosed with pre-diabetes, respectively. A total of 76 common diseases of various body systems were selected as adverse health outcomes for analysis.

Results Among 64 523 individuals with pre-diabetes in the UK Biobank, the mean age was 60 years, 35 304 (54.7%) were female. There were 24 non-overlapping diseases associated with pre-diabetes with significant multiple test results in both databases, and most of them are circulatory system diseases. Compared with normoglycaemia, the confounder-adjusted HR in the UK Biobank for pre-diabetes was 1.46 (95% CI 1.43 to 1.49) for accompanying complex multimorbidity (ie, four or more pre-diabetes-related diseases), the corresponding confounder-adjusted OR in the NIS study was 10.03 (95% CI 9.66 to 10.40).

Conclusion Pre-diabetes was associated with a significantly higher risk of multimorbidity. Pre-diabetes, thus, might represent an important target for multimorbidity prevention, and stronger emphasis on its management seems necessary to reduce the risk of the development of multiple comorbidities, especially before the onset of overt diabetes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Multimorbidity refers to the existence of multiple medical conditions in a single individual, which is a growing global health concern and the available evidence on its causes and treatment is currently inadequate.

⇒ The lack of data on the relationship between pre-diabetes and multimorbidity has led to great attention being focused on diabetes, both by the general public and health professionals, while pre-diabetes receives comparatively less focus.

WHAT THIS STUDY ADDS

⇒ Pre-diabetes was significantly associated with an increased risk of 24 diseases across multiple body systems.

⇒ Individuals with pre-diabetes faced a higher risk of complex multimorbidity (defined as four or more pre-diabetes-related diseases) compared with those with normoglycaemia.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Pre-diabetes is linked to multimorbidity, similar to diabetes, suggesting that addressing pre-diabetes could improve public health, and the data atlas of correlations between pre-diabetes and 76 health outcomes offers a valuable reference for future research on the health effects of pre-diabetes.

INTRODUCTION

Pre-diabetes represents a high-risk state for the development of diabetes. Pre-diabetes is defined as raised blood glucose levels above the normal range but below the diabetes diagnostic threshold, along with impaired glucose tolerance (IGT) and impaired fasting glucose (IFG).[1] The prevalence of pre-diabetes globally has shown a sustained increasing trend. It is estimated that there were 541 million adults with IGT and 319 million adults with

IFG worldwide in 2021, and the figures are expected to reach 730 million and 441 million, respectively, by 2045.[2] This high global prevalence of pre-diabetes undoubtedly represents a tremendous burden to the global healthcare system in addition to a large societal challenge.

Patients with diabetes are at high risk of living with multiple co-occurring conditions, such as cardiovascular-related disease, microvascular complications, depression, as well as an increased risk for dementia.[3 4] Similar to diabetes, pre-diabetes can also cause multiple systemic damage. It has been reported that pre-diabetes is linked to a wide range of clinical conditions, including diseases of multiple systems, such as the circulatory,[5–7] neurological,[8] endocrine[9] and genitourinary systems,[5] as well as eye,[10] and ear pathologies.[11] To date, there has been no systematic and comprehensive analysis to explore whether these diseases occur as comorbidities in individuals with pre-diabetes.

Multimorbidity refers to the existence of more than one serious long-term medical condition in a single individual, which is generally recognised as a growing global health challenge, especially given the difficulties in managing the competitive demands of multiple conditions.[12] Patients suffering from multimorbidity have a greater risk of disability and also have a lower quality of life.[13] A number of studies have provided evidence that patients with diabetes are associated with diverse, increasing disease burdens[14] and most of them have multimorbidity.[4] However, data on the relationship between pre-diabetes and multimorbidity are lacking, and thus it remains uncertain whether pre-diabetes can lead to multiple medical conditions, not just type 2 diabetes. In addition, few studies have characterised a wide array of pre-diabetes-related conditions that result in complex multimorbidity (ie, four or more comorbid diseases).

To address this important knowledge gap, we used data from a prospective cohort study (UK Biobank) and a cross-sectional study (Nationwide Inpatient Sample, NIS) to explore the association of pre-diabetes with the risks of adverse health outcomes and complex multimorbidity.

METHODS

Study design and participants

The UK Biobank is a large, prospective, population-based cohort of more than 500 000 participants from the UK who were 38–73 years old, and the collection of baseline data and samples was between 13 March 2006 and 1 October 2010.[15] In the present study, UK Biobank participants were linked to the UK NHS Hospital Episode Statistics database for hospital admissions, and follow-up for hospital admissions occurred through 30 November 2021. Subjects with hemoglobin A1c (HbA1c) measured and HbA1c<15% at enrolment, and complete covariate data at baseline were included (figure 1).

To further observe the impact of pre-diabetes on the risk of adverse clinical outcomes from different populations, data from the NIS database (2016–2018) were used for the current study. The study design based on NIS data was a cross-sectional study.[16] A total of 21 400 282 patients who were admitted to the hospital were identified in the NIS database by using the corresponding International Classification of Diseases-10th Revision (ICD-10) diagnostic and procedure codes. During the initial screening process, we excluded patients who were under 18 years of age and those missing data on age or sex. Finally, 17 548 442 patients were included in the analysis. Further details

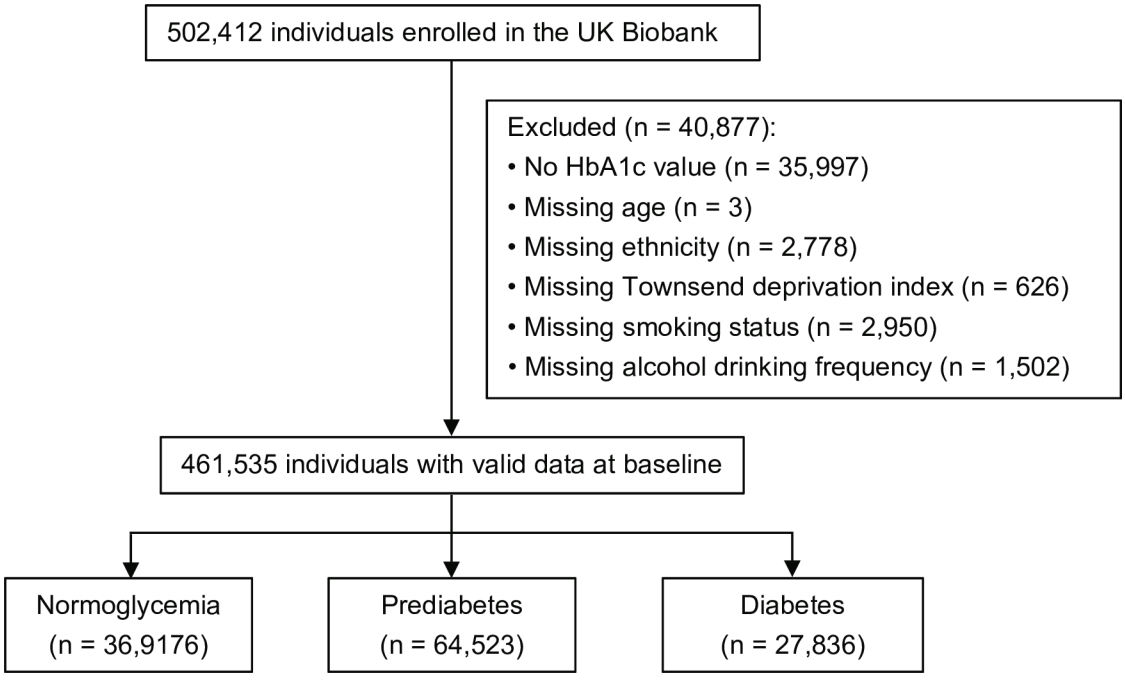

Figure 1 Flow chart of data screening in the UK Biobank study. HbA1c, hemoglobin A1c

on cohort descriptions are provided in online supplemental figure 1.

Exposure and covariates

The glycaemic status included normoglycaemia, pre-diabetes and diabetes. Pre-diabetes refers to an intermediate stage between normoglycaemia and overt diabetes mellitus.[17] In the UK Biobank database, diabetes was defined as self-reported diabetes (type 1 or type 2 diabetes), HbA1c≥6.5% or self-reported use of insulin or hospital records of diabetes; pre-diabetes was defined as no self-reported diabetes, and HbA1c≥5.7 and <6.5% (in accordance with the American Diabetes Association definition[18]) and/or hospital records of pre-diabetes; normoglycaemia was defined as no self-reported diabetes and HbA1c<5.7%. The ICD-10 codes for pre-diabetes and diabetes were R73, R73.0, R73.9 and E10–E14, respectively.

Race was self-reported and categorised as white and non-white. The Townsend Deprivation Index is a comprehensive measure of socioeconomic deprivation, assigned by the UK Biobank based on the participants' postcodes of residence. The index is calculated using national census data on car ownership, household overcrowding, home ownership and unemployment. Higher Townsend scores indicate greater levels of socioeconomic deprivation.

Participants reported their history of smoking status (current vs former vs never) and current alcohol intake frequency (≥3 vs <3 times/week vs never) at enrolment. Body mass index (BMI) was measured as part of the examination in the UK Biobank. BMIs were categorised as underweight (<18.5 kg/m^2), healthy weight (18.5–24.9 kg/m^2), overweight or obesity (≥25.0 kg/m^2). According to the WHO 2020 guidelines on physical activity, ideal physical activity was defined as ≥150 min/week of moderate-intensity, or ≥75 min/week of vigorous-intensity, or ≥150 min/week of moderate-intensity and vigorous-intensity physical activity.[19]

In the NIS database, patients were classified into three categories based on ICD-10 diagnostic codes for blood glucose levels: normoglycaemia (those without pre-diabetes or diabetes), pre-diabetes (R73.01, R73.02, R73.01) and diabetes (E10–E14). The corresponding codes were not necessarily the primary reason for hospitalisation and may have been listed as secondary diagnoses. Patients' characteristics, including race (white vs non-white), smoking (yes vs no) and alcohol abuse/dependence (yes vs no), were also obtained from the NIS database according to the corresponding ICD-10 code.

Ascertainment of outcomes

In the two studies, diseases were coded using ICD-10, encompassing a total of 1204 three-character diagnostic codes. Our analysis focused on a predefined list of 76 common ICD-10 disease chapters and diagnostic groups constructed for outcome-wide studies based on previous research.[5–11 20] The related ICD-10 code of these diseases is provided in online supplemental table 1.

Statistical analysis

We used the means±SDs and frequencies (percentages) for descriptive analysis. T-test was used to compare normally distributed continuous variables by glycaemic status, while χ^2 test was used for categorical variables. We examined associations between pre-diabetes and the 76 health outcomes in unadjusted and adjusted models using Cox proportional hazards regression models in the UK Biobank cohorts. In these analyses, follow-up started from glycaemic status assessment (baseline, at study entry) and did not account for changes in status over time. It continued until the onset of the diseases of interest, death (linked data from the Death Registry) or end of follow-up, whichever occurred first. For each disease analysis, we excluded patients who had been diagnosed with the disease prior to baseline. HRs and 95% CIs for pre-diabetes, with normoglycaemia as the reference, were adjusted for age, sex and race, Townsend Deprivation Index, smoking status and alcohol intake frequency. In the cross-section study based on data from NIS, the ORs and 95% CIs of 76 health outcomes associated with pre-diabetes were estimated using binary logistic regression models, adjusted for age, sex, race, smoking and alcohol abuse/dependence. To focus on common diseases in patients with pre-diabetes, we considered only pre-diabetes–disease associations that yielded HRs≥1.0 in the UK Biobank study and the corresponding ORs≥1.0 in the NIS study, meanwhile, they were significant at a Bonferroni corrected α level, with a p value of less than 6.6×10^{-4} (76 tests).[21]

Further analyses focused on pre-diabetes-related diseases after excluding overlapping diagnoses based on ICD-10 code. To investigate the relationship between pre-diabetes and the co-occurrence of pre-diabetes-related diseases, we constructed four outcomes based on the number of diseases: the onset of one, two, three and four or more pre-diabetes-related diseases. Co-occurrence of two pre-diabetes-related diseases was defined as simple multimorbidity and four or more pre-diabetes-related diseases was defined as complex multimorbidity.[22] In addition to HRs and ORs, we calculated population attributable fractions (PAFs) to evaluate the potential reduction in pre-diabetes-related multimorbidity if exposure to pre-diabetes was removed.

Age and sex are considered important factors, as they are closely related to metabolic health and influence the incidence of various chronic diseases. To assess the impact of age and sex on the association between pre-diabetes and multimorbidity, we included their interaction terms in the Cox regression model. Additionally, stratified analyses were conducted to further explore the moderating effects of these factors in different subgroups. The stratified analyses in the UK Biobank study were based on (1) sex (male, female); (2) age (young and middle-aged group: ≤59 years; older group: >60 years).

In order to explore which disease is the most common among pre-diabetes patients with complex multimorbidity, the frequency of pre-diabetes-related disease during follow-up was computed and displayed with column diagram.

Statistical analyses were performed using R V.4.0.2 (R Foundation for Statistical Computing).

RESULTS

Of 461 535 participants aged 38 years or older from the UK Biobank who had been tested for HbA1c, 369 176 (80.0%) had normoglycaemia, 64 523 (14.0%) had pre-diabetes, and 27 836 (6.0%) had diabetes at baseline. Among individuals with pre-diabetes, the median follow-up time was 12.78 years (12.1, 13.55), the mean age was 60 (SD 7) years, with 35 304 participants (54.72%) being female and 58 649 participants (90.90%) being white (table 1). Compared with participants with normoglycaemia, those with pre-diabetes and diabetes were older, had lower socioeconomic status and were more likely to smoke (table 1). In addition, individuals with pre-diabetes and diabetes had higher BMI and a lower rate of reaching the level of ideal physical activity. In the NIS database, the average age of the pre-diabetes group is 63 years, which is significantly older than that of the normoglycaemic group (online supplemental table 2).

In the UK Biobank study, each of the 76 diseases has its own follow-up period, with a median follow-up time of 12.72 years across all diseases (online supplemental table 3). The results of multivariable Cox models examining the

Table 1 Baseline characteristics of the study population from the UK Biobank database

	Normoglycaemia (n=369 176)	Pre-diabetes (n=64 523)	Diabetes (n=27 836)	P value
Median follow-up time*, median (IQR)	12.86 (12.16,13.57)	12.78 (12.1,13.55)	12.74 (12.05,13.54)	
Age, years				<0.0001
Mean (SD)	56 (8)	60 (7)	59 (7)	
<60	223 132 (60.44)	26 649 (41.30)	11 648 (41.85)	
≥60	146 044 (39.56)	37 874 (58.70)	16 188 (58.15)	
Women	204 221 (55.32)	35 304 (54.72)	10 917 (39.22)	<0.0001
Race/ethnicity				<0.0001
White	355 469 (96.29)	58 649 (90.90)	24 439 (87.80)	
Non-white	13 707 (3.71)	5874 (9.10)	3397 (12.20)	
Townsend Deprivation Index	−1.45 (3)	−1.02 (3.23)	−0.45 (3.41)	<0.0001
Smoking status				<0.0001
Never	208 167 (56.39)	31 469 (48.77)	12 769 (45.87)	
Former	125 582 (34.02)	23 049 (35.72)	11 853 (42.58)	
Current	35 427 (9.60)	10 005 (15.51)	3214 (11.55)	
Alcohol drinking frequency, times/week				<0.0001
Never	25 020 (6.78)	7205 (11.17)	4466 (16.04)	
<3	174 906 (47.38)	33 715 (52.25)	14 963 (53.75)	
≥3	169 250 (45.85)	23 603 (36.58)	8407 (30.20)	
BMI, kg/m^2				<0.0001
Mean (SD)	26.85 (4.39)	28.9 (5.24)	31.37 (5.88)	
<18.5	2048 (0.55)	286 (0.44)	39 (0.14)	
18.5–24.9	132 631 (35.93)	14 266 (22.11)	3124 (11.22)	
≥25	233 287 (63.19)	49 651 (76.95)	24 434 (87.78)	
Missing	1210 (0.33)	320 (0.5)	239 (0.86)	
Ideal physical activity				<0.0001
Yes	174 401 (47.24)	27 516 (42.65)	10 045 (36.09)	
No	132 942 (36.01)	22 871 (35.45)	11 533 (41.43)	
Missing	61 833 (16.75)	14 136 (21.91)	6258 (22.48)	

Data are presented as median with IQR, counts (n) with percentages (%) or as means with SD.
*Follow-up time refers to the time until the end of follow-up for participants who did not develop the outcome.
BMI, body mass index.

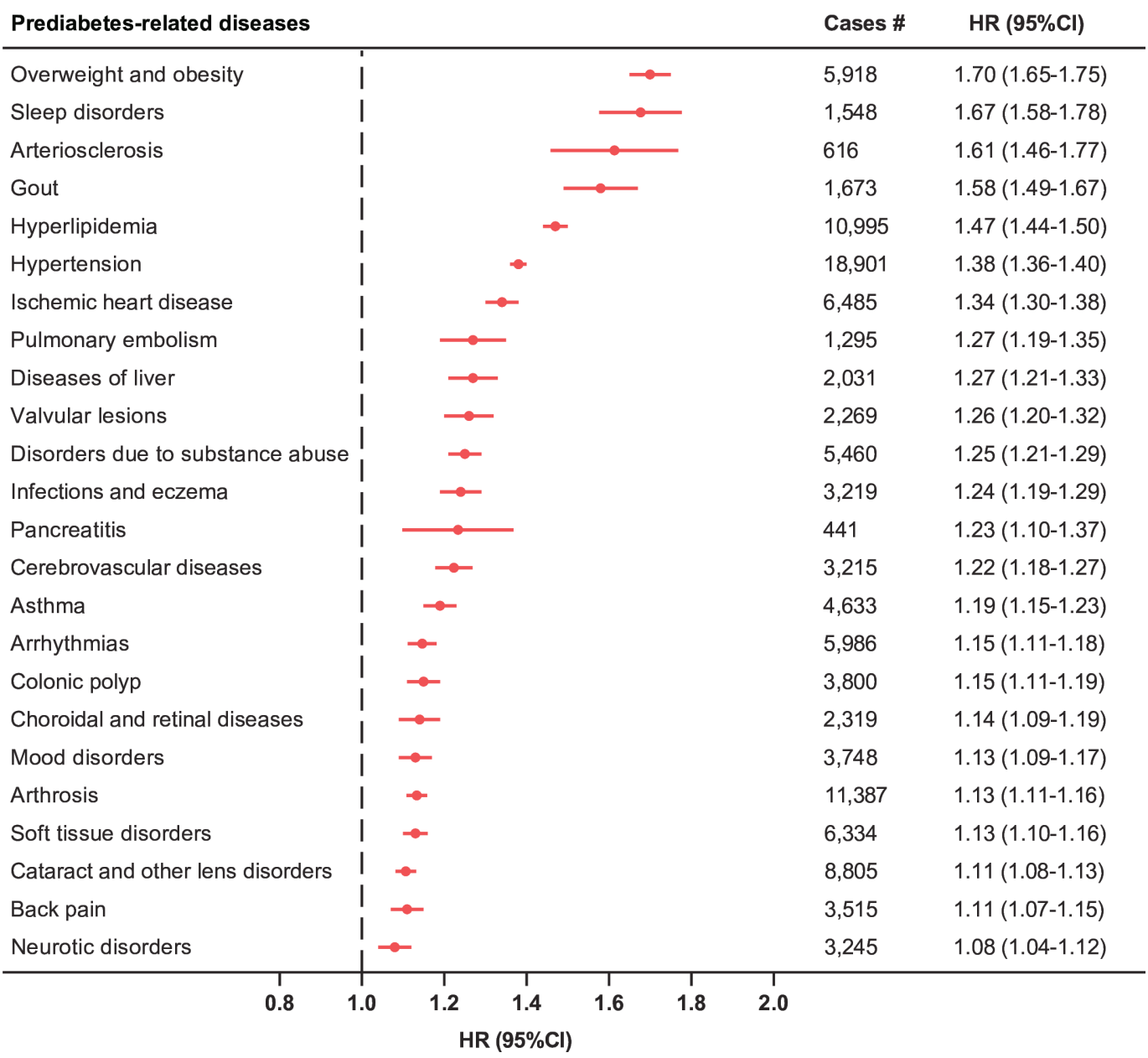

Figure 2 The HRs of pre-diabetes-related diseases for pre-diabetes compared with normoglycaemia in the UK Biobank study. Each round mark of the forest plot indicates the HRs and CI for individual disease. The model was adjusted for age, sex, race, Townsend Deprivation Index, smoking status and alcohol drinking frequency. #The number of cases for each disease in the pre-diabetes group. All p values are less than 0.00066 (Bonferroni correction for multiple testing).

effects of pre-diabetes on an array of health outcomes are shown in online supplemental table 4, revealing that 45 out of the 76 diseases studied associated with pre-diabetes ($p<0.00066$). Furthermore, the number of diseases significantly related to diabetes was more than that of pre-diabetes (online supplemental table 5). In order to identify common diseases significantly related to pre-diabetes, we additionally estimated the corresponding ORs for 76 diseases predefined in the NIS study, and 32 pre-diabetes-related diseases were the same as those obtained from the UK Biobank database (online supplemental table 6). After excluding several pre-diabetes-related diseases with overlapping ICD-10 codes or appearing only in the female population, we found that 24 common diseases were significantly associated with pre-diabetes (figure 2, online supplemental figure 2), most of them are cardiovascular diseases.

Further analyses of pre-diabetes and multimorbidity were based on the 24 non-overlapping pre-diabetes-related diseases mentioned above, including endocrine (overweight and obesity and hyperlipidaemia), mental and behavioural disorders (disorders due to substance abuse, mood disorders and neurotic disorders), nervous system (sleep disorders), eye (choroidal and retinal diseases, cataract and other lens disorders), cardiovascular (hypertension, ischaemic heart disease, pulmonary embolism, arrhythmias, valvular lesions, cerebrovascular diseases and arteriosclerosis), respiratory (asthma),

Table 2 Association of glycaemic status with pre-diabetes-related disease and multimorbidity in the UK Biobank study

	Cases, n (%)	HR (95%CI)*	PAF (95%CI)
One pre-diabetes-related disease			
Normoglycaemia	71 539 (19.4)	1 (ref)	0% (ref)
Pre-diabetes	12 150 (18.8)	1.10 (1.08 to 1.12)	2.7% (2.5% to 2.9%)
Diabetes	4392 (15.8)	1.44 (1.40 to 1.49)	1.6% (1.4% to 1.8%)
Two pre-diabetes-related diseases			
Normoglycaemia	47 475 (12.9)	1 (ref)	0% (ref)
Pre-diabetes	10 094 (15.7)	1.22 (1.19 to 1.24)	5.7% (5.4% to 6.0%)
Diabetes	4372 (15.7)	2.18 (2.11 to 2.25)	4.7% (4.5% to 4.9%)
Three pre-diabetes-related diseases			
Normoglycaemia	30 148 (8.2)	1 (ref)	0% (ref)
Pre-diabetes	7293 (11.3)	1.29 (1.26 to 1.33)	8.0% (7.6% to 8.4%)
Diabetes	4145 (14.9)	2.80 (2.71 to 2.90)	8.2% (7.9% to 8.5%)
Four or more pre-diabetes-related diseases			
Normoglycaemia	39 299 (10.7)	1 (ref)	0% (ref)
Pre-diabetes	12 287 (19.0)	1.46 (1.43 to 1.49)	11.2% (10.8% to 11.5%)
Diabetes	10 017 (36.0)	3.22 (3.14 to 3.29)	12.9% (12.6% to 13.2%)

*Adjusted for age, sex, race, Townsend Deprivation Index, smoking status and alcohol drinking frequency.
PAF, population attributable fraction.

digestive (diseases of liver, pancreatitis, colonic polyp), skin (infections and eczema), musculoskeletal (gout, arthrosis, back pain and soft tissue disorders) diseases. In addition, endometrial cancer and polycystic ovary syndrome were also associated with pre-diabetes, due to the two diseases only existing in the female population, further sex-specific analysis was performed to test the sex-related differences.

The risks of developing one, two, three and four or more pre-diabetes-related diseases (ie, the number of additional diseases beyond pre-diabetes) by glycaemic status, along with the corresponding PAFs in the UK Biobank study, are presented in table 2. Compared with participants with normoglycaemia, those with pre-diabetes were at a higher risk of developing pre-diabetes-related multimorbidity, the adjusted HR was 1.22 (95% CI 1.19 to 1.24; PAF 5.7% (95% CI 5.4 to 6.0)) for developing two pre-diabetes-related diseases (simple multimorbidity), 1.29 (95% CI 1.26 to 1.33; 8.0% (95% CI 7.6% to 8.4%)) for developing three diseases, and 1.46 (95% CI 1.43 to 1.49; 11.2% (95% CI 10.8% to 11.5%)) for developing four or more diseases (complex multimorbidity). The 24 pre-diabetes-related diseases that occurred most frequently in individuals with pre-diabetes and complex multimorbidity were hypertension (8243 (67.1%) of 12 287 patients), followed by hyperlipidaemia (6242 (50.8%)) and arthrosis (5587 (45.5%)) (figure 3). In the NIS study, patients with pre-diabetes had an increased risk of coexisting simple multimorbidity (adjusted OR 4.30 (95% CI 4.14 to 4.47)) and complex multimorbidity (10.03, 95% CI 9.66 to 10.40) compared with those with normoglycaemia (online supplemental table 7). Among patients with complex multimorbidity in the NIS study, the most common pre-diabetes-related diseases were also hypertension and hyperlipidaemia (online supplemental figure 3). These results were roughly consistent with the findings above, indicating that pre-diabetes is associated with an increased risk of pre-diabetes-related multimorbidity in both datasets.

We examined the age and sex interactions between pre-diabetes and multimorbidity. The results showed that after including the age interaction term, the HR for the interaction term was less than 1, while the HR of pre-diabetes for complex multimorbidity significantly increased, indicating that the impact of pre-diabetes on the young and middle-aged population is more pronounced (online supplemental table 8). In the interaction analysis by sex, with females as the reference group, we found that gender did not show a significant moderating effect on the relationship between pre-diabetes and the outcome (online supplemental table 9). In the subgroup analysis, we observed that the incidence rate of each outcome was higher in the older age group compared with the young and middle-aged group (online supplemental table 10). However, pre-diabetes before the age of 60 was more strongly associated with the development of complex multimorbidity (HR 2.06, 95% CI 1.98 to 2.14) than pre-diabetes at older ages (HR 1.42, 95% CI 1.39 to 1.46). This indicates that younger and middle-aged individuals with pre-diabetes are at greater risk of developing complex multimorbidity. Additionally, the prevalence of pre-diabetes-related complex multimorbidity in men was moderately higher than that of women (online supplemental table 11).

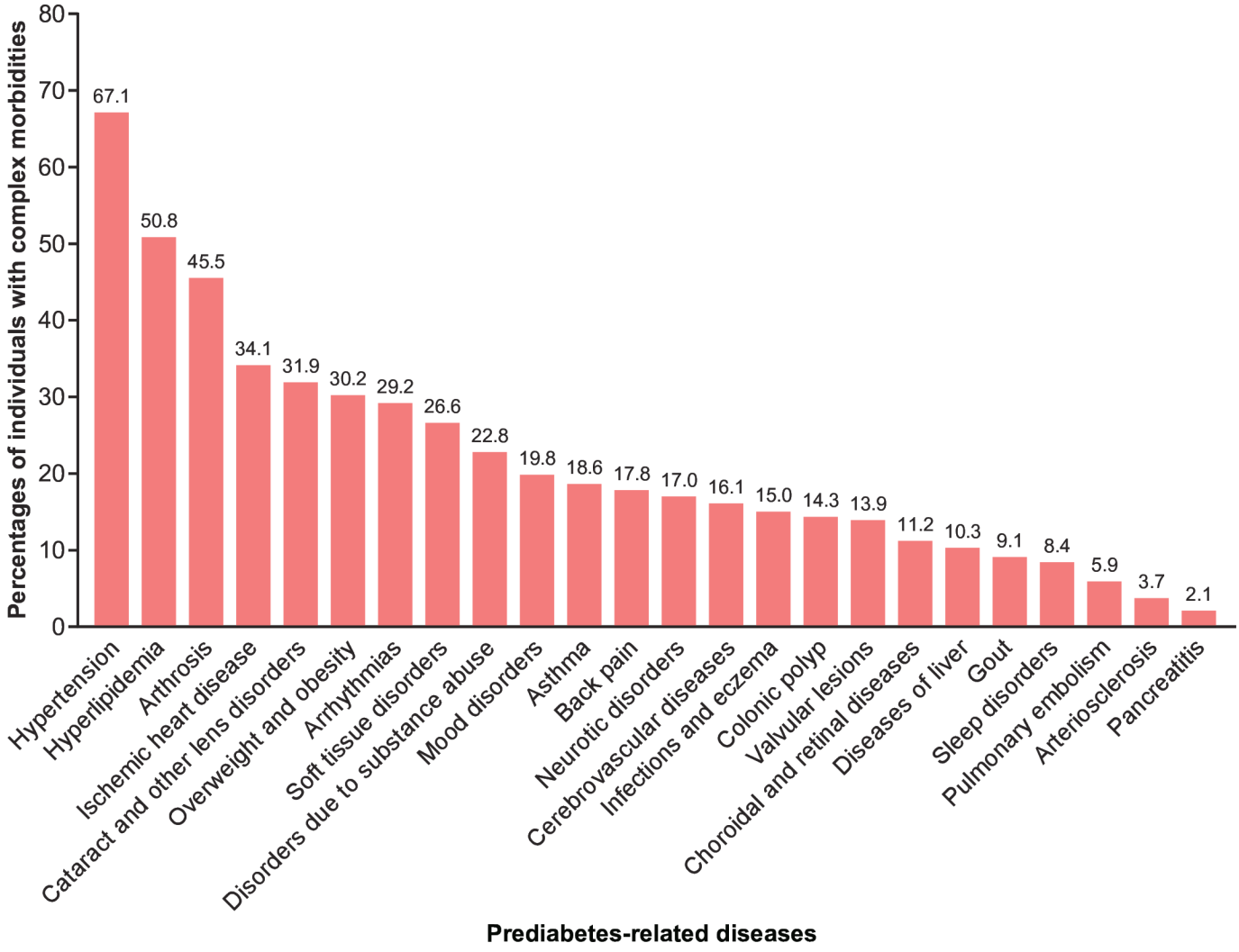

Figure 3 Percentages of 24 pre-diabetes-related diseases among pre-diabetes patients with complex multimorbidity in the UK Biobank study. Diseases are shown by descending incidence.

DISCUSSION

In this study, associations between pre-diabetes and a range of diseases are well recognised, we also have two key findings that are novel and better described than previous studies. First, a comprehensive analysis of 76 disease outcomes, which facilitates a deeper understanding of the health effects of pre-diabetes, showed that pre-diabetes is robustly associated with 24 non-overlapping diseases across multiple organ systems. Second, people with pre-diabetes are at a significantly increased risk of developing multimorbidity compared with those with normoglycaemia. Our findings imply that a more aggressive management and care of pre-diabetes is likely warranted to prevent the accompanying development of complex comorbidity, thus improving the quality of life.

The present study has innovatively displayed those individuals with pre-diabetes are associated with increased risks of gout, pulmonary embolism, diseases of liver, valvular lesions, colonic polyp, arthrosis and back pain, which have not been reported in previous studies. Our study finds that the positive correlations between pre-diabetes and multiple vascular diseases are consistent with the results of previous studies.[5 23 24] With regard to cardiovascular diseases, an analysis from the UK Biobank indicated that pre-diabetes was associated with elevated cardiovascular disease risk even before progression to type 2 diabetes.[5] Individuals with pre-diabetes may have more significant early arteriosclerosis,[23] and they were at an increased risk of developing atrial fibrillation.[24] The recent meta-analysis also summarised that pre-diabetes is positively associated with the risk of multiple cardiovascular outcomes.[25] Indeed, retinopathy is a common microvascular complication in patients with diabetes, and pre-diabetes before the diagnosis of type 2 diabetes is associated with an increased risk of microvascular disease.[26] In our predefined list of three eye diseases and diagnostic groups, pre-diabetes increases the risk of choroidal and retinal diseases, cataract and other lens disorders. A meta-analysis that included nine cross-sectional studies also showed that pre-diabetes was associated with a higher prevalence of retinopathy compared with normoglycaemia.[27] Early detection of pre-diabetes may provide an opportunity to reduce the burden of macrovascular

and microvascular disease, as such diseases can precede the development of overt diabetes.

In addition to common vascular diseases, some other pre-diabetes-related diseases are also consistent with previous studies. We observed that people with pre-diabetes were at an increased risk of sleep disorders. The results from a multiethnic cohort showed that sleep duration was independently associated with %HbA1c in adults with pre-diabetes, and %HbA1c was significantly higher in those reporting <5 or >8 hours of sleep per night.[28] Patients with pre-diabetes had a higher risk of incident asthma, which was generally similar to a study using a claims-based obese asthma cohort that compared with individuals with normal %HbA1c, those in the pre-diabetes range had a higher asthma exacerbation rate.[29] Our research also indicated the association of pre-diabetes with a high risk of mood disorders, which further confirmed the findings of a previous cross-sectional study.[30]

Our data expound that people with pre-diabetes have a higher risk of co-existing multimorbidity, further filling the evidence gap regarding the causes of multimorbidity. Compared with those with normoglycaemia, people with pre-diabetes were at a greater risk of developing complex multimorbidity. Meanwhile, patients with complex multimorbidity were more likely to coexist with hyperlipidaemia or hypertension. An analysis based on the National Health and Nutrition Examination Survey (NHANES) study also pointed out that the absolute number of adults with pre-diabetes was large, and about half of the people with pre-diabetes suffered from comorbidities, such as hypertension, dyslipidaemia or both, leading to excess cardiovascular and renal disease risk.[31] In our analysis, pre-diabetes has the highest overweight and obesity risk, and a recent study proved that pre-diabetes with obesity had a higher risk of incident cardiovascular disease.[7] Such findings reveal that accompanying multiple diseases simultaneously becomes highly prevalent in adults with pre-diabetes, mainly related to vascular disease. Our study provides an update on this evidence with a more comprehensive view of the whole body and a more diverse set of conditions.

Our study found that older adults (aged 60 and above) had a higher rate of developing multiple pre-diabetes-related diseases compared with those under 60. This is consistent with a national dataset of 1 751 841 individuals, which showed that multimorbidity was prevalent in most people aged 65 and older.[32] It is worth noting that multimorbidity is more common in older people, and patients suffering from multiple medical condition are at a higher risk of disability and early death and also have a lower quality of life.[12] Our findings also indicated that the risk of multimorbidity associated with pre-diabetes among young and middle-aged people was higher than that of older people, which emphasised the significance of early detection and intervention of pre-diabetes.

It is worth noting that the cross-sectional prevalence in the NIS study was quite low, approximately 0.7%, which was far lower than the prevalence of pre-diabetes reported in previous articles.[33] This low prevalence may be that the diagnosis of pre-diabetes only relies on the ICD-10 code, there is a lack of more rigorous methods, such as oral glucose tolerance tests (OGTT). It is precise because of the low proportion of inpatients with pre-diabetes, there must be a huge number of undiagnosed patients with pre-diabetes. As an abnormal state of glucose metabolism, pre-diabetes may cause serious damage to human health like diabetes, but it is often ignored in public health management. The potential harm of pre-diabetes is far more dangerous than we have seen.

In terms of strengths, the UK Biobank study, with its longitudinal design, provides robust evidence for exploring the causal relationships between pre-diabetes and various diseases. Additionally, the inclusion of HbA1c data offers valuable insights into the long-term effects of pre-diabetes on health outcomes. Our study clarified the relationship of pre-diabetes with a range of diseases and multimorbidity, which has practical significance for clinical practice. Meanwhile, the findings of this investigation should be interpreted in the context of potential limitations. First, the diagnosis of pre-diabetes or diabetes in the two databases used in our study was based on hospitalisation data. This reliance on hospitalisation records may lead to an underestimation of disease prevalence, as some patients may not have been hospitalised. Additionally, pre-diabetes is often not formally coded, and OGTTs are not routinely performed. Thus, pre-diabetes may be underdiagnosed, as well as IFG and IGT cannot be distinguished either. Furthermore, blood glucose abnormalities might have been identified during hospitalisation for unrelated reasons, and some diseases may precede the onset of pre-diabetes, potentially resulting in a confounding effect due to reverse causality. Therefore, further studies combined with other data such as clinic medical record are needed to verify our conclusions. Second, common health outcomes were identified depending on ICD-10 codes, and it may have coding errors (ie, miscoding and undercoding). The use of electronic health records means that our study did not include undiagnosed conditions and those that seldom lead to hospitalisation. Third, due to the limitations of the UK Biobank database, we were unable to obtain specific information on diabetes medications other than insulin. Although we adjusted for potential confounders, the possibility of unmeasured factors or unconsidered confounding could not be entirely ruled out in this observational, non-randomised study. In addition, our study focused on the exposure status at baseline and did not take into account the dynamic changes in exposure status, which requires further exploration in future research. Fourth, we selected a list of pre-diabetes-related diseases that were significant in both databases, which limits our definition of pre-diabetes-related complex multimorbidity to diseases both robustly associated with pre-diabetes and common causes of disease burden. In the future, we will conduct OGTT in

large-scale population, recruit pre-diabetes population based on strict diagnostic criteria and perform follow-up study to explore the impact of pre-diabetes on the onset of disease outcomes and multimorbidity.

CONCLUSIONS

In conclusion, pre-diabetes is closely related to multimorbidity from a series of common diseases. These findings emphasise that pre-diabetes is a significant, manageable target for disease prevention, which can overcome the difficulty of dealing with each disease separately to a certain extent. Furthermore, these results reinforce the idea that implementing risk-reduction strategies for adults with pre-diabetes is essential to decrease the coexistence of pre-diabetes-related diseases, which may have clinical and public health implications.

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Contributors JZ and YSong conceived and designed the study. YW, XFan, YShi and ZY had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. YW, YShi, YZhang, JH, YZ-S and ML performed statistical analyses and interpreted data. YW, XFan, YC, ZW, RX and QG drafted the article. XFan, ZY, XFeng, YD, YT, HD and JZ revised the manuscript. All authors have final approval of the submitted and published versions. JZ takes full responsibility for the finished work and/or the conduct of the study, had access to the data and controlled the decision to publish.

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Competing interests None declared.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants. The UK Biobank study received approval from the North West Multi-Centre Research Ethics Committee (Ref: 11/NW/0382). Participants provided electronic informed consent forms for baseline assessments and register linkage. For the NIS database, as all data are deidentified, secondary data analysis using this database does not require institutional review board approval or informed consent from study participants. Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available in a public, open-access repository. This study used data from the UK Biobank (application number 89483). Registered researchers can access the database by applying through the UK Biobank website (https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access) and completing the necessary application and approval process. The initial protocol of the UK Biobank study is publicly available online. For more details, please contact access@ukbiobank.ac.uk. The NIS database covering the years 2016–2018 is part of the Healthcare Cost and Utilisation Project (HCUP) family of databases, funded by the Agency for Healthcare Research and Quality. This study obtained permission from HCUP and adhered to the data-use agreement. The NIS database is derived from hospital billing data submitted to statewide organisations across the USA. It provides validated patient linkage numbers, enabling patient tracking across hospitals within each state, while strictly adhering to privacy protection regulations, including compliance with HIPAA standards.

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