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Longitudinal association between body weight, health behaviors, and development of prediabetes over 8 years in the Rancho Bernardo Study

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Longitudinal association between body weight, health behaviors, and development of prediabetes over 8 years in the Rancho Bernardo Study

A thesis submitted in partial satisfaction of the requirements for the Master's degree
in
Public Health

by
Takeshi Yamamoto

Committee in charge
Professor Job Godino, Chair
Professor Brittany Larsen, Co-Chair
Professor Suzi Hong

2021

The thesis of Takeshi Yamamoto is approved, and it is acceptable in quality and form for publication on microfilm and electronically.

University of California San Diego
2021

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ABSTRACT OF THE THESIS

Longitudinal association between body weight, health behaviors, and development of prediabetes over 8 years in the Rancho Bernardo Study

by

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Master of Public Health

University of California San Diego, 2021

Professor Job Godino, Chair

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Background

The purpose of this study is to examine the association between changes in body mass index (BMI) and the development of prediabetes diagnosed by oral glucose tolerance test (OGTT) over 8 years in an existing longitudinal cohort study of older adults aged $\geq$ 60 years old.

Methods

Participants enrolled in the Rancho Bernard Study, who took an OGTT at the 4th measurement visit (between 1984-1987) and at the 7th measurement visit (between 1992-1996) and had normal glucose tolerance (NGT) at the 4th measurement visit were included (n = 532). Prediabetes status was determined using WHO criteria. Health behaviors and demographic characteristics were self-reported at both timepoints. We evaluated the association between changes in BMI and the development of prediabetes using Poisson regression.

Results

At the baseline, participants had a mean age of 64.7 years, 58.8% were female, and mean BMI was 24.5 kg/m^2. Over 8 years, 173 of 532 NGT participants (32.5%) developed impaired glucose metabolism. The burden of prediabetes increased by approximately 12% (95% confidence interval (CI) 1.04 to 1.21) for each unit increase of BMI. The corresponding prevalence ratio increased after adjustment for demographics (1.15, 95% CI 1.07 to 1.25) and changes in health behaviors (1.17, 95% CI 1.07 to 1.26).

Conclusion

Among a population of older adults, increases in body weight were associated with the development of prediabetes. Furthermore, the association was not attenuated by health behaviors and demographics, suggesting that progression of prediabetes may be largely driven by pathophysiological complications attributable to increased adiposity.

Introduction

The prevalence of diabetes is rising rapidly worldwide, and it is associated with costly complications including cardiovascular disease, neuropathy, and blindness, as well as premature mortality. [1-6] In the US, it is estimated that as many as 34 million people suffer from diabetes and an additional 88 million have prediabetes. [7] The prevalence of both diabetes and prediabetes is highest among adults aged 65 years and older, 26.8% and 46.6%, respectively [8]. Prediabetes is not only a high-risk state for the development of diabetes, but it is also an independent risk factor for micro and macrovascular disease [9] Recent systematic reviews and metanalyses have shown that among individuals who have not yet progressed to diabetes, there is a positive linear association between increasing glucose levels and cardiovascular disease and mortality[10].

The pathology of prediabetes follows two patterns, including impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). The World Health Organization has defined IFG and IGT in the 10th revision of the International Classification of Diseases as follows: IFG is defined as a fasting plasma glucose (FPG) level >110mg/dl (6.1mmol/l), and IGT is defined as a 2 hours plasma glucose level (2hPG) in oral glucose tolerance test (OGTT) > 140 mg/dl (7.8mmol/l).[11] Prior research has shown that IFG increases the likelihood of developing diabetes more than IGT regardless of the diagnostic threshold used[12-14], and both are associated with increased risk of micro and macrovascular complications[10,15-18]. Given this elevated risk, there have been increasing calls for identifying and treating prediabetes to optimize glycemic control.[19] However, knowledge gaps exist regarding how best to make prognostication highly sensitive and specific in predicting who will develop diabetes. Furthermore, there is a need for continued surveillance of the prevalence of prediabetes in diverse samples of aging adults and examination of the impact of longitudinal changes in risk factors on the development of prediabetes.

To date, there have been limited number of studies designed to reveal the pathology of the development of prediabetes. Nine cross-sectional studies have identified a strong positive association between the prevalence of prediabetes and body mass index (BMI, kg/m^2), which is the primary risk factor for development of diabetes.[20-29] According to these studies, the odds ratio of having prediabetes among those who are overweight (BMI>25 kg/m^2) ranges from 1.36 to 1.85. Additionally, only two longitudinal cohort studies have focused on the development of prediabetes. These studies show that BMI>30 kg/m^2 at baseline increased the likelihood of developing prediabetes by 220% over 10 years.[30,31] However, the findings from these two cohort studies are limited by a lack of data on the impact of changes in health behaviors known to independently influence body weight and glycemic control. More specifically, each study relied on health behavior measures taken at one timepoint (i.e., baseline) and consequently were unable to evaluate the influence of simultaneous changes in body weight and health behaviors during the study period. Therefore, not only is there a need to replicate the findings from existing longitudinal research, but there is also a need to better assess the metabolic and behavioral determinants of prediabetes. A better understanding of the phenotype-specific pathophysiology of prediabetes may add value to identifying appropriate interventions for patients with prediabetes.

In order to address the aforementioned gaps in the literature, we assessed the association between changes in BMI and health behaviors with the development of prediabetes defined by measures of IFG and IGT over 8 years in an existing longitudinal cohort study of older adults aged 60 years and older. Furthermore, we examined the extent to which demographic characteristics and changes in health behaviors impacted the association.

Methods

The Rancho Bernardo Study of Healthy Aging (RBS) is an ongoing longitudinal cohort study launched in 1972 in San Diego, California.[32] Rancho Bernardo is a northern suburb of San Diego that has been marketed as a retirement community. Therefore, the RBS cohort consists of male and female participants, more than half of whom were over 60 years old at the study baseline. The participants have undergone a medical check every 4 to 5 years. The study was approved by the University of California San Diego (UCSD) institutional review board. All participants of RBS provided written informed consent.

Procedures

The participants came to the Rancho Bernardo study clinic and were seen by trained nurses and interviewers at 7AM to 11AM on clinic visit day. They needed to come with 12-16 h fasting. Oral glucose tolerance test (OGTT) was administrated and fasting and 2 hours later blood sample were drawn. Blood sample was collected from cubital vein.

Measures

Prediabetes.

Over the course of 50-years history of the study, participants took an oral glucose tolerance test (OGTT) twice; once at the 4th measurement visit (between 1984-1987) and once at the 7th visit (between 1992-1996) about 8 years later. The presence of prediabetes or diabetes was defined by OGTT. Prediabetes and diabetes were diagnosed *by WHO criteria; FPG>110mg/dl (5.6 mmol/l) or 2hPG<140mg/dl (7.8 mmol/l), FPG>126mg/dl (7.0 mmol/l) and 2hPG<200mg/dl (11.1 mmol/l), restrictively.*

Body mass index (BMI).

Weight and height were measured by a trained investigator, with participants wearing light clothing and no shoes. BMI was then calculated as weight (kilograms) divided by square of the height (meters).

Health behaviors.

At each measurement visit, participants also completed a self-reported, interviewer administered questionnaire on health behaviors. Smoking status change was assessed and categorized into 4 groups; non-smoker at the 4th visit and non-smoker at the 7th visit (NO-NO), non-smoker at the 4th visit and current-smoker at the 7th visit (NO-YES), smoker at the 4th visit and non-smoker at the 7th visit (YES-NO), and current smoker at the 4th visit and current smoker at the 7th visit (YES-YES). Similarly, alcohol consumption status was assessed and change was categorized into 4 groups (NO-NO, NO-YES, YES-NO, YES-YES) by whether the participant drank more than 3 times or more per week or not. Engagement in exercise was assessed and change was categorized into 4 groups (NO-NO, NO-YES, YES-NO, YES-YES) by whether the participant engaged in exercise 3 times or more per week or not.

Demographics

Demographic characteristics were self-reported to a trained interviewer and included age (years), sex (male or female), race (white or non-white), and family history of diabetes.

Data analysis

Descriptive statistics (proportions, means, and standard deviations) were used to describe the demographics and health behaviors of participants with and without development of prediabetes. Paired t-test and McNemar testing were performed in analysis comparing baseline (4th visit) participants' characteristics and that of 7th visit. Three Poisson regression models with robust error variances were used to examine the association of BMI with the prevalence rate of prediabetes. An unadjusted crude model included BMI change alone (model 1), model 2 included BMI change and demographics, and model 3 included BMI change, demographics, and changes in health behaviors (smoking, alcohol consumption and exercise). Missing data were excluded from the analysis. The predefined cut-off for statistical significance was set at $P < 0.05$. All analyses were performed using JMP® 15 (SAS Institute Inc., Cary, NC, USA).

Results

Figure.1 shows how the study participants were selected for the analyses of this study. Among all enrolled RBS participants (N=6,726), 12.8% (n=859) took an oral glucose tolerance test at both visits 4 and 7. Of those, we excluded 38.1% (n=327) who had prediabetes or diabetes at visit 4. Our final sample consisted of 532 participants.

The mean (standard deviation) age at visit 4 was 64.7 (9.8) years old, 58.8% were female, 99.2% were white, and mean (standard deviation) BMI was 24.5 (3.4) kg/m2. Approximately 25% percent of participants had a family history of diabetes, 45% smoked cigarettes, and 55% drank alcohol more than 3 times per week. A total of 85% percent of participants reported engaging in exercise 3 times or more per week.

Over the study period, 173 of 532 (32.5%) NGT participants developed prediabetes or diabetes (only 2 participants developed impaired glucose metabolism such that it met the criteria for a diagnosis of diabetes. They were treated the same as prediabetics in subsequent analyses). 2hPG among this population increased greatly significantly as expected, from 110 mg/dl to 169 mg/dl. Table 1 shows the participants' change from visit 4 to visit 7. BMI increased in both groups; the group including those with NGT and the group including those with prediabetes at visit 7. Participants who developed prediabetes had higher BMI at visit 4 and experienced a larger increase in BMI through to visit 7. Changes in BMI was larger in participants who developed prediabetes than those who stayed NGT ($p<0.05$). Age changed from about 64 years old to 72 years old in both groups. In regard to health behavior change, the proportion of people who regularly drank alcohol decreased in both groups, whereas the proportion who smoked did not change in both groups. These trends did not change in both health behaviors p=0.41, p=0.90, respectively). The proportion of people who exercised regularly decreased in the group that developed prediabetes or diabetes, although did not change in NGT group.

The unadjusted prevalence ratio for developing prediabetes (Model 1) was 1.12 (95% Confidence Interval (CI) 1.04 to 1.21), indicating a significant 12% increase in prediabetes per unit increase of BMI change (Table 2). Model 2 included adjustment for demographics, which resulted in a stronger association between BMI change and the development of prediabetes (1.15, 95% CI 1.07 to 1.25). Model 3 included adjustment for both demographics and health behavior change, which resulted in a stronger association between BMI change and the development of prediabetes (1.17, 95% CI 1.07 to 1.26).

Discussion

The present study adds findings to a limited body of research that reports a positive association between body weight and the development of prediabetes by further considering key demographics and health behaviors. As expected, the results suggest that the burden of prediabetes increased with increases in BMI over an 8-year period among a cohort of older adults. Importantly, adjustment for demographic and health behavior changes did not attenuate the association. Rather, the strength of the association increased. This suggests that the progression from NGT to prediabetes may be largely driven by pathophysiological complications attributable to increased adiposity.

Increased weight and adiposity is well known to be a risk factor for developing impaired glucose metabolism[33]. However, most research has focused on the phase of developing diabetes from prediabetes. For example, Oguma et al. reported that increased weight gain over 30 years among 20,186 university alumni was associated with the development of diabetes.[34] Only Hwang (2007), Aekplacorn (2006), Zang (2018), and Gautier (2010) have performed prospective cohort studies that used OGTT to accurately describe the development of prediabetes, and they too found that increased weight gain was associated with the development of impaired glucose metabolism[35-38]. Importantly, these studies did not characterize the impact of changes in demographics and health behaviors. However, Henninger (2015) and Ranjit (2015) did conduct prospective-cohort studies that included a consideration of health behaviors[39,40], but their reports were limited by the fact that the health behaviors were only evaluated at baseline. Thus, the present study makes a unique contribution to the evidence on the association between weight gain and prediabetes, because it takes into account demographic and health behavior change.

The strengths of this study include the use of data from a relatively large longitudinal cohort study. Additionally, the study included repeated administrations of OGTT. This provides a high level of validity to the diagnosis of prediabetes. Furthermore, consecutive measurement of health behaviors allowed us to adjust for factors that are known to influence both weight and risk of diabetes (e.g., smoking and exercise). Lastly, our study obtained data from a population of older adults who were enrolled without impaired diabetes metabolism, which means that study data reflect the natural development of prediabetes among this population.

This study is not without its limitations. First, a substantial portion of the overall sample did not complete the sequential OGTT, which limits the generalizable of the results. Second, all health behaviors were measures using methods of self-report which are known to have limited validity and reliability. Third, the study did not include repeated measures of caloric intake. However, one previous study using RBS data showed no correlation between fasting glucose level and the healthy eating index, suggesting that atherogenic food intake may not be associated with fasting glucose and impaired glucose metabolism[41]. Lastly, the RBS cohort does not reflect general social constructs since most participants were White. Importantly, however, the two previously mentioned longitudinal cohort studies that took into account changes in health behavior were both conducted among Hispanic/Latino populations and our results are in alignment with their findings, suggesting that this association may be strong even after taking into account a range of sociological constructs known to impact both weight and the development of impaired glucose metabolism.

Conclusions

According to the findings from this study, increases in body weight are significantly associated with the development of prediabetes among older adults. Furthermore, the association was not attenuated by changes in health behaviors and demographics, suggesting that progression from NGT to prediabetes may be largely driven by pathophysiological complications attributable to increased adiposity. Additional longitudinal research that includes robust measures of change in markers of glucose tolerance, health behaviors, and demographic characteristics including the social determinants of health are warranted. Future studies should be designed to include more detailed and quantifiable measures of health behavior change in particular. As the population ages, the burden of impaired glucose tolerance will likely increases. This study highlights the need for continued surveillance of this burden, as well as a better understanding of the phenotype-specific pathophysiology of prediabetes, which may inform effective interventions for patients with prediabetes.

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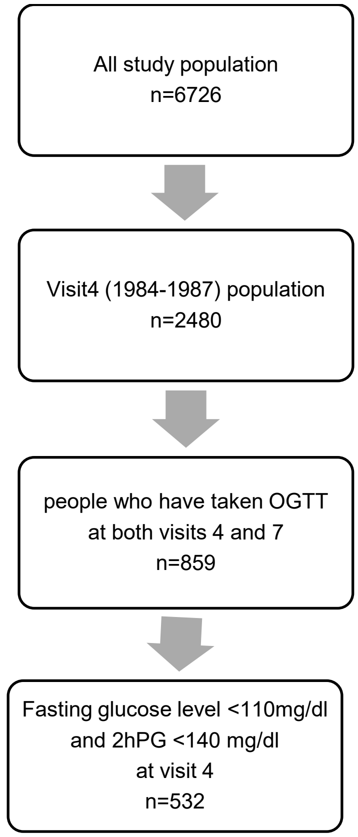

OGTT: Oral glucose tolerance test

Figure 1: Procedure of selecting the subjects from Rancho Bernardo Study database

Table1: Subjects characteristics at baseline (4th visit)

N (M/F)	532 (219/313)
Age (y/o)	64.7 + 9.8
Race	
Whites	522 (99.2)
Not Whites	4 (0.7)
Missing	6
BMI (kg/m2)	24.5 + 3.4
Family history of diabetes	
Yes	131 (25.0)
No	393 (75.0)
Missing	8
Smoking history	
Present smoker	233 (44.0)
Former smoker	229 (43.2)
Non-smoker	68 (12.8)
Missing	2
Alcohol	
Everyday	236 (45.2)
3-4 days/week	54 (10.3)
1-2 days/ week	75 (14.4)
1-2 days/ month	66 (12.6)
<1days/ month	51 (9.7)
Non-drinker	40 (7.7)
Missing	10
Exercise 3 times or more/week	
Yes	453 (85.1)
No	79 (14.9)
Missing	0

Table 2: Profile change from Visit 4 to 7 by the incidence of impaired glucose metabolism at Visit7

	Overall (n=532)			NGT (n=359)			Any prediabetes (n=173)			Difference between NGT and any prediabetes
	Visit4	Visit7	p	Visit4	Visit7	p	Visit4	Visit7	p	p
Age	63.4 ± 8.9	71.6 ± 8.9	<.01	62.9 ± 8.9	71.2 ± 9.0	<.01	64.3 ± 8.7	72.6 ± 8.7	<.01	0.52
BMI	24.7 ± 3.4	25.2 ± 3.7	<.01	24.3 ± 3.1	24.6 ± 3.3	<.01	25.4 ± 3.8	26.3 ± 4.3	<.01	<.01
FPG	94.2 ±8.5	94.0 ± 13.5	.71	93.8 ±8.2	91.5 ± 7.0	<.01	95.2 ± 8.9	99.2 ± 20.5	.02	<.01
2hPG	103.6 ± 20.6	127.5 ± 38.8	<.01	100.5 ± 21.0	107.7 ± 19.1	<.01	110.2 ± 17.8	168.6 ± 37.1	<.01	<.01
Smoking YES/ NO (%)	233/297 (44.0)	242/289 (45.6)	.09	165/192 (46.2)	172/187 (47.9)	.11	68/105 (39.3)	70/102 (40.7)	.71	.41
Alcohol 3days or more/ week YES/ NO (%)	290/232 (55.6)	248/283 (46.7)	<.01	195/157 (55.4)	167/192 (46.5)	<.01	95/75 (55.9%)	81/91 (47.1)	<.01	.90
Exercise 3 times or more/week YES / NO (%)	453/79 (85.2)	406/126 (76.3)	<.01	296/63 (82.5)	281/78 (78.3)	.10	157/16 (90.8)	125/48 (72.3)	<.01	.01

Table3: BMI Poisson model with the incidence of any prediabetes as a dependent variable

	Prediabetes or diabetes (n=173)
Model 1 Crude (BMI only)	1.12 (1.04-1.21)
Model 2 Model 1 + demographics	1.15 (1.07-1.25)
Model 3 Model 2 + Changes in health behaviors	1.17 (1.08-1.26)