THE 3C NUTRITION ANCILLARY STUDY: DESCRIBING THE INTEGRATION OF DIET AND DISEASE SELF-MANAGEMENT AMONG ADOLESCENTS AND ADULTS WITH TYPE 1 DIABETES IN CHINA

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A dissertation submitted to the faculty at the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Nutrition (Epidemiology) in the Gillings School of Global Public Health.

Chapel Hill
2014

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ABSTRACT

Lindsay M. Jaacks: The 3C Nutrition Ancillary Study: describing the integration of diet and disease self-management among adolescents and adults with type 1 diabetes in China
(Under the direction of Elizabeth J. Mayer-Davis)

The incidence of type 1 diabetes (T1D) is increasing in China and morbidity and mortality may be substantially higher there than in the U.S. While results of clinical trials support intensive disease self-management to reduce the risk of complications, our knowledge of self-management practices in China is limited in scope and outdated.

In order to address this gap, a cross-sectional study was conducted in Beijing from January-August 2013. Data collection entailed a fasting blood draw, a questionnaire, and three 24-hour dietary recalls. Telephone administration of the 24-hour recalls was validated against in-person administration in a pilot study. Data on individuals without diabetes were from the China Health and Nutrition Survey. The aims were three-fold: among individuals with T1D in Beijing, 1) to describe the contribution of nutrition education to disease self-management and diet, 2) to compare their dietary intake to individuals without diabetes in Beijing, and 3) to use reduced rank regression to identify dietary pattern(s) that maximize the explained variation in key cardiometabolic risk factors.

Participants (*n*=100) averaged 41.7 ±16.3 years old, diabetes duration, 11.8 ±9.7 years. Fewer than half of participants had “ever” met with a dietitian and only 18% had attended a diabetes education session that covered nutrition in the past 12 months. Nutrition therapy for T1D typically involved matching fixed insulin doses to a diet that was rigid with respect to amount and timing, rather than an individualized, flexible approach recommended by

international Diabetes Associations. One effect of this was that participants with T1D had a significantly lower mean percentage of energy from carbohydrates and higher mean percentages of energy from fat and protein compared to a cohort of individuals without diabetes in Beijing. Finally, we identified a dietary pattern characterized by high intakes of wheat products and low-sugar cakes, and low intakes of beans and pickled vegetables that was significantly associated with lower HbA1c and LDL cholesterol.

Together, these results highlight an important need for nutrition counseling for individuals with T1D in China that is consistent with current clinical practice guidelines to promote health and reduce risk for complications of diabetes.

To my parents, for their unceasing support and encouragement.

ACKNOWLEDGEMENTS

I am indebted to the individuals with type 1 diabetes in Beijing and the surrounding area whose participation made this study possible, and to my interviewers: Yang Xiao, Jing Lv, Wenjia Yang, Jia Liu, Han Feifei, and Lihua Zhang. I would also like to thank Wei Liu, who was integral to completing data collection in Beijing. Finally, I would like to acknowledge Linong Ji, who first invited me to China to learn about a disease, and ended up teaching me about a culture.

This project was supported by funding from the Sanofi Global Scholars Program and the Fogarty International Center (5D43TW009077) and National Center for Advancing Translational Sciences (ULTR000083) of the U.S. National Institutes of Health. None of the aforementioned funding sources had a role in the design, analysis, or writing of this dissertation.

PREFACE

Parts of this work were done in collaboration with other scientists. The 3C Nutrition Ancillary Study (3CNAS) was designed in collaboration with Linong Ji at Peking University People's Hospital and with the help of Elizabeth Mayer-Davis, Barry Popkin, Shufa Du, and Michelle Mendez at The University of North Carolina, Chapel Hill. Wei Liu at Peking University People's Hospital was a co-project manager throughout the duration of data collection and was in charge of verifying the translation and submitting necessary documents to the Peking University Institutional Review Board. Without her ongoing assistance with data collection this project would not have been possible.

Chapters 2 and 3 contain material published prior to writing this dissertation with the following citation:

> Jaacks LM, Liu W, Ji L, Mendez M, Du S, Crandell J, Rosamond W, Mayer-Davis EJ. Diabetes nutrition therapy and dietary intake among individuals with type 1 diabetes in China. *Diabetic Medicine*, 2014.

Permission to include the article in its entirety in a Ph.D. dissertation was retained from John Wiley & Sons, Inc. (publisher of *Diabetic Medicine*). All co-authors have given me permission to include this work in my dissertation.

Chapter 4 contains material accepted for publication in the *Asia Pacific Journal of Clinical Nutrition* published by HEC press. Chapter 5 represents unpublished research. I prepared the 3CNAS dataset, completed all statistical analyses, and wrote the manuscript drafts corresponding to these chapters. For Chapter 4, Shufa Du assisted with preparing and cleaning the China Health and Nutrition Survey dataset.

My committee, as well as Shufa Du, Wei Liu, Linong Ji, and for Chapter 5, Archana Lamichhane, provided valuable feedback throughout the analysis and writing process.

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LIST OF ABBREVIATIONS

3CNAS	3C Nutrition Ancillary Study
ADA	American Diabetes Association
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
ACE	Angiotensin-converting enzyme
ARB	Angiotensin receptor blocker
BMI	Body mass index
CVD	Cardiovascular disease
CHNS	China Health and Nutrition Survey
CIDE	China Initiative for Diabetes Excellence
DAISY	Diabetes Autoimmunity Study in the Young
DCCT	Diabetes Control and Complications Trial
DERI	Diabetes Epidemiology Research International
DIPP	Diabetes Prediction and Prevention Project
DSME	Diabetes self-management education
DKA	Diabetic ketoacidosis
DBP	Diastolic blood pressure
EMR	Electronic medical records
EDIC	Epidemiology of Diabetes Interventions and Complications
GAD	Glutamic acid decarboxylase
HbA1c	Hemoglobin A1c
HDL	High-density lipoprotein
HLA	Human leukocyte antigen

IRB	Institutional review board
IA	Insulinoma-associated
IDF	International Diabetes Federation
ISPAD	International Society for Pediatric and Adolescent Diabetes
ICC	Intraclass correlation coefficients
LDL	Low-density lipoprotein
MDI	Multiple daily injections
PEDC	Pittsburgh Epidemiology of Diabetes Complications
RAPIA	Rapid assessment protocol for insulin access
RRR	Reduced rank regression
SEARCH	SEARCH for Diabetes in Youth Study
SMBG	Self-monitoring of blood glucose
SBP	Systolic blood pressure
TEDDY	The Environmental Determinants of Diabetes in the Young
T1D	Type 1 diabetes
T2D	Type 2 diabetes
WHO	World Health Organization

CHAPTER 1: BACKGROUND AND RATIONALE

Section 1.1 Pathophysiology of type 1 diabetes

Section 1.1.1 Classification

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from impairments in insulin production, insulin action, or both. The American Diabetes Association (ADA) classifies diabetes into four clinical categories: type 1 diabetes (T1D), type 2 diabetes (T2D), gestational diabetes, and other diabetes including diabetes due to genetic defects and drug- and chemical-induced diabetes.[1] The vast majority of diabetes cases are either T1D (5-10% of cases) or T2D (90-95% of cases), where T1D is an autoimmune disease resulting in insulin deficiency and T2D is insulin resistance often associated with obesity;[1] however, in some cases this distinction may not be clear-cut. For example, among youth (<20 years old) with physician-diagnosed T1D in the United States, 15% did not test positive for autoantibodies and 26% had insulin resistance.[2] The situation is further complicated in individuals with so-called "latent autoimmune diabetes in adults," a classification that is still under debate.[3-5] Much of this uncertainty stems from the fact that we do not understand immune-mediated beta cell failure in adults >30 years old.[3] The work presented herein concerns autoimmune T1D occurring at any age that results in an absolute deficiency of endogenous insulin production.

Section 1.1.2 Etiology

The interaction of genetic predisposition and environmental factors triggers a T-cell mediated autoimmune response that results in pancreatic islet inflammation (insulitis), beta cell apoptosis, and ultimately overt T1D.[6-8] Support for the autoimmune pathogenesis of T1D comes from the presence of one or more markers of the humoral immune response at diagnosis in about 85-90% of patients,[2,9,10] most commonly autoantibodies to insulin (IAA),[11] glutamic acid decarboxylase (GAD65),[12] the tyrosine phosphatase-like insulinoma-associated protein 2 (IA-2A),[13] and the cation efflux transporter ZnT8 (ZnT8Ab).[9] However, the observation that insulitis affects few islets and is only present in about one-third of T1D cases highlights the fact that we do not fully understand the etiology of T1D.[14] Three important studies, Diabetes Autoimmunity Study in the Young (DAISY) in the United States,[15] Type 1 Diabetes Prediction and Prevention Project (DIPP) in Finland,[16,17] and BABYDIAB in Germany,[18] will continue to provide insight into the etiological processes leading up to T1D onset.

Genetic susceptibility to T1D is predominantly determined by human leukocyte antigen (HLA) genotypes, though 41 other genetic loci have been identified in genome-wide association studies.[19] The environmental trigger for T1D is unknown, though there is evidence to support a role of viral infection, the gut microbiome, vitamin D deficiency, and cow's milk during infancy.[20] The Environmental Determinants of Diabetes in the Young (TEDDY) Study in the United States, Finland, Sweden, and Germany will prospectively explore these potential triggers in newborns born between 2004 and 2009 and followed for 15 years.[21]

Section 1.1.3 Diagnosis

To date, most studies of T1D incidence (number of new cases each year) have only enrolled children and adolescents, and have reported a peak age of onset of 10-14 years.[22] However, the disease can occur at any age. Indeed, life-table methods have estimated that the cumulative recurrence risk of T1D in siblings of individuals with T1D up to 18 years of age is

2.5%, up to 30 years is 6.4%, and up to 60 years is 9.6%.[23] Furthermore, studies from South Africa,[24] Ethiopia,[25] and China[26] have reported much later peak onset ages (early- to mid-twenties). In younger patients, onset tends to be more acute with rapid beta cell destruction, while in older patients, symptoms are more moderate and beta cell destruction is less rapid making it difficult to distinguish from T2D.[27]

Clinical manifestation of T1D is very heterogeneous, likely due to the multifactorial etiology of the disease and different ages of onset, discussed previously. Symptoms of the hyperglycemia that accompanies the onset of T1D typically include polyuria (excessive passage of urine), polydipsia (excessive thirst), weight loss, and in some cases polyphagia (excessive hunger) and blurred vision.[1] Without medical attention, severe hyperglycemia can lead to diabetic ketoacidosis (DKA), and in serious cases, coma and even death.[28] The prevalence of DKA at diagnosis of T1D in youth (<20 years) in the United States was most recently reported to be 31.1% (2008-2010), and has remained stable over time (30.2%, 2002-2003, and 29.1%, 2004-2005).[29] In Europe, the prevalence tends to be lower: 17.9% in Denmark (1996-2009),[30] 18.9% in northern Finland (1992-2001),[31] and 26.3% in southwestern Germany (1987-1997).[32]

Section 1.2 Epidemiology of type 1 diabetes

Section 1.2.1 Prevalence and incidence

Worldwide, longitudinal prevalence and incidence data on T1D largely come from three studies of children and adolescents: the SEARCH for Diabetes in Youth Study (SEARCH) in the United States,[33] the EURODIAB Study in Europe,[34] and the World Health Organization's (WHO) Multinational Project for Childhood Diabetes (DIAMOND Project).[35] The DIAMOND Project collected data on T1D incidence from 50 countries worldwide between 1990 and 1999, and reported a 350-fold difference in T1D incidence in 0-14 year-olds between the lowest (China, 0.1 cases per 100,000 per year) and highest (Sardinia, 36.8 cases per 100,000 per year) countries.[22]

More recently, results from SEARCH indicated that the prevalence of T1D in children and adolescents <20 years old in the United States in 2001 was 1.48 per 1000 and in 2009 it was 1.93 per 1000, an increase of 21.1% over 8 years after adjustment for completeness of ascertainment.[36] The incidence of T1D in non-Hispanic SEARCH participants is also increasing: the age- and sex-adjusted incidence of T1D was 24.4 per 100,000 in 2002 and 27.4 per 100,000 in 2009, a relative annual increase of 2.72%.[37] Similarly, in Canada, the incidence in 0-14 year-olds increased by a factor of 1.03 per 100,000 per year between 1987 and 2010,[38] and in Europe (EURODIAB Study), the incidence increased by an average of 3-4% per year between 1989 and 2008.[39] Some countries in Europe have reported a plateau in the incidence of T1D in children 0-14 years old: in Finland, the incidence increased annually by 3.6% from 1988 to 2005 and then leveled off from 2005 to 2011,[40] and in Sweden, the incidence leveled off from 2000 to 2007.[41]

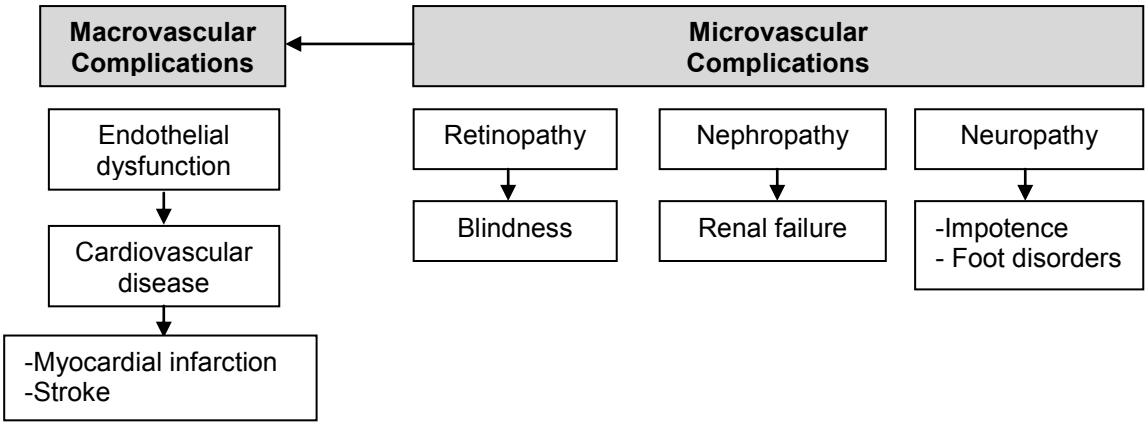
A few studies have also explored incidence rates in older age groups. One study in northern Italy reported an average annual increase of 4.3% in children (0-14 years old) and 2.8% in young adults (15-29 years old) between 1984 and 2004 (difference not statistically significant).[42] Further age-stratification in that study revealed the largest annual increase was in the 0-4 year-olds: 4.3% compared to 2.8% in 5-9 year-olds and 2.7% in 10-14 year-olds, but again, the difference was not statistically significant.[42] Studies in Finland reported an average annual increase of 4.2% in children (0-14 years old)[22] and 3.9% in young adults (15-39 years old) between 1992 and 2001.[43] A study in West Yorkshire, United Kingdom, found that the incidence rate was stable in 15-29 year-olds (0.2% average increase per year) from 1991 to 1999 while it increased, on average, 5.9% per year in 0-14 year-olds.[44] In Antwerp, Belgium, an average annual increase of 1.8% was observed in 0-14 year-olds and 5.0% in 0-5 year-olds, but an average annual *decrease* of 3.8% was observed in 15-39 year-olds.[45] Similar results were reported in 0-34 year-olds in Sweden between 1983 and 1998.[46] Together, this scientific evidence suggests that the global increase in T1D is not only the result of an overall increase in

disease incidence, but also earlier disease onset. Additional research, particularly in young adults, is needed to understand these complex age-period-cohort effects.

Section 1.2.2 Long-term complications and mortality

As the natural history of T1D progresses, individuals are at risk of developing several complications (**Figure 1.1**). Two seminal studies of T1D in the United States, the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications [DCCT/EDIC][47,48] and the Pittsburgh Epidemiology of Diabetes Complications (PEDC) study,[49] have reported the cumulative incidence of complications after a T1D duration of 30 years (individuals diagnosed in the 1980s). In the observational study (PEDC), 47% of participants developed retinopathy, 17% developed nephropathy, and 14% developed cardiovascular disease (CVD).[50] The trial (DCCT/EDIC) participants who were randomized to conventional treatment had similar cumulative incidence rates to the observational cohort: 50% retinopathy, 25% nephropathy, and 14% CVD.[50] However, the trial participants who were randomized to intensive treatment had lower cumulative incidence rates: 21% retinopathy, 9% nephropathy, and 9% CVD.[50] While these numbers are much improved relative to outcomes of individuals diagnosed in the 1950s-1970s,[51-53] CVD rates remain significantly higher in adults with T1D relative to the general population.[52]

Figure 1.1 Summary of long-term complications of type 1 diabetes



Diabetic retinopathy is the leading cause of blindness among adults aged 20-74 years,[54] however, the absolute risk of this functional impairment in the United States is actually quite low. For example, in the DCCT/EDIC conventional and intensive treatment groups, only 0.1% and 1% of participants, respectively, developed blindness after 12 years of follow-up.[50] In the PEDC study, only 4% of participants developed blindness after 18 years of follow-up.[50] The cumulative incidence rate of blindness after 25 years of follow-up in a Danish registry was higher at 7.5%, a difference the authors attributed to lower rates of loss-to-follow-up in registry studies compared to other observational cohorts (blind patients may be more likely to drop out).[55]

The number one cause of death among individuals with T1D is CVD.[56-58] While mortality rates among individuals with T1D have improved over time, they remain significantly higher than that of the general population.[52,59,60] A recent analysis of 10 European countries (EURODIAB study) found that there were twice as many deaths as expected from national mortality rates among individuals diagnosed with T1D in childhood (<15 years of age).[61] Age of onset influences mortality, with excess mortality compared to the general population being lower in individuals with late onset T1D (aged 15-29 years) versus individuals with early onset T1D

(aged 0-14 years),[51] an observation consistent with lower rates of complications such as end-stage renal disease, proliferative retinopathy, and microalbuminuria in those with later onset T1D.[62-65] However, one study in Finland reported that individuals with early onset T1D had improved survival over time (1970 to 2007) while those with late onset T1D had an increase in mortality since the 1980s (though the cumulative mortality in the late onset group was quite low, 1-1.5% over the first 15 years of the study).[51] Furthermore, there is substantial geographic variation in mortality rates even among developed countries,[66,67] suggesting that improvements in T1D treatment have not been shared equally across the globe.

Section 1.3 Treatment of type 1 diabetes

Treatment goals for T1D are two-fold: 1) maintain tight glycemic control (**Table 1.1**) and 2) reduce CVD risk factors such as hypertension and dyslipidemia.[68] The most commonly used measure of glycemic control is glycated hemoglobin A1c (HbA1c), which is formed in a non-enzymatic process when circulating hemoglobin in red blood cells is exposed to glucose, and therefore correlates with average blood glucose levels.[69]

Table 1.1 Age-specific glycemic control targets for individuals with type 1 diabetes

Age	HbA1c target [68]	Corresponding 3-month average blood glucose [69]
≥20 years	<7%	154 mg/dL
13-19 years	<7.5%	169 mg/dL
6-12 years	<8%	183 mg/dL
0-6 years	<8.5%	198 mg/dL

Section 1.3.1 Self-monitoring of blood glucose and insulin therapy

The DCCT provided unequivocal evidence that tight glycemic control significantly reduces the risk of developing chronic complications of T1D.[70,71] This level of glycemic control is typically achieved through intensifying self-monitoring of blood glucose (SMBG) and insulin dose adjustments.[68,69] The ADA[68] and other national standards of medical care, including those in Canada[72] and Europe,[73] now emphasize the use of a flexible T1D treatment regimen (**Figure 1.2**). This involves using data from SMBG (typically 6-8 tests per day) to adjust insulin (typically 3-4 injections per day of basal and prandial insulin analogs or an insulin pump), dietary intake, and physical activity in order to achieve blood glucose goals. A summary of self-management recommendations, goals, and corresponding patient education is provided in **Table 1.2**.

Figure 1.2 Hypothetical blood insulin levels on a) basal-bolus insulin regimens and b) pre-mixed twice-daily insulin regimens. Arrows indicate insulin injections

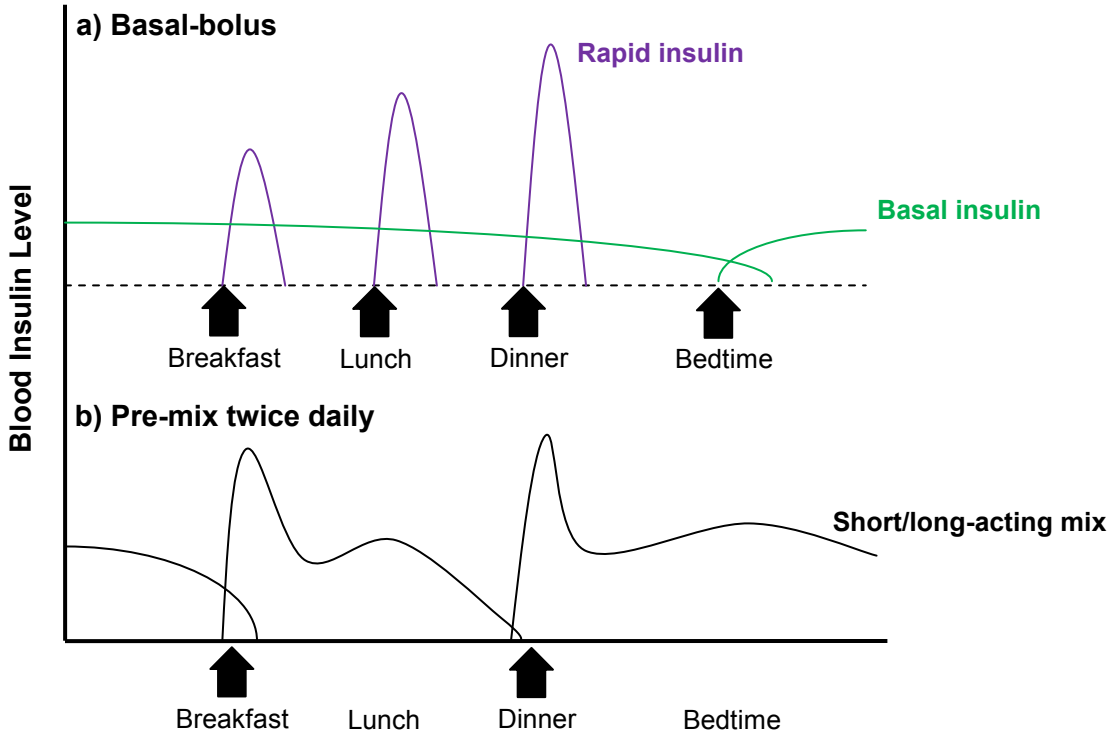


Table 1.2 Summary of the American Diabetes Association's recommendations for self-monitoring of blood glucose (SMBG), HbA1c testing, and insulin therapy for patients with type 1 diabetes

	Recommendations [68]	Goals	Education
SMBG	Prior to meals and snacks, occasionally postprandially, at bedtime, prior to exercise, when hypoglycemia is suspected, after treating hypoglycemia, and prior to critical tasks (e.g. driving) 6-8 times per day	Pre-prandial blood glucose 70-130 mg/dL Peak postprandial blood glucose <180 mg/dL Prevent hypoglycemia	What target blood glucose is How to use data to adjust food intake and exercise to achieve glycemic goals
HbA1c testing	4 times per year Decrease to 2 times per year if in good control	Achieve HbA1c targets Goal should be individualized based on diabetes duration, age, comorbidities, and hypoglycemic unawareness	What target HbA1c is
Insulin therapy	Multiple-dose insulin injections (3-4 per day of basal and prandial insulin) or insulin pump Match prandial insulin to carbohydrate intake, pre-prandial blood glucose, and anticipated physical activity Use of insulin analogs (especially if hypoglycemia is a problem)	Achieve HbA1c targets Prevent hypoglycemia	How to adjust insulin to achieve glycemic goals

Section 1.3.2 Diabetes nutrition therapy

The coordination of insulin with dietary intake is essential among patients with T1D in order to maintain near-normal blood glucose levels and prevent acute and chronic complications. Both national[72,74,75] and international[76] Diabetes Associations recognize individualized diabetes nutrition therapy as an integral part of diabetes self-management. Several approaches are available for patients with T1D, including use of nutrient-based approaches (e.g. counting carbohydrates), glycemic index, and food-based approaches (e.g.

dietary exchanges). Evidence among youth with T1D in the United States suggests that the vast majority of patients have been taught carbohydrate counting[77] and that use of this diabetes nutrition therapy approach is associated with improved glycemic control and reduced CVD risk.[78,79] The ability of other diabetes nutrition therapy approaches to improve clinical outcomes among patients with T1D is not well-established.[80]

Adherence to dietary recommendations has also been associated with improved metabolic outcomes[81] and lower hypertension risk[82] among individuals with T1D. However, neither youth[83] nor adults[84-87] with T1D in the United States and Europe are consuming healthful diets, particularly with respect to total fat, saturated fat, and sucrose.

Section 1.3.3 Comorbidities

Individuals with T1D have higher rates of hypertension compared to the general population.[88] For example, in the United States (2000-2002), the prevalence of hypertension in a cohort of T1D patients with no history of coronary artery disease (mean age 37 years) was 43% compared to only 15% in control participants (mean age 39 years).[88] While patients with T1D in that study were significantly more likely to receive treatment for their hypertension compared to controls (87% versus 47%, respectively), only 64% of patients with T1D who received treatment achieved blood pressure control.[88] The prevalence of hypertension was lower in the EURODIAB study (1989-1990; mean age 33 years): on average, across 16 countries, 24%.[89] Furthermore, the proportion of patients with T1D and hypertension who were receiving treatment in the EURODIAB study was much lower: only 42.2%.[89] These observations are especially disconcerting because hypertension is a major risk factor for both CVD and microvascular complications (e.g. nephropathy).[90]

Because of this increased risk of hypertension among individuals with T1D, blood pressure control is a key target of T1D care. The ADA recommendation for blood pressure is <140/80 mmHg (systolic blood pressure [SBP]/diastolic blood pressure [DBP]).[90] Treatment to

reduce blood pressure includes lifestyle modifications (weight loss if overweight, DASH dietary pattern reducing sodium intake and increasing potassium intake, increased physical activity, and moderation of alcohol intake) and pharmacological therapy (angiotensin-converting enzyme [ACE] inhibitor or angiotensin receptor blocker [ARB] or multiple-drug therapy).[90]

The prevalence of dyslipidemia is also very high among individuals with T1D. For example, in the EURODIAB study, 45% of participants had a low-density lipoprotein (LDL) cholesterol >3.35 mmol/L and 12% of men and 8% of women had triglyceride levels >1.7 mmol/L.[91] In a large cohort of German and Austrian youth (0-26 years old) with T1D, 28.6% had dyslipidemia, but only 0.4% received medical treatment.[92] Similarly, in a cohort of youth (mean age 15 years) with T1D in the United States (SEARCH study), 18.1% had high triglycerides and 10.1% had high-density lipoprotein (HDL) cholesterol levels <40 mg/dL.[93] Another key target of T1D care is therefore lipid management. The target for blood lipids are as follows: LDL cholesterol <100 mg/dL (2.6 mmol/L), triglycerides <150 mg/dL (1.7 mmol/L), and HDL cholesterol >40 mg/dL (1.0 mmol/L) for men and >50 mg/dL (1.3 mmol/L) for women.[90] Similar to hypertension, treatment recommendations for dyslipidemia include both lifestyle modifications (reducing saturated fat, trans fat, and cholesterol intake, increasing omega-3 fatty acid and fiber intake, weight loss if overweight, and increased physical activity) and pharmacological therapy (statins).[90]

Section 1.4 Burden of type 1 diabetes in China

We do not know how many people in China are currently living with T1D. However, we do have some information regarding how many people develop T1D annually. Between 1990 and 1999, the WHO DIAMOND Project[94-99] was conducted at 23 centers across China covering a population of 19.5 million children, or about 7% of this age group in China.[22] Two papers have been published regarding this data and have reported drastically different incidence rates. The first used data spanning a nine-year period (1988-1996) and excluding three of the 23 centers

that were missing data from a secondary independent source (Guilin, Xuzhou, and Zunyi).[100] A total of 883 cases were registered at the remaining 20 centers and an overall incidence rate of 0.59 per 100,000 person-years was reported.[100] The second used data spanning a seven-year period (1990-1996), excluded only one of the 23 centers (Xuzhou), and reported an overall incidence rate of 0.1 per 100,000 person-years (ranging from 0.1 per 100,000 person-years in Zunyi to 4.5 per 100,000 person-years in Wuhan).[22]

Beginning in 2000, the International Diabetes Federation (IDF) has published the *Diabetes Atlas*, a compilation of prevalence and incidence estimates for T1D and T2D around the world. The most recent edition (6th), published in 2013, continues to use estimates from the WHO DIAMOND Project (1990-1996) for T1D incidence in China.[101]

Since the completion of the WHO DIAMOND Project, many of the participating centers have continued to register T1D cases. In Shanghai, for example, the WHO DIAMOND Project documented an average incidence rate of 0.61 per 100,000 person-years between 1980 and 1991,[102] and two subsequent studies have reported mean annual incidence rates: 0.96 per 100,000 between 1989 and 1993[99] and 3.1 per 100,000 person-years between 1997 and 2011.[103] Similarly, a study conducted in Harbin between 1990 and 2000 reported a mean annual incidence rate of 0.73 per 100,000 person-years and a mean annual increase of 7.4% per year.[104]

A national, hospital-based T1D registry in China (10 centers) is under development and will provide updated estimates of the incidence and the first estimates of the prevalence of T1D in China.

Section 1.5 Type 1 diabetes treatment barriers in China

Implementation of standards of medical care for T1D requires affordable and accessible insulin and self-monitoring supplies (e.g. glucose meters, lancets, and strips); a multidisciplinary healthcare team trained in T1D care; continuing diabetes education for patients; and familial,

institutional, and community support. These aspects of care are beginning to be addressed in urban China, but in most parts of the country, the implementation of standards of medical care remains an insurmountable challenge. Barriers to achieving treatment goals are discussed in detail in the sections that follow.

Section 1.5.1 Limitations of healthcare providers and the healthcare system

It is common for Chinese specialists such as endocrinologists to meet with over 100 patients per day in outpatient departments, spending about 3 minutes with each patient.[105] These severe time limitations have undoubtedly contributed to poor patient-provider relationships in China, which in turn have led to a crisis of violence against healthcare providers.[106] Another substantial barrier to improving interactions with patients in China is the lack of adoption of electronic medical records (EMR) despite research supporting positive effects on efficiency and effectiveness of care as well as provider and patient satisfaction.[107] While the Communist Party of China Central Committee emphasized that hospital EMRs should be a priority of healthcare reform in 2007[108] and the Central Government allocated 1.5 billion USD to promote the use of health information technology in 2011,[109] the use of this technology to monitor chronic diseases such as T1D over time has been limited. Patients continue to carry hard copies of their health records to outpatient department visits. Indeed, most research on EMR implementation in China has been conducted in inpatient departments with outcomes relating to hospitalization and infectious diseases.[110,111]

Given the low incidence rate of T1D in China,[22] physicians, including endocrinologists, rarely encounter T1D. In contrast, T2D is increasingly common throughout China: the prevalence among adults (≥18 years of age) is 11.6% (113.9 million adults),[112] compared to 12.3% among adults (≥20 years of age) in the United States.[113] This lack of familiarity with T1D relative to T2D could lead to misdiagnosis or mistreatment, especially in more remote hospitals, as has been reported in other low- and middle-income countries.[114] National healthcare provider

education programs such as the China Initiative for Diabetes Excellence (CIDE) have been shown to significantly improve diabetes knowledge,[115] but largely focus on T2D. T1D-specific modules integrated into ongoing healthcare provider training have the potential to improve care, but must be tested in the context of China.

Section 1.5.2 Diabetes self-management education is difficult to obtain

The ADA and the International Society for Pediatric and Adolescent Diabetes (ISPAD) recommend ongoing, tailored diabetes self-management education (DSME) provided by a multidisciplinary healthcare team.[68,116] DSME is typically divided into primary diabetes education (survival skills) and secondary diabetes education (continuing diabetes education curriculum contributing to an in-depth understanding of self-management).[116] Survival skills include blood glucose targets, basic nutrition advice, an explanation of what to do for hyper- and hypoglycemia, how to handle diabetes during illness, and psychological issues concerning diabetes.[116] Continuing diabetes education curriculums include, for example, meeting with a dietitian annually and receiving information about diabetes camps and other support groups.[116]

The difficulty in obtaining DSME, particularly continuing diabetes education, is a major treatment barrier for patients with T1D in China. The first evidence of structured diabetes education in Mainland China was in 1990[117] yet in 2004 fewer than 500 nurses were trained diabetes educators and few of these nurses had participated in a standardized training program.[118] Indeed, there is currently no Chinese equivalent of the professional certified diabetes educator found in the United States and Europe, and therefore not only the quantity, but also the quality of diabetes education in China may be deficient. There are some signs of improvements in this area, particularly in Beijing, Shanghai, Jiangsu, and Guangdong, where a diabetes specialist training program for nurses has been initiated.[119] Most patient education is administered by nurses or physicians, though dietitians have become increasingly accessible in endocrinology departments at tertiary hospitals. Multidisciplinary care is rare. Interestingly, a

recent systematic review of diabetes education interventions in China reported that half of the interventions were conducted in inpatient settings.[117] The lack of diabetes educators and the common requirement for inpatient admission to receive diabetes education are significant barriers for patients with T1D.

Section 1.5.3 Blood glucose monitoring and insulin regimens remain suboptimal

Between 2001 and 2002, the IDF found that children and adolescents with T1D in China had the lowest mean daily insulin dose and the lowest frequency of SMBG among Western Pacific countries.[120] Only 76% of youth in this study practiced SMBG, checking their blood glucose, on average, 8 times *per month*. This is a stark contrast to youth in the United States, 75% of whom test ≥4 times *per day*.[121] Furthermore, most children (68%) with T1D in China in the IDF study were on 1-2 insulin injections per day,[120,121] in comparison to the United States, where only 27% of children are on 1-2 insulin injections per day.[121]

The acute outcome of these suboptimal treatment regimens is poor glycemic control. Only 53% of patients in the IDF study had the recommended ≥3 HbA1c tests in the past year and the HbA1c for the sample at the time of the study was (mean ±SD) 9.5 ±1.9%,[120] one percentage point higher than the average HbA1c among children with T1D in the United States (8.5 ±1.5%).[121] Even children on 1-2 insulin injections per day in the United States achieved HbA1c levels (8.6 ±1.7%) lower than that reported in China.[121]

Recent clinical trials conducted in China suggest that more intensive insulin regimens are safe and improve glycemic control in this population.[122-124] However, cost remains a substantial barrier preventing patients from receiving adequate self-management supplies. Insulin is covered by insurance, but insulin injection tools (e.g. pens, needles, syringes, and pumps), blood glucose testing strips, and blood glucose meters are not. On average, one-third of an urban family's income in China is spent on care for a patient with T1D.[125] In rural villages it is conceivable that a more substantial proportion of the family's income will be spent on care

and that families must make sacrifices in diabetes self-management (e.g. testing infrequently and using less insulin than prescribed) in order to accommodate this expense.

Section 1.6 Comorbidities, complications, and mortality in China

No study has evaluated the effectiveness of prevention interventions such as the DCCT in China, where the coexistence of diabetes with other CVD risk factors is exceptionally high.[120,126] Data from 1998-1999 (Diabcare-Asia Study) suggest that 30% of patients with T1D in Asia also have hypertension and 11% smoke.[126] More recent data from Guangdong, China, suggest that a similar proportion of T1D patients smoke (11.3%).[26] Estimates from 2001-2002 of hypertension in youth <15 years old with T1D in two centers in China suggest a hypertension prevalence of 24%.[120]

There is limited data on complications and mortality from China. However, data from other East Asian countries may be informative. The Diabetes Epidemiology Research International (DERI) mortality study was launched in 1986 in four countries (United States, Finland, Japan, and Israel) and reported that Japan had a markedly higher age-adjusted mortality rate compared to the other three countries: 681 deaths per 100,000 person-years of diabetes in Japan compared to, for example, 230 deaths per 100,000 person-years of diabetes in the United States.[127] At follow-up in that study (1985), 20% of Japanese participants diagnosed at 15-17 years of age had died compared to <8% of participants from the other three countries.[127] The leading causes of death in the Japanese cohort were acute complications (42% of deaths) and end-stage renal disease (33% of deaths).[128] More recent follow-up (2005) of the DERI cohort in Japan has shown that among individuals with T1D for more than 20 years, the leading cause of death is CVD.[129] Of note, a comparison of participants within the DERI cohort in Japan showed that those who visited an integrated management system under specialists and a multidisciplinary team were three times less likely to die and five times less likely to develop end-stage renal disease compared to those who did not.[130]

The Thailand Diabetes Registry Project has also provided valuable insight into T1D complications in Asia. In 2003, the Registry reported a prevalence of diabetic retinopathy among patients with T1D (mean T1D duration 9.2 years) of 21.6% and of diabetes-related legal blindness of 1.0%.[131] A study conducted in Japan in 2004 (mean T1D duration 26.9 years) reported that 25.0% of males and 31.1% of females had proliferative diabetic retinopathy and 25.0% of males and 22.2% of females had diabetic nephropathy.[132] The prevalence of comorbidities was also high in this cohort: 53.6% of males and 42.2% of females had hypertension and 39.3% of males and 26.7% of females had dyslipidemia.[132] An earlier study (1995) also conducted in Japan found a high prevalence of blindness: 23.3% in those diagnosed with T1D between 1965 and 1969 and 2.1% in those diagnosed with T1D between 1975 and 1989, representing a significant decrease in the proportion of patients diagnosed with blindness over time.[133]

Section 1.7 Need for Chinese standards of medical care for type 1 diabetes

Although general treatment goals for T1D care (e.g. glycemic control and reducing CVD risk) are not different across countries and cultures, the optimal approach to achieving these goals will likely differ.

Section 1.7.1 Unique and dynamic Chinese food environment

Dietary intake is uniquely complex in China due to shared dishes, highly variable recipes, and a rapidly changing food environment. The China Health and Nutrition Survey (CHNS) has monitored the dietary intake of the Chinese general population since 1989.[134] Together, results from CHNS and several cross-sectional studies have improved our understanding of changes in dietary intake in China over the past 25 years (**Table 1.3**). In China, as in many other low- and middle-income countries, consumption of vegetable oils from frying food, animal-source foods, and away-from-home foods are increasing, as are snacking

behaviors.[135-137] Given this confluence of factors, studies and recommendations based on Western diets, while increasingly more relevant in China, may not be entirely culturally appropriate.

Table 1.3 Summary of reported dietary intakes of populations in China

Ref	Study Sample Size; Age (mean or range)	Method	Energy (kcal/day)	Carbohydrates	Fat	Fiber (g/day)	Rice (g/day)	Fruits (g/day)	Vegetables (g/day)
137	China Health and Nutrition Survey 5000; 18-45 years	24-hr recall	2150	Not reported	Not reported	Not reported	348	Not reported	Not reported
138	Chinese National Nutrition and Health Survey 140,010; >18 years	FFQ	Not reported	48.5% total kcal (urban)	35.0% total kcal (urban)	Not reported	Not reported	Not reported	Not reported
139	Shanghai Women's Health Study 191; 55.4 years	FFQ	1665	284.2 g/day	27.4 g/day	9.9	310	377	335
140	Shanghai Men's Health Study 195; 54.8 years	FFQ	1929.5	318.5 g/day	32.5 g/day	11.5	364.3	132.3	348.8

Section 1.7.2 Evidence of positive effect of recommendations in China

Implementation of population-specific recommendations by healthcare providers in China has the potential to result in improved adherence and glycemic control, and subsequently the prevention of complications. Researchers in Guangzhou Province recently reported that receiving a recommendation from a provider to get regular eye examinations was associated with having an eye examination in the last year among patients (>18 years) with diabetes.[141] A individualized nutrition therapy intervention among 20 children (5-12 years) with T1D conducted in Sichuan Province in China reported significant improvements in nutrition knowledge and quality of life.[142]

Section 1.8 The 3C Nutrition Ancillary Study: improving our understanding of current self-management practices among adolescents and adults with type 1 diabetes in China

The incidence of T1D is increasing in China and morbidity and mortality in this population may be higher than in developed countries. While results of randomized controlled trials in the United States and Europe support intensive disease self-management to achieve tight glycemic control and reduce diabetes-related complications, our knowledge of self-management practices in China is limited in scope and outdated. In order to address this gap, a cross-sectional study, called the 3C Nutrition Ancillary Study (3CNAS), was conducted in Beijing, China, from January to August 2013. Individuals were recruited from the participant roster of the 3C Study, an epidemiological study of the coverage, cost, and care of diabetes in Beijing and Shantou conducted in 2011. Data collection for 3CNAS entailed a fasting blood draw for risk factor assessment, a questionnaire for nutrition education and self-management practices, and three 24-hour recalls for dietary intake. Telephone administration of the 24-hour recalls was validated against in-person administration in a pilot study. The aims of the main study were three-fold: 1) to describe the contribution of diabetes nutrition therapy to disease self-management and dietary intake among individuals with T1D in Beijing, 2) to compare the

dietary intake of individuals with T1D to those without diabetes in Beijing, and 3) to use reduced rank regression (RRR) to identify dietary patterns maximizing the explained variation in two key health indicators, HbA1c and LDL cholesterol, among individuals with T1D in Beijing. All procedures were approved by the University of North Carolina Office of Human Research Ethics and the Peking University Biomedical Institutional Review Board, and all participants provided written informed consent (≥18 years of age) or written parent permission and participant assent (<18 years of age). The pilot study and each of the three aims are described in detail in the chapters that follow.

CHAPTER 2: RELATIVE VALIDITY OF TELEPHONE VERSUS FACE-TO-FACE 24-HOUR DIETARY RECALLS IN ADULTS WITH TYPE 1 DIABETES IN CHINA

2.1 Introduction

While studies in Europe[143,144] and the United States[145-147] have not found significant differences in self-reported dietary intake when 24-hour recalls are administered via telephone instead of face-to-face, no study has evaluated the relative validity of 24-hour recalls administered via telephone in China where the diet is uniquely complex. Compounding the challenge of dietary assessment, individuals who are diagnosed with T1D are considered 'monsters' by society.[148] Because of this stigma, individuals with T1D often hide their disease; thus it would not be culturally acceptable for research staff to visit participants at their homes to conduct face-to-face 24-hour recalls. Furthermore, the participant burden of traveling to a clinic site to complete the multiple 24-hour recalls needed to assess usual dietary intake would be prohibitive, resulting in low compliance. These barriers could be addressed by using telephone administered 24-hour recalls.

The aim of the Relative Validity Study presented in this chapter was to compare the results of two approaches to measuring dietary intake in individuals with T1D in China: the proposed method, telephone 24-hour recalls, and the widely accepted and implemented method in China, face-to-face 24-hour recalls.

2.2 Methods

Informed by *a priori* power calculations, a random subset of 19 adults was selected to participate in the Relative Validity Study from a pool of 159 eligible 3C Study participants. Eligibility criteria included: ≥18 years of age, no severe diabetes complications (e.g. advanced micro- and macrovascular complications, including nephropathy and stroke), Beijing resident, and in-service telephone number available. Individuals expressing an interest in participating during a recruitment call were mailed an introductory packet containing instructions for a previous-day dietary recall, blank food and recipe record forms, and a portion size picture guide developed by the Chinese Center for Disease Control. Within one week of mailing the introductory packet participants were randomized to receive either the face-to-face interview followed by the telephone interview or vice-versa (46% telephone first). Participants were instructed to record their intakes using the forms provided on the day prior to the scheduled interviews, to be used as a memory prompt as in other studies.[149,150] Interviews were conducted by trained study staff in Chinese on the same day with a minimum of six hours in between.

The 24-hour recall was administered using a two-pass approach: 1) collect a detailed food list and 2) review and confirm the detailed food list. During the first pass, an outline of the previous day's intake was collected. Interviewers probed for meal type, preparation setting, preparation method, and detailed information on any additions to the food, food type, brand names and portion size. During the second pass, the detailed food list was re-read and missing foods, beverages, and eating occasions were probed.

Food lists were converted into nutrients and food groups using the most recent versions of the Chinese Food Composition Tables.[151,152] Due to the non-normal distribution of the nutrients and food groups, aggregate agreement was evaluated using nonparametric Wilcoxon's matched-pairs signed rank tests. Individual agreement between the two methods was visualized using Bland-Altman plots, and quantified using intraclass correlation coefficients (ICC) and Spearman's rank correlation coefficients (rho). A sensitivity analysis was conducted comparing

the first and second interview, regardless of interview type; no differences were found between median intakes for any of the nutrients or food groups reported (all p >0.05). All statistical analyses were conducted using SAS 9.2 (SAS Institute, Cary, North Carolina).

2.3 Results

Of the 19 eligible participants recruited, two declined to participate due to time limitations, three did not attend their scheduled visit, and one refused to provide written consent (enrollment rate: 68%). Participants (n=13; 62% male) were (mean ±SD) 37 ±11 years old and had a T1D duration of 11 ±8.6 years.

There were no statistically significant differences between median intakes for any of the nutrients or food groups reported by telephone versus face-to-face interview (all p<0.05; **Table 2.1**). Power calculations for paired t-tests (α=0.05, n=13, SD=160 kcal, within-subject correlation=0.8) indicated that we had a 74% power to detect a mean difference in total energy intake of 80 kcal.

The mean ICC was 0.79, ranging from 0.46 for fiber to 0.97 for energy (**Table 2.1**). Similarly, all rho values were significantly different from zero and all but two rho values (fiber, rho=0.60 and eggs, rho=0.61) were ≥0.75. The percent of participants with perfect agreement between telephone and face-to-face interviews for reported grams of the food groups ranged from 15% (n=2) for vegetables to 85% (n=11) for fruits. The percent of participants with agreement within 100 g was >90% for all food groups except vegetables (69%; n=9). Bland-Altman plots did not support the existence of systematic biases between telephone and face-to-face interviews (for example, percentage of total calories from fat, **Figure 2.1**).

In sensitivity analyses, there were no differences between median intakes for any of the nutrients or food groups reported comparing the first versus second interview (all p >0.05; data not shown).

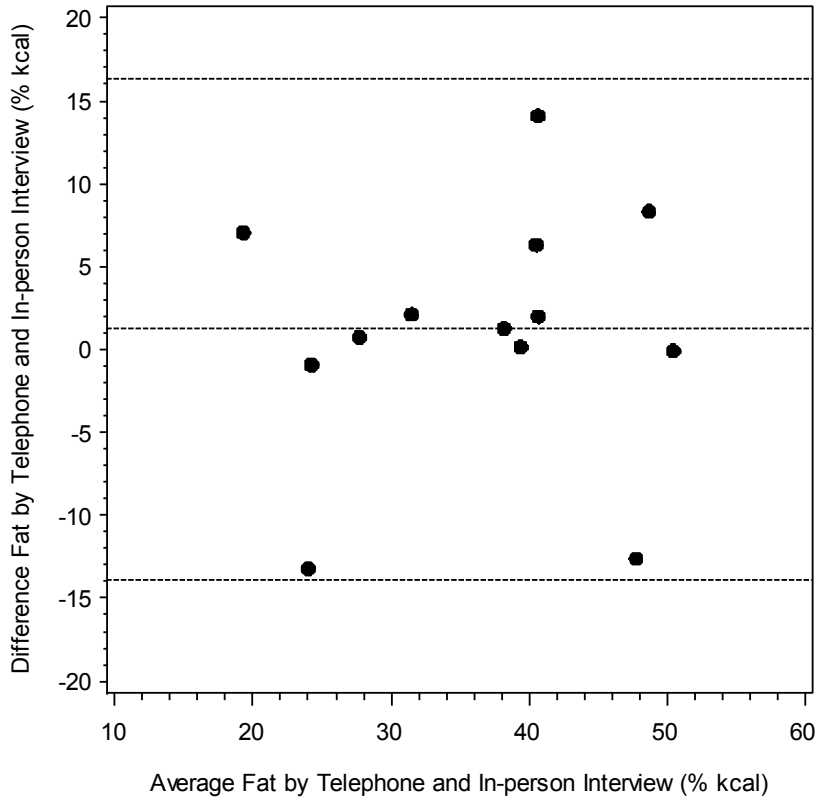
Table 2.1 Agreement between face-to-face and telephone administered 24-hour dietary recalls among adults with type 1 diabetes in China (*n*=13)

	Administration Method		Difference in Means [1]	P-value [2]	ICC	rho
	Face-to-face Median (25^{th}-75^{th} percentile)	**Telephone** Median (25^{th}-75^{th} percentile)				
Energy (kcal/day)	1467 (1334 – 1946)	1459 (1323 – 2134)	54 ± 101	0.07	0.97	0.96
Fat (% kcal)	39.5 (28.1 – 43.7)	37.4 (30.5 – 39.7)	1.2 ± 7.6	0.24	0.77	0.75
Carbohydrate (% kcal)	44.8 (41.0 – 53.2)	50.7 (41.3 – 52.4)	-0.5 ± 6.0	0.79	0.86	0.92
Protein (% kcal)	15.3 (13.1 – 17.2)	15.5 (14.2 – 17.7)	-0.6 ± 2.1	0.17	0.71	0.77
Fiber (g/1000 kcal)	7.3 (5.7 – 9.8)	8.4 (6.6 – 9.5)	-0.2 ± 3.3	0.38	0.46	0.60
Rice (g/day)	100 (75 – 200)	106 (80 – 190)	28 ± 94	0.63	0.68	0.91
Wheat (g/day)	100 (70 – 110)	90 (20 – 200)	-16 ± 65	0.63	0.86	0.94
Vegetables (g/day)	260 (163 – 520)	265 (199 – 560)	-3 ± 126	0.65	0.86	0.89
Fruit (g/day)	0 (0 – 200)	0 (0 – 175)	18 ± 53	0.50	0.93	0.98
Red meat (g/day)	50 (0 – 75)	50 (0 – 80)	-6 ± 16	0.25	0.93	0.93
Eggs (g/day)	60 (60 – 70)	60 (50 – 60)	2 ± 23	0.90	0.64	0.61

[1] Mean ± SD difference between nutrient and food group means reported in face-to-face and telephone interviews. Negative values indicate telephone > face-to-face

[2] Wilcoxon signed rank test

Figure 2.1 Bland-Altman plot for percentage of total energy from fat showing mean agreement (---) and 95% limits of agreement (—) between telephone and face-to-face administration of 24-hour recalls



2.4 Discussion

To our knowledge, this is the first study to evaluate the relative validity of telephone versus face-to-face 24-hour recalls in China. For all nutrients and food groups analyzed, results supported that telephone interviews are a reliable method compared to face-to-face interviews among individuals with T1D in China. A limited number of relative validity assessments have been conducted previously in China, all in non-diabetic adults, including a study validating a combined 24-hour recall and weighed household food record against doubly-labeled water,[153] and a study validating face-to-face 24-hour recalls against household weighed food records.[154]

Although food frequency questionnaires have been validated for urban Chinese populations in the past 5 years,[155,156] their use would not have been appropriate for our target population given that the diets of individuals with T1D may differ significantly from non-diabetics, especially in settings with limited access to blood glucose testing supplies and insulin. Because of the acute effects of dietary intake on blood glucose levels in individuals using exogenous insulin, we hypothesized that our target population would be more "food aware," meaning that they could more easily recall foods and portion sizes than the general population. Furthermore, given that previous studies in China have reported the use of fixed insulin regimens among individuals with T1D,[120] we anticipated that their dietary intake would have low day-to-day variability. Indeed, previous studies in China have reported very low day-to-day variability in the general population compared to the United States and Europe.[157] Together, these factors could partially explain the high level of agreement between interviews and further support the use of telephone administered 24-hour recalls in our target population.

Energy intake in this sample was low: median intake from the telephone interview was only 1459 kcal/day. Two clinical factors may explain this: anthropometrics and insulin dose. The average height of participants was 169 cm (approximately 5.5 feet) and the average BMI was 21.5 kg/m^2. Because greater food intakes, particularly carbohydrate staples such as rice and wheat noodles, require greater insulin doses to achieve near-normal blood glucose levels, individuals with T1D in China may be reducing dietary intake in order to accommodate smaller insulin doses. Indeed, one study reporting caloric intake in Taiwanese youth with T1D found that 21% consumed >30% fewer calories than recommended and 27% consumed 10-30% fewer calories than recommended.[158] Families may be making sacrifices in diabetes self-management (e.g. using less insulin) in order to accommodate the expense of T1D. This represents an important phenomenon to explore in future research.

There are several notable strengths of the developed method. Food records enabled participants to query restaurants, wives, and other persons who may be preparing their food,

thereby reducing recall biases and improving recipe reporting. Additional strengths include training interviewers and using a culturally appropriate portion size picture guide.

Food records were used to reduce reliance on memory and allow participants to collect recipe information, which resulted in more complete and accurate food lists. However, actively recording food may have led to changes in behavior. In additional to *actual* behavior changes, we recognize that *reported* behavior changes may occur. However, purposeful dietary misreporting may be uncommon in China.[153] In our study, approval biases were addressed by using interviewers who were not the participants' healthcare providers and training them to use a standardized protocol and neutral probes.[159] Finally, while the sample size was relatively small, we were powered to detect expected observable differences in mean nutrient intake.

In conclusion, we determined that telephone administration of a 24-hour recall is a reasonably accurate and practical method for assessing dietary intake in individuals with T1D in China compared to a 24-hour recall administered face-to-face.

CHAPTER 3: DIABETES NUTRITION EDUCATION AND DIETARY INTAKE AMONG INDIVIDUALS WITH TYPE 1 DIABETES IN CHINA

3.1 Introduction

The coordination of insulin with dietary intake is essential among individuals with T1D in order to maintain near-normal blood glucose levels and prevent acute and chronic complications.[160] This integration is achieved through individualized diabetes nutrition therapy, which typically involves one of two approaches: (1) fixed daily insulin doses matched to consistent carbohydrate intake with respect to time and amount or (2) flexible daily insulin doses accommodating variability in food intake, typically using carbohydrate counting.[161] There is not a "one-size-fits-all" eating pattern for diabetes.[161] Healthcare providers—preferably dietitians or their equivalent—should collaboratively develop eating plans with each individual with diabetes and provide ongoing implementation support.[161]

To date, no study has evaluated diabetes nutrition therapy among individuals with T1D in China. Understanding current practices is an essential first step for developing interventions and policies to improve T1D care. The aims of this study were: 1) to describe the contribution of diabetes nutrition education and therapy to disease self-management among individuals with T1D in China and 2) to estimate the association of diabetes nutrition education and therapy with dietary intake.

3.2 Methods

3.2.1 Sample population

The 3C Study was an epidemiological study of the coverage, cost, and care of T1D in China.[162] Dietary intake in the 3C Study was assessed using the Summary of Diabetes Self-Care Activities measure, which includes four questions relating to general dietary intake.[163] A follow-up study, 3CNAS, was conducted, on average, 1.6 ±0.2 years later and expanded the 3C Study to include comprehensive information on diabetes nutrition therapy and dietary intake. 3C Study participants who met the following criteria were eligible for 3CNAS: Beijing resident, ≥12 years of age, no severe diabetes complications (e.g. advanced micro- and macrovascular complications, including nephropathy and stroke), and in-service telephone number available.

3.2.2 Diabetes nutrition therapy assessment

Trained interviewers administered a survey during the 3CNAS visit that queried recommendations received from healthcare providers relating to general diabetes care and nutrition. Specifically, participants were asked how often, if ever, they had met with a dietitian; if they had received an eating plan and if yes, how often they followed it; and if they had ever been taught carbohydrate counting and if yes, who taught them and how often they use it. An open-ended question was also asked relating to what the participant would like to know about how food interacts with their diabetes care.

Information on insulin administration method, type and dose, and SMBG were also collected during the 3CNAS visit. Four insulin regimens were defined as follows: (1) multiple daily injections (MDI; ≥3 injections) with glargine or detemir plus more than/or other than rapid-acting insulin (“MDI: With basal”), (2) continuous subcutaneous infusion (“Pump”), (3) MDI with any insulin types excluding glargine and detemir (“MDI: No basal”), and (4) 1-2 injections per day of any insulin types (“1-2 injections”).

3.2.3 Dietary intake assessment

At the end of the 3CNAS visit, participants were trained by dietitians to record their dietary intake on food records provided in an introductory packet. Emphasis was placed on estimating portion sizes using food samples, an electronic scale, and a culturally appropriate portion size picture guide. On average, beginning 3.0 ±2.8 days after this visit, participants completed three telephone administered 24-hour recalls. The 24-hour recall food lists were converted into nutrients and food groups using the Chinese Food Composition Tables.[151,152]

3.2.4 Covariates

Demographic and socioeconomic data were collected via an interviewer-administered survey during the 3C Study visit. Diabetes duration was calculated as the period from July 1 of the year of diagnosis (because the 3C Study only queried year of diagnosis) to the 3CNAS visit.

A blood sample was collected by venipuncture during the 3CNAS visit and HbA1c was measured using standardized procedures in whole blood with an automated high-performance liquid chromatography system (Primus Ultra^2, Trinity Biotech, Bray, Co Wicklow, Ireland).

3.2.5 Statistical analysis

Univariate descriptive statistics were used to summarize diabetes nutrition therapy and dietary intake. Differences in diabetes nutrition therapy across disease self-management subgroups were evaluated using chi-square tests for categorical variables and Kruskal-Wallis tests for continuous variables. The association between diabetes nutrition therapy and dietary intake was estimated using analysis of covariance (ANCOVA). Potential confounders, including age, diabetes duration, sex, education, household income, occupation, marital status, medical insurance coverage, and urban versus rural residence were evaluated by examining their independent associations with the exposures and outcomes, and using directed acyclic graphs[164] (for example, meeting with a dietitian and fruit intake, **Supplemental Figure S3.1**).

The final adjustment set included age and occupation. All statistical analyses were conducted using SAS 9.2 (SAS Institute, Cary, North Carolina).

3.3 Results

A total of 195 3C Study participants met the inclusion criteria. Of these, 72 (37%) refused to participate and 23 (12%) dropped out before the 3CNAS visit. The final sample size was therefore 100. There were no differences in diabetes duration, sex, education, or urban versus rural residence between those who participated and those who refused or dropped out (all p >0.05). However, those who participated tended to be older (p=0.001), have higher household incomes (p=0.05), and be retired/unemployed/never worked (p=0.06) and married/cohabitating (p=0.02).

Participants were 41.7 ±16.3 years old, had a diabetes duration of 11.8 ±9.7 years, and an HbA1c of 8.22 ±1.77% (**Table 3.1**). Approximately one-third of participants were on insulin regimens classified as “MDI: No basal”; the most common insulin combination in this category was 3 injections/day of short-acting insulin (Regular) and 1 injection/day of intermediate-acting insulin (NPH). SMBG frequency was low: only 8% of participants reported testing ≥ 3 times/day.

Fewer than half of participants reported “ever” meeting with a dietitian (**Table 3.2**) and only one participant reported meeting with a dietitian in the past 12 months. While a greater proportion of participants reported attending an education session in the past 12 months that covered nutrition, the number was still low: only 18%.

Table 3.1 Demographic and clinical characteristics of individuals with type 1 diabetes in China participating in the 3C Nutrition Ancillary Study

	All *n*=100	**Males** *n*=54	**Females** *n*=46
Age, years	41.7 (16.3)	41.1 (16.7)	42.4 (15.8)
Diabetes duration, years	11.8 (9.7)	9.8 (7.4)	14.2 (11.4)
Highest level of education			
<University	32 (32%)	13 (25%)	19 (41%)
Junior University	16 (16%)	8 (15%)	8 (17%)
≥University	51 (52%)	32 (60%)	19 (41%)
Household income, RMB/month			
<3000	20 (20%)	10 (19%)	10 (22%)
3000 - <5000	23 (23%)	12 (22%)	11 (24%)
5000 - <10 000	30 (30%)	16 (30%)	14 (30%)
≥10 000	27 (27%)	16 (30%)	11 (24%)
Occupation			
Non-government worker	31 (31%)	20 (37%)	11 (24%)
Government worker	17 (17%)	8 (15%)	9 (20%)
Student	17 (17%)	12 (22%)	5 (11%)
Farmer	7 (7%)	4 (7%)	3 (7%)
Retired/unemployed	28 (28%)	10 (19%)	18 (39%)
Marital status			
Married/cohabitating	58 (60%)	31 (61%)	27 (60%)
Single/divorced/widowed	38 (40%)	20 (39%)	18 (40%)
Medical insurance			
Urban employee	47 (47%)	26 (48%)	21 (46%)
Urban resident	26 (26%)	12 (22%)	14 (30%)
New cooperative	15 (15%)	8 (15%)	7 (15%)
Other	7 (7%)	4 (7%)	3 (7%)
None	5 (5%)	4 (7%)	1 (2%)
Residency status			
Urban	82 (85%)	44 (85%)	38 (84%)
Rural	15 (15%)	8 (15%)	7 (16%)
Met glycemic control goal [1]			
Yes	24 (24%)	13 (24%)	11 (24%)
No	75 (76%)	41 (76%)	34 (76%)

Values are given as mean (SD) or n (%)

[1] HbA1c <7.0% for participants >19 years old and <7.5% for participants ≤19 years old

In regards to diabetes nutrition therapy strategies, 64% of participants reported that they had been taught carbohydrate counting (**Table 3.2**) and the majority of these had been taught by a physician (56%). The remaining participants were taught by dietitians (30%), diabetes educators (5%) or some other source including printed educational materials (3%), the Internet (2%), and nurses (3%). The vast majority (81%) of participants taught carbohydrate counting reported "never" using this self-management tool. Only two participants who had been taught carbohydrate counting reported practicing carbohydrate counting every day. Participants who had been taught carbohydrate counting by dietitians were nearly twice as likely to report sometimes using it (26%) compared to participants who had been taught by physicians (14%), but the difference was not statistically significant (p=0.51).

While a slightly greater proportion of participants (72%) had been given an eating plan by a healthcare provider (**Table 3.2**) relative to being taught carbohydrate counting (64%), participants only followed their prescribed eating plans, on average, 2.6 ±3.2 days in the past week. Of note, 11% of participants had never been taught carbohydrate counting and had never been given an eating plan by a healthcare provider.

Dietary flexibility in this sample was low: 67% of participants reported eating about the same amount of food at the same time everyday (**Table 3.2**). When participants were asked to describe what they do when they eat more or less food than usual, 20% reported that they do nothing because they have a rigid diet. In response to a query about what they would like to know about how food interacts with their diabetes care, 14% of participants responded that they wanted to know how they could eat fruit and 4% explicitly asked if a rigid diet is necessary for patients with T1D and how they could increase the diversity of their diets.

Participants on pumps had the highest dietary flexibility: over half of participants in this group reported eating different amounts or at different times every day and 0% reported doing nothing if their diet varies (**Table 3.2**). Participants on 1-2 injections/day were least likely to

adjust their insulin in response to eating more or less than usual. Participants on pumps had higher fruit (p=0.07) and dairy (p=0.04) intakes relative to other participants.

Participants who tested ≥1 time/day were more likely to report adjusting insulin in response to dietary variability and less likely to report doing nothing because they have a rigid diet (p=0.05) (**Supplemental Table S3.1**). They also had significantly (p=0.005) higher fruit intakes compared to participants testing with lower frequencies.

Participants who had ever met with a dietitian or who had attended an education session in the past 12 months that covered nutrition were marginally significantly more likely to have been given an eating plan (**Supplemental Table S3.2**). While a greater proportion of participants who had attended an education session that covered nutrition had been taught carbohydrate counting and used it sometimes (22%) compared to those who did not attend such a session (10%), the difference was not statistically significant (p=0.31).

Participants who attended an education session that covered nutrition in the past 12 months tended to be (p=0.11) more likely to achieve HbA1c goals compared to participants who did not attend such a session: 29% of participants attending a session met HbA1c goals compared to only 15% of participants not attending a session (**Supplemental Table S3.3**). While a greater proportion of participants who had ever met with a dietitian met HbA1c goals (58%) compared to those who had never met with a dietitian (44%), the difference was not statistically significant (p=0.22).

Table 3.2 Diabetes nutrition therapy and dietary intake according to insulin regimen among individuals with type 1 diabetes in China

	All *n*=100	**MDI: With basal** *n*=42	**Pump** *n*=9	**MDI: No basal** *n*=30	**1-2 injections** *n*=19	**P-value** [1]
Self-monitoring of blood glucose						
<1 time/week or do not test	31 (31%)	6 (14%)	1 (11%)	17 (57%)	7 (37%)	0.005
1-2 times/week	27 (27%)	10 (24%)	2 (22%)	8 (27%)	7 (37%)	
3-6 times/week	12 (12%)	7 (17%)	2 (22%)	2 (7%)	1 (5%)	
≥1 time/day	30 (30%)	19 (45%)	4 (44%)	3 (10%)	4 (21%)	
Dietary flexibility						
Eat same amount at same time everyday	67 (67%)	32 (76%)	4 (44%)	17 (57%)	14 (74%)	0.14
Eat different amounts or at different times everyday	33 (33%)	10 (24%)	5 (56%)	13 (43%)	5 (26%)	
Action if diet varies						
Adjusts insulin	57 (57%)	26 (62%)	6 (67%)	17 (57%)	8 (42%)	0.21
Adjusts insulin or exercise	8 (8%)	5 (12%)	2 (22%)	0 (0%)	1 (5%)	
Adjusts exercise	15 (15%)	5 (12%)	1 (11%)	5 (17%)	4 (21%)	
Nothing, rigid diet	20 (20%)	6 (14%)	0 (0%)	8 (27%)	6 (32%)	
Ever met with a dietitian						
Yes	48 (48%)	22 (52%)	4 (44%)	15 (50%)	7 (37%)	0.71
No	52 (52%)	20 (48%)	5 (56%)	15 (50%)	12 (63%)	
Attended education session in past 12 months that covered nutrition						
Yes	18 (18%)	10 (24%)	0 (0%)	5 (17%)	3 (16%)	0.39
No	82 (82%)	32 (76%)	9 (100%)	25 (83%)	16 (84%)	
Carbohydrate counting						
Taught and use sometimes	12 (12%)	6 (14%)	1 (11%)	4 (13%)	1 (5%)	0.20
Taught but never use	52 (52%)	26 (62%)	6 (67%)	13 (43%)	7 (37%)	
Never taught	36 (36%)	10 (24%)	2 (22%)	13 (43%)	11 (58%)	
Eating plan						
Given and use sometimes	32 (32%)	16 (38%)	1 (11%)	11 (37%)	4 (21%)	0.32
Given but never use	40 (40%)	17 (40%)	5 (56%)	12 (40%)	6 (32%)	
Never given	28 (28%)	9 (21%)	3 (33%)	7 (23%)	9 (47%)	

Nutrients						
Fat (% kcal)	35.9 (7.9)	36.1 (7.0)	35.7 (9.7)	35.3 (8.1)	36.5 (8.9)	0.80
Carbohydrates (% kcal)	47.1 (8.4)	46.5 (7.7)	49.6 (11.3)	46.5 (8.1)	48.0 (9.4)	0.77
Protein (% kcal)	16.3 (3.0)	16.9 (2.9)	15.7 (3.3)	16.3 (3.1)	15.3 (2.8)	0.28
Fiber (g/1000 kcal)	7.5 (2.6)	7.8 (2.4)	7.2 (2.9)	6.9 (2.3)	7.8 (3.1)	0.37
Iron (mg/1000 kcal)	11.2 (2.6)	11.6 (2.3)	11.1 (3.2)	11.2 (2.7)	10.2 (2.7)	0.15
Food groups (g/1000 kcal)						
Rice	79 (52)	79 (48)	91 (58)	62 (47)	101 (62)	0.10
Wheat products	107 (72)	89 (48)	106 (112)	130 (87)	108 (59)	0.10
Beans & bean products	45 (44)	42 (39)	40 (26)	47 (43)	53 (60)	0.98
Vegetables	257 (138)	288 (143)	238 (117)	217 (118)	260 (158)	0.18
Fruit	49 (59)	51 (55)	70 (66)	31 (53)	63 (70)	0.07
Red meat	44 (32)	49 (37)	40 (30)	39 (30)	42 (24)	0.81
Eggs	31 (21)	31 (18)	27 (23)	34 (25)	30 (21)	0.75
Milk & milk products	138 (93)	146 (102)	190 (81)	135 (78)	99 (89)	0.04

Values are given as mean (SD) or n (%)

[1] Chi-square test for categorical variables and Kruskal-Wallis test for continuous variables

MDI; multiple daily injections

There were few differences in dietary intake across subgroups of diabetes nutrition therapy (**Table 3.3**). Participants who had ever met with a dietitian had higher mean iron (p=0.007) and egg (p=0.03) intakes compared to participants who had never met with a dietitian. Participants who had attended an education in the past 12 months that covered nutrition had higher mean vegetable intakes (p=0.02) compared to those who had not. Finally, participants who had been given an eating plan but never used it had a lower mean percent of calories from fat (p=0.01) and a higher mean percent of calories from carbohydrate (p=0.05) compared to those who had been given an eating plan and used it and those who had never been given an eating plan.

Table 3.3 Estimated mean (standard error) nutrient and food group intakes, adjusted for age and occupation, across groups of diabetes nutrition education and therapy among individuals with type 1 diabetes in China

	Ever met with a dietitian			Attended education session in past 12 months that covered nutrition		
	Yes *n*=52	**No** *n*=48	**P-value** [1]	**Yes** *n*=18	**No** *n*=82	**P-value** [1]
Nutrients						
Fat (% kcal)	36.2 (1.2)	35.6 (1.2)	0.72	37.6 (1.9)	35.5 (0.9)	0.33
Carbohydrates (% kcal)	46.6 (1.2)	47.5 (1.2)	0.64	45.3 (2.0)	47.5 (0.9)	0.34
Protein (% kcal)	16.8 (0.4)	15.8 (0.4)	0.13	16.4 (0.7)	16.3 (0.3)	0.83
Fiber (g/1000 kcal)	7.6 (0.4)	7.4 (0.4)	0.72	7.6 (0.6)	7.5 (0.3)	0.82
Iron (mg/1000 kcal)	11.9 (0.4)	10.5 (0.4)	0.007	12.0 (0.6)	11.0 (0.3)	0.12
Food Groups (g/1000 kcal)						
Rice	81 (7.9)	78 (7.5)	0.81	77 (13)	80 (5.8)	0.86
Wheat products	111 (11)	103 (10)	0.62	107 (17)	107 (8)	0.99
Beans & bean products	44 (6.5)	46 (6.3)	0.85	48 (10)	45 (4.8)	0.79
Vegetables	274 (21)	241 (20)	0.26	329 (32)	241 (15)	0.02
Fruit	42 (8.8)	55 (8.4)	0.32	48 (14)	49 (6.5)	0.96
Red meat	47 (4.9)	41 (4.7)	0.38	54 (7.8)	42 (3.6)	0.15
Eggs	37 (3.1)	27 (2.9)	0.03	34 (5.0)	31 (2.3)	0.51
Milk & milk products	145 (14)	130 (13)	0.45	146 (22)	136 (10)	0.66

Values are given as mean (standard error), adjusted for age and occupational status

[1] Pr >F from analysis of covariance, adjusted for age and occupational status

Table 3.3 Continued

	Carbohydrate counting				Eating plan			
	Taught and sometimes use *n*=12	**Taught but never use** *n*=52	**Never taught** *n*=36	**P-value** [1]	**Given and sometimes use** *n*=32	**Given but never use** *n*=40	**Never given** *n*=28	**P-value** [1]
Nutrients								
Fat (% kcal)	37.0 (2.4)	36.8 (1.1)	34.2 (1.3)	0.31	37.0 (1.4)	33.0 (1.3)	38.8 (1.5)	0.01
Carbohydrates (% kcal)	45.8 (2.5)	46.8 (1.2)	48.0 (1.4)	0.68	46.0 (1.4)	49.6 (1.3)	44.6 (1.5)	0.05
Protein (% kcal)	15.9 (0.9)	16.2 (0.4)	16.5 (0.5)	0.77	16.3 (0.5)	16.2 (0.5)	16.4 (0.6)	0.99
Fiber (g/1000 kcal)	7.0 (0.7)	7.7 (0.4)	7.4 (0.4)	0.67	7.4 (0.4)	7.4 (0.4)	7.7 (0.5)	0.85
Iron (mg/1000 kcal)	11.0 (0.8)	10.9 (0.4)	11.6 (0.4)	0.51	10.7 (0.5)	11.7 (0.4)	11.0 (0.5)	0.28
Food Groups (g/1000 kcal)								
Rice	81 (15)	71 (7.2)	90 (8.7)	0.24	67 (9.2)	94 (8.4)	72 (9.9)	0.10
Wheat products	97 (21)	106 (9.8)	110 (12)	0.85	98 (13)	116 (11)	103 (13)	0.56
Beans & bean products	57 (13)	38 (6.0)	51 (7.2)	0.27	43 (7.8)	46 (7.2)	48 (8.4)	0.89
Vegetables	275 (41)	258 (19)	249 (23)	0.85	229 (25)	268 (23)	272 (27)	0.40
Fruit	46 (18)	48 (8.2)	51 (9.9)	0.95	64 (10)	46 (9.5)	36 (11)	0.17
Red meat	31 (9.7)	46 (4.6)	45 (5.4)	0.36	48 (5.8)	38 (5.3)	49 (6.3)	0.35
Eggs	45 (6.1)	28 (2.8)	31 (3.4)	0.05	30 (3.8)	33 (3.4)	31 (4.0)	0.85
Milk & milk products	163 (27)	131 (13)	139 (15)	0.56	148 (16)	142 (15)	119 (17)	0.44

Values are given as mean (standard error), adjusted for age and occupational status

[1] Pr >F from analysis of covariance, adjusted for age and occupational status

3.4 Discussion

This is the first study to assess the integration of diabetes nutrition education, self-management practices, and dietary intake among T1D patients in a developing country. Fewer than half of participants had "ever" met with a dietitian and the frequency of diabetes nutrition therapy approaches such as carbohydrate counting was low. Results indicate that diabetes nutrition therapy in China typically involves matching fixed insulin doses to a diet that is rigid with respect to amount and timing. While the consistency of this self-management regimen may be appropriate for some participants, others expressed a desire to diversify their diets, particularly with respect to fruit intake.

The ADA recommends meeting with a dietitian annually or attending a diabetes self-management education program that includes instruction on nutrition therapy.[161,165] Only one out of the 100 participants in this sample—an older male in poor control with possible microalbuminuria—had met with a dietitian in the past 12 months suggesting that dietitians may only be used in high-risk situations in China. A larger proportion of participants had attended an education session that covered nutrition in the past 12 months, but the proportion was still dismally low at only 18%. This may explain why only 12% of participants sometimes use carbohydrate counting and only 32% sometimes follow an eating plan given to them by their healthcare provider. This is a stark contrast to youth with T1D in the United States, 97% of whom have been taught carbohydrate counting and 86% of whom report using this approach "often."[77]

Although participants on MDI with basal or pumps had significantly higher SMBG frequencies compared to participants on other insulin regimens, only about half of them tested ≥1 time/day. The ADA recommends SMBG prior to all meals and snacks, occasionally postprandially, and at bedtime, in addition to other situations (e.g., when hypoglycemia is suspected)—a total of 6-8 times/day.[68] The reportedly low frequency of SMBG in this sample population, which is consistent with the most recently published data in China (from 2001-2002;

average SMBG of 8 times/month),[120] may help explain why diabetes nutrition therapy frequency is so low and why such a large proportion of participants on MDI reported having rigid dietary intakes. This low SMBG frequency poses a significant barrier for physicians in China who cannot advise patients appropriately with respect to diet due to a lack of information on SMBG (most patients do not bring SMBG results to their outpatient visits). For example, a patient may ask a physician in the outpatient department how she can eat fruit, but without data on SMBG the physician's ability to advise the patient is severely limited.

In this sample, vegetable and fruit intakes were below the Chinese Food Guide Pagoda recommendations: mean of 389 g/day of vegetables compared to 400-500 g/day recommended and mean of 78 g/day of fruit compared to 100-200 g/day recommended.[166] This may have contributed to the observed fiber intakes, which were half that recommended by the U.S. Institute of Medicine.[167] Interestingly, 14% of participants responded that they wanted to know how they could eat fruit, which indicates that individuals with T1D in China are purposefully restricting fruit intake. This phenomenon has also been reported in the United States: in a small focus group study of youth, although all participants perceived fruit as healthful, a few parents reported limiting or even excluding fruit consumption because of risk of postprandial hyperglycemia.[168] In our study, participants on pumps and those who tested more frequently had higher fruit intakes relative to other participants, suggesting that these may be viable self-management options for participants wishing to increase their fruit intakes.

In this sample, participants who attended an education session that covered nutrition in the past 12 months tended to be more likely to achieve HbA1c goals compared to participants who did not attend such a session. A similar trend was observed for ever meeting with a dietician, but it was not significant, perhaps because only one participant had met with a dietitian in the past 12 months. It may be the case that more frequent nutrition education and contact with dietitians are needed in China in order to observe more significant improvements in glycemic control.

We did not find a clear association between diabetes nutrition therapy and dietary intake in this sample of individuals with T1D in China. Evidence from both structured[169,170] and psychosocial[171] education interventions suggests that nutrition education can lead to improvements in dietary intake and guideline adherence among individuals with T1D. Furthermore, studies in Europe[172-174] have reported adoption of healthier diets with the receipt of nutrition recommendations as part of routine care, where routine care varied from a single, 5-day in-patient education program in France[172] to meeting with a dietitian during routine outpatient medical consultations every 3 months[173] or twice per year[174] in Italy. There are several potential reasons why no consistent association was observed between diabetes nutrition therapy and dietary intake in this sample of individuals with T1D in China. Perhaps chief among them is that nutrition education was infrequent and as a result, implementation support may be insufficient to empower patients to make modifications to their diet. Indeed, 74% of participants in our study wanted to know more about how food interacts with their diabetes care. Patients in China often express discontent with the education they are currently receiving, complaining that they have not been given the tools they need to understand their body's glycemic response to food and how to appropriately respond. To address this gap in knowledge, trained clinical dietitians are urgently needed in China and should be integrated into routine patient care. This would require a shift in the role of dietitians to support patient counseling in addition to their traditional role of advising hospital kitchens.

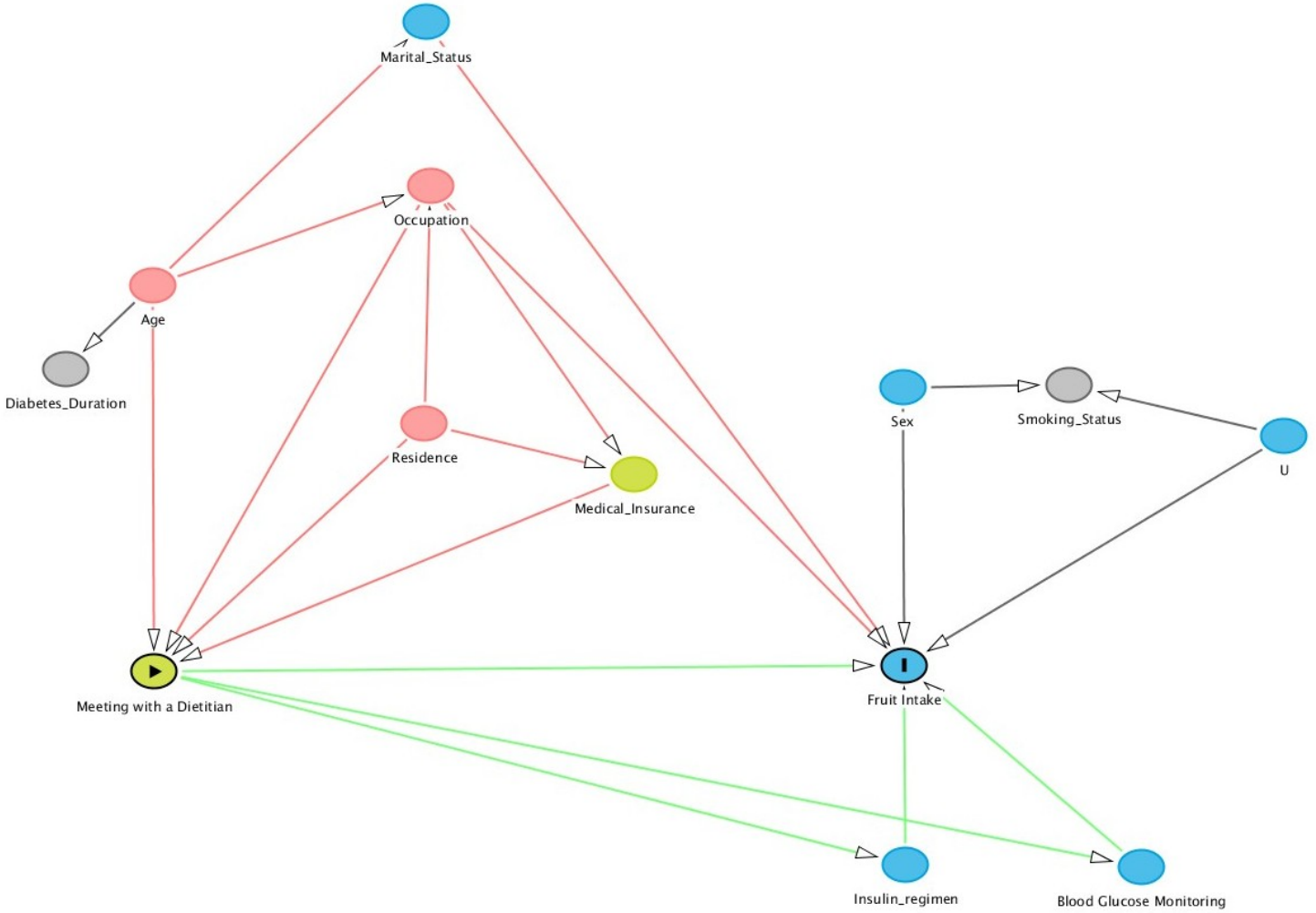
There are several strengths and challenges associated with this study. An important limitation is the use of self-reported diabetes nutrition therapy: participants may have modified their responses according to what they perceive to be socially desirable, which may have resulted in misclassification. The potential for this bias was addressed by using interviewers who were not the participants' healthcare providers and training them to use a standardized protocol and neutral probes.[159] Compared to ineligible participants and refusals, individuals who completed this study were older, and as a result were more likely to be married and to not be

working. In order to improve participant enrollment and generalizability, study visits were conducted both in urban Beijing and in a rural Beijing suburb. Nonetheless, we recognize that as with all observational studies, the generalizability of the results presented here may be limited. Finally, the sample size of the study was small and therefore limited our power to detect significant differences. Nonetheless, the thoroughness and quality of the data are valuable for improving our grasp of the situation in China and informing future, larger studies.

In this sample of individuals with T1D in China there is little dietitian involvement in continuing diabetes education and very few participants practice carbohydrate counting. While most participants had been given an eating plan by their healthcare provider, few reported using this plan regularly. In order to improve health outcomes for individuals with T1D in China, greater access to nutrition education led by dietitians and diabetes nutrition therapy as appropriate for patient preferences and insulin regimen is needed.

3.5 Supplemental figures and tables

Supplemental Figure S3.1 Directed acyclic graph for relationship between meeting with a dietitian and fruit intake as drawn using the tool, www.dagitty.net. Two minimal sufficient adjustment sets were identified for estimating the total effect of meeting with a dietitian on fruit intake: {age, occupation} and {marital status, occupation}



Supplemental Table S3.1 Diabetes nutrition therapy and dietary intake according to self-monitoring of blood glucose among individuals with type 1 diabetes in China

	All *n*=100	**<1 time/week or do not test** *n*=31	**1-2 times/week** *n*=27	**3-6 times/week** *n*=12	**≥1 time/day** *n*=30	**P-value** [1]
Dietary flexibility						
Eat same amount at same time everyday	67 (67%)	17 (55%)	22 (81%)	8 (67%)	20 (67%)	0.20
Eat different amounts or at different times everyday	33 (33%)	14 (45%)	5 (19%)	4 (33%)	10 (33%)	
Action if diet varies						
Adjusts insulin	57 (57%)	14 (45%)	13 (48%)	9 (75%)	21 (70%)	0.05
Adjusts insulin or exercise	8 (8%)	1 (3%)	2 (7%)	0 (0%)	5 (17%)	
Adjusts exercise	15 (15%)	5 (16%)	6 (22%)	1 (8%)	3 (10%)	
Nothing, rigid diet	20 (20%)	11 (35%)	6 (22%)	2 (17%)	1 (3%)	
Ever met with a dietitian						
Yes	48 (48%)	12 (39%)	13 (48%)	5 (42%)	18 (60%)	0.39
No	52 (52%)	19 (61%)	14 (52%)	7 (58%)	12 (40%)	
Attended education session in past 12 months that covered nutrition						
Yes	18 (18%)	4 (13%)	6 (22%)	2 (17%)	6 (20%)	0.81
No	82 (82%)	27 (87%)	21 (78%)	10 (83%)	24 (80%)	
Carbohydrate counting						
Taught and use sometimes	12 (12%)	1 (3%)	7 (26%)	1 (8%)	3 (10%)	0.23
Taught but never use	52 (52%)	17 (55%)	13 (48%)	7 (58%)	15 (50%)	
Never taught	36 (36%)	13 (42%)	7 (26%)	4 (33%)	12 (40%)	
Eating plan						
Given and use sometimes	32 (32%)	12 (39%)	7 (26%)	5 (42%)	9 (27%)	0.69
Given but never use	40 (40%)	13 (42%)	10 (37%)	5 (42%)	12 (40%)	
Never given	28 (28%)	6 (19%)	10 (37%)	2 (17%)	10 (33%)	
Nutrients						
Fat (% kcal)	35.9 (7.9)	35.1 (8.7)	35.7 (7.6)	40.9 (9.0)	34.9 (6.4)	0.24
Carbohydrates (% kcal)	47.1 (8.4)	47.6 (9.0)	46.9 (8.9)	42.8 (8.9)	48.4 (6.8)	0.38
Protein (% kcal)	16.3 (3.0)	15.8 (3.1)	16.3 (2.5)	16.5 (3.6)	16.7 (3.0)	0.56
Fiber (g/1000 kcal)	7.5 (2.6)	7.3 (2.9)	7.4 (2.5)	7.6 (2.6)	7.8 (2.4)	0.65
Iron (mg/1000 kcal)	11.2 (2.6)	10.6 (2.6)	11.6 (2.8)	11.1 (2.2)	11.3 (2.6)	0.60

Food groups (g/1000 kcal)						
Rice	79 (52)	73 (53)	93 (55)	91 (35)	68 (54)	0.06
Wheat	107 (72)	128 (94)	110 (72)	84 (44)	91 (44)	0.22
Beans	45 (44)	41 (39)	51 (55)	58 (23)	39 (42)	0.25
Vegetables	257 (138)	220 (127)	328 (166)	259 (86)	230 (118)	0.02
Fruit	49 (59)	38 (70)	35 (39)	58 (72)	68 (52)	0.005
Red meat	44 (32)	43 (33)	37 (23)	66 (44)	42 (29)	0.26
Eggs	31 (21)	27 (21)	39 (19)	38 (28)	26 (18)	0.05
Dairy	138 (93)	109 (82)	158 (109)	145 (108)	146 (78)	0.17

Values are given as mean (SD) or n (%)

[1] Chi-square test for categorical variables and Kruskal-Wallis test for continuous variables

Supplemental Table S3.2 Relationship between diabetes nutrition therapy variables among individuals with type 1 diabetes in China

	Ever met with a dietitian			Attended education session in past 12 months that covered nutrition		
	Yes *n*=52	**No** *n*=48	**P-value** [1]	**Yes** *n*=18	**No** *n*=82	**P-value** [1]
Dietary flexibility						
Eat same amount at same time everyday	31 (65%)	36 (69%)	0.62	13 (72%)	54 (66%)	0.60
Eat different amounts or at different times everyday	17 (35%)	16 (31%)		5 (28%)	28 (34%)	
Carbohydrate counting						
Taught and use sometimes	6 (13%)	6 (12%)	0.87	4 (22%)	8 (10%)	0.31
Taught but never use	26 (54%)	26 (50%)		9 (50%)	43 (52%)	
Never taught	16 (33%)	20 (38%)		5 (28%)	31 (38%)	
Eating plan						
Given and use sometimes	16 (33%)	16 (31%)	0.12	9 (50%)	23 (28%)	0.11
Given but never use	23 (48%)	17 (33%)		7 (39%)	33 (40%)	
Never given	9 (19%)	19 (37%)		2 (11%)	26 (32%)	

Values are given as n (%)

[1] Chi-square test

Supplemental Table S3.3 Comparison of characteristics of individuals with type 1 diabetes in China meeting HbA1c goals and not meeting HbA1c goals

	Met HbA1c Goal [1] *n*=24	Did Not Meet HbA1c Goal [1] *n*=75	P-value [2]
Ever met with a dietitian			
Yes	58.3% (14)	44.0% (33)	0.22
No	41.7% (10)	56.0% (42)	
Attended education session in past 12 months that covered nutrition			
Yes	29.2% (7)	14.5% (11)	0.11
No	70.8% (17)	85.3% (64)	
Ever taught carbohydrate counting			
Yes	66.7% (16)	64.0% (48)	0.81
No	33.3% (8)	36.0% (27)	
Who taught carbohydrate counting			
Physician	50.0% (8)	58.3% (28)	0.73
Dietitian	37.5% (6)	27.1% (13)	
Other	12.5% (2)	14.6% (7)	
Ever given eating plan			
Yes	66.7% (16)	73.3% (55)	0.53
No	33.3% (8)	26.7% (20)	

[1] HbA1c <7.0% for participants >19 years old and <7.5% for participants ≤19 years old

[2] Chi-square test

CHAPTER 4: COMPARISON OF THE DIETARY INTAKES OF INDIVIDUALS WITH AND WITHOUT TYPE 1 DIABETES IN CHINA

4.1 Introduction

Modifications to dietary intake have consistently been an essential component of T1D treatment.[175-177] In a considerable shift from the prescriptive diets characteristic of much of the 20th century,[175-181] in 1994, the ADA published nutrition recommendations emphasizing individualization of dietary advice with a focus on the effects of nutrition therapy on metabolic control.[182] The most recent ADA recommendations (2013) reiterate that there is no "one-size-fits-all" diet for individuals with diabetes and that food choices should only be limited when supported by scientific evidence.[161]

There is a dearth of information on the dietary intakes of individuals with T1D from low- and middle-income countries where economic development and urbanization have resulted in a transition from traditional foods to foods high in saturated fat and sugar, and low in fiber.[183,184] Whether this nutrition transition has also impacted the dietary intakes and self-management practices of individuals with T1D in these countries has yet to be explored.

China has undergone dramatic changes in diet over the past 20 years:[137,185-187] increases in snacking episodes and shifts in consumption of steamed and boiled foods to fried foods are just two examples of the many changes that have been documented.[136] The objective of the study presented in this chapter was to compare the dietary intakes of individuals with T1D in China to those of individuals without diabetes in Beijing. Such a comparison will improve our understanding of how patients with T1D are modifying their diet relative to the general population in order to manage their condition and will inform future interventions and policies to improve the lives of individuals with T1D in China.

4.2 Methods

4.2.1 Study samples

Data on individuals with T1D are from 3CNAS, described in **Chapter 3**. Data on individuals without T1D residing in Beijing came from the most recent (2011) CHNS. CHNS is an ongoing open cohort of the health and nutritional status of the Chinese population.[134] For the first time in 2011, 24 communities from Beijing were included in the survey. CHNS participants who met the following criteria were eligible for this analysis: Beijing resident, ≥12 years old, no diagnosed diabetes, and dietary data available.

4.2.2 Dietary intake assessment

Dietary intake in 3CNAS was assessed using three (two weekdays and one weekend day) telephone administered 24-hour recalls assisted by food records. Telephone administration was used to overcome the cultural stigma associated with T1D in China, which precluded visiting the homes of participants. This method was validated against in-person administration in a subset of participants.[188] At the end of the 3CNAS visit, participants were trained by dietitians to record their dietary intake on food records provided in an introductory packet. Emphasis was placed on estimating portion sizes using food samples, an electronic scale, and a culturally

appropriate portion size picture guide. On average, beginning 3.0 ±2.8 days after this visit, participants completed the three 24-hour recalls.

Dietary intake in CHNS was assessed using three consecutive in-person administered 24-hour recalls randomly allocated to start between Monday and Sunday in combination with a household food inventory conducted over the same 3-day period.[186] Food models and picture aids were used by trained interviewers to assist with estimating portion sizes. For dishes prepared at home, the recipe components were taken from the household food inventory and portion sizes were based on the proportion of the dish reportedly consumed by the participant.

For both 3CNAS and CHNS, the 24-hour recall food lists were converted into nutrients using the Chinese Food Composition Tables.[151,152] Nutritionally meaningful food groups were derived by a collaborative working group that included researchers at The University of North Carolina, Chapel Hill, and the Chinese National Institute of Nutrition and Food Safety.[186] Nutrients were specified continuously as energy densities.[189] Due to the non-normal distribution of some food groups largely stemming from large proportions of non-consumers, food groups were specified as binary variables. Food groups with ≥ 80% consumers (*n*=5/17 food groups, including rice, wheat, vegetables, red meat, and eggs) were dichotomized as below versus above the median of the corresponding food group distribution in g/1000 kcal among participants without diabetes, and food groups with <80% consumers (*n*=12/17 food groups, including beans & bean products, fruit, poultry, fish & shellfish, milk & milk products, low-fat cakes, high-fat cakes, fried foods, nuts & seeds, fungi & seaweed, sugar-sweetened beverages, and fast food) were dichotomized as non-consumers versus consumers.

4.2.3 Covariate assessment

Self-reported demographic and socioeconomic data were collected via interviewer-administered questionnaires during the 3C Study visit and the CHNS visit. Both studies used standardized protocols to measure weight and height. BMI was calculated as weight in

kilograms divided by height in meters-squared. Underweight and overweight for adults (≥18 years) were defined according to the World Health Organization's recommendation as underweight, BMI <18.5 kg/m^2, and overweight, BMI ≥25 kg/m^2,[190] and for adolescents (<18 years) using the sex- and age-specific cut-points recommended by the International Obesity Task Force.[191,192]

Information on insulin administration method, type, and dose were collected during the 3CNAS visit. Two insulin regimens were defined as follows: (1) "basal-bolus," including continuous subcutaneous infusion and regimens with ≥ 3 daily injections that included glargine or detemir and (2) "fixed," including regimens with ≥ 3 daily injections with any insulin types excluding glargine and detemir and regimens with 1-2 injections per day of any insulin types.

4.2.4 Statistical analysis

Descriptive statistics were used to summarize sample characteristics, and differences between participants with and without diabetes were evaluated using analysis of variance (ANOVA) for continuous variables and chi-square tests for categorical variables.

Potential confounders, including age, sex, marital status, household income, residence status, education, occupation, medical insurance coverage, smoking status, and BMI status, were explored using a directed acyclic graph[164] (**Supplemental Figure S4.1**) and formally evaluated by estimating their associations with both the exposure (diabetes status) and outcomes (nutrients and food groups). We found that BMI status was a collider in the directed acyclic graph analysis, being both the result of diabetes status and dietary intake. We therefore did not include BMI status in our final models as adjustment for colliders results in biased estimates.[193,194] The final adjustment set included sex, age (<22 years versus ≥22 years), and residence status (urban versus rural) as these factors were associated with the exposure (**Table 4.1**) and the outcomes (data not shown). Because *n*=3 participants with T1D were missing

residence status, the final sample size for this analysis was *n*=1059 without diabetes and *n*=97 with T1D (*n*=49 on basal-bolus insulin regimens and *n*=48 on fixed insulin regimens).

Confounder-adjusted differences were calculated using ANCOVA for continuous variables (nutrients) and multivariable logistic regression for binary variables (food groups). Given that dietary recommendations for T1D management are specific to an individual's insulin regimen, and differ between flexible, basal-bolus regimens and fixed regimens [195], analyses were conducted with 1) all participants with T1D combined and 2) participants with T1D stratified by insulin regimen (basal-bolus versus fixed).

All statistical analyses were conducted using SAS 9.2 (SAS Institute, Cary, North Carolina). Values presented are mean ±SD or % (n) unless otherwise indicated.

4.3 Results

Participants with T1D were more likely to be <22 years old (p=0.04) and single/divorced/widowed (p<0.0001), had higher incomes (p=0.002) and education (p=0.01), and were more likely to be underweight and less likely to be overweight (p<0.0001) compared to participants without diabetes (**Table 4.1**). There were no statistically significant differences in medical insurance coverage or smoking status (all p>0.05). Participants with T1D on fixed insulin regimens were more likely to be male compared to the other two groups (p=0.04), and participants with T1D on basal-bolus insulin regimens were more likely to be urban residents (p=0.008) compared to the other two groups.

The macronutrient composition of the diets of participants with and without T1D differed substantially, particularly with respect to carbohydrate content (**Table 4.2**). Participants with T1D had a significantly (p=0.01) lower adjusted mean percent of energy from carbohydrates compared to participants without diabetes: approximately 47% kcal from carbohydrates in those with T1D versus 50% in those without diabetes. Consistent with this observation, participants with T1D had a significantly higher adjusted mean percent of energy from fat (p=0.04) and from

protein (p=0.02). Stratification by insulin regimen revealed that the differences in carbohydrate and fat were stronger among participants with T1D on fixed insulin regimens, while the difference in protein was more evident in participants on basal-bolus insulin regimens. No statistically significant differences were observed in adjusted mean fiber intake.

Table 4.1 Comparison of demographic and clinical characteristics between participants without diabetes and those with type 1 diabetes (T1D) in China, combined and stratified by insulin regimen

	No diabetes *n*=1059	**T1D** *n*=97	**Basal-bolus insulinT1D** *n*=49	**Fixed insulin T1D** *n*=48	**P-value combined T1D** [1]	**P-value stratified T1D** [2]
Age, years	43.1 (15.3)	41.3 (16.3)	41.9 (17.4)	40.7 (15.3)	0.28	0.52
Age						
<22 years	8.3 (88)	14.4 (14)	16.3 (8)	12.5 (6)	0.04	0.10
≥22 years	91.7 (971)	85.6 (83)	83.7 (41)	87.5 (42)		
Diabetes duration, years	N/A	11.6 (9.3)	13.6 (10.9)	9.5 (6.9)	N/A	0.03
Sex						
Female	53.2 (563)	46.4 (45)	57.1 (28)	35.4 (17)	0.20	0.04
Male	46.8 (496)	53.6 (52)	42.9 (21)	64.6 (31)		
Marital status						
Married/cohabitating	88.0 (871)	59.6 (56)	52.2 (24)	66.7 (32)	<0.0001	<0.0001
Single/divorced/widowed	12.0 (119)	40.4 (38)	47.8 (22)	33.3 (16)		
Household income, RMB/month						
<3000	22.4 (234)	19.0 (18)	12.8 (6)	25.0 (12)	0.002	0.009
3000 - <5000	25.3 (264)	23.2 (22)	23.4 (11)	22.9 (11)		
5000 - <10,000	39.9 (417)	31.6 (30)	34.0 (16)	29.2 (14)		
≥10,000	12.4 (130)	26.3 (25)	29.8 (14)	22.9 (11)		
Residence						
Urban	78.9 (836)	84.5 (82)	95.9 (47)	72.9 (35)	0.19	0.008
Rural	21.1 (223)	15.5 (15)	4.1 (2)	27.1 (13)		
Highest level of education						
<University	48.0 (506)	32.3 (31)	25.0 (12)	39.6 (19)	0.01	0.02
Junior college	12.4 (131)	14.6 (14)	14.6 (7)	14.6 (7)		
≥University	39.6 (417)	53.1 (51)	60.4 (29)	45.8 (22)		
Occupation						
Non-government worker	37.5 (364)	30.9 (30)	28.6 (14)	33.3 (16)	<0.0001	<0.0001
Government worker	22.8 (221)	17.5 (17)	16.3 (8)	18.8 (9)		
Student	1.8 (17)	17.5 (17)	16.3 (8)	18.8 (9)		
Farmer	1.4 (14)	7.2 (7)	4.1 (2)	10.4 (5)		
Retired or not working	36.5 (354)	26.8 (26)	34.7 (17)	18.8 (9)		
Medical insurance coverage						
Yes	94.7 (1000)	95.9 (93)	95.9 (47)	95.8 (46)	0.62	0.88
No	5.3 (56)	4.1 (4)	4.1 (2)	4.2 (2)		

Smoking status						
Non-smoker	79.1 (834)	80.4 (78)	85.7 (42)	75.0 (36)	0.77	0.41
Smoker	20.9 (220)	19.6 (19)	14.3 (7)	25.0 (12)		
BMI status [3]						
Underweight	3.1 (33)	16.5 (16)	14.3 (7)	18.8 (9)	<0.0001	<0.0001
Normal weight	55.0 (580)	73.2 (71)	67.4 (33)	79.2 (38)		
Overweight	41.8 (441)	10.3 (10)	18.4 (9)	2.1 (1)		

Values are given as mean (SD) or percentage (*n*)

[1] Chi-square test for categorical variables and ANOVA for continuous variables comparing participants without diabetes and participants with T1D

[2] Chi-square test for categorical variables and ANOVA for continuous variables comparing participants without diabetes, participants with T1D on basal-bolus insulin regimens, and participants with T1D on fixed insulin regimens

[3] Underweight and overweight for adults (≥18 years) were defined according to the WHO's recommendation as underweight, BMI <18.5 kg/m^2, and overweight, BMI ≥25 kg/m^2, and for adolescents (<18 years) using the sex- and age-specific cut-points recommended by the International Obesity Task Force

Table 4.2 Comparison of nutrient intake between participants without diabetes and those with type 1 diabetes (T1D) in China, combined and stratified by insulin regimen

	No diabetes *n*=1059	**T1D** *n*=97	**Basal-bolus insulin T1D** *n*=49	**Fixed insulin T1D** *n*=48	**P-value T1D vs. no diabetes** [1]	**P-value basal-bolus vs. no diabetes** [2]	**P-value Fixed vs. no diabetes** [2]
Energy intake (kcal/day)	1769 ±18	1560 ±60	1543 ±85	1578 ±86	0.001	0.01	0.03
Fat (% kcal)	33.8 ±0.3	36.0 ±1.0	35.7 ±1.5	36.4 ±1.5	0.04	0.21	0.08
Carbohydrate (% kcal)	49.9 ±0.3	47.2 ±1.0	47.5 ±1.4	46.8 ±1.4	0.01	0.10	0.04
Protein (% kcal)	15.3 ±0.1	16.2 ±0.4	16.3 ±0.5	16.1 ±0.5	0.02	0.06	0.15
Fiber (g/1000 kcal)	8.2 ±0.1	7.4 ±0.5	7.4 ±0.7	7.4 ±0.7	0.13	0.27	0.27

Values are given as LS mean ±SD from analysis of covariance, adjusted for sex (male versus female), age (<22 years versus ≥22 years), and residence status (urban versus rural)

[1] Pair-wise comparison of LS means from analysis of covariance. Pr > |t| for H_0: LS mean(T1D) = LS mean(no DM)

[2] Pair-wise comparison of LS means from analysis of covariance. Pr > |t| for H_0: LS mean(basal-bolus or fixed) = LS mean(no DM)

Participants with T1D in both insulin regimen groups were significantly (p <0.05) more likely to be consumers of low-fat cakes and fungi & seaweed compared to participants without diabetes: adjusted odds ratio (OR) (95% confidence interval [CI]) comparing T1D combined to no diabetes (referent) 3.19 (1.99, 5.10) for low-fat cakes and 2.69 (1.76, 4.12) for fungi & seaweed (**Table 4.3**). They were also significantly more likely to be above the median intake for vegetables: adjusted OR (95% CI) comparing T1D combined to no diabetes (referent) 8.33 (4.37, 15.86).

Participants with T1D on basal-bolus insulin regimens had several distinct dietary modifications (**Table 4.3**): they were less likely to be consumers of fried foods (adjusted OR [95% CI], 0.48 [0.23, 1.00]) and more likely to be consumers of fish & shellfish (adjusted OR [95% CI], 1.95 [1.08, 3.52]) compared to participants without diabetes.

Participants with T1D on fixed insulin regimens also had several distinct dietary modifications (**Table 4.3**): they were more likely to be above the median intake for wheat products (adjusted OR [95% CI], 2.03 [1.08, 3. 18]), and they were more likely to be consumers of high-fat cakes (adjusted OR [95% CI], 2.73 [1.25, 5.95]) and milk & milk products (adjusted OR [95% CI], 2.57 [1.19, 5.53]). Furthermore, they were less likely to be consumers of fruit (adjusted OR [95% CI], 0.47 [0.26, 0.87]). Indeed, only 54% of participants with T1D on fixed insulin regimens reported consuming fruit compared to 82% of those on basal-bolus insulin regimens and 74% of those without diabetes.

Table 4.3 Comparison of food group intake between participants without diabetes and those with type 1 diabetes (T1D) in China, combined and stratified by insulin regimen

	No diabetes *n*=1059	T1D *n*=97	Basal-bolus insulin T1D *n*=49	Fixed insulin T1D *n*=48	OR (95% CI)		
					T1D vs. no diabetes (ref) [2]	Basal-bolus vs. no diabetes (ref) [2]	Fixed vs. no diabetes (ref) [2]
Rice							
≤ Median [1] (ref)	50.1 (530)	56.7 (55)	55.1 (27)	58.3 (28)	0.74	0.81	0.68
> Median	50.0 (529)	43.3 (42)	44.9 (22)	41.7 (20)	(0.49, 1.13)	(0.45, 1.45)	(0.38, 1.23)
Wheat products							
≤ Median [1] (ref)	50.1 (530)	38.1 (37)	44.9 (22)	31.3 (15)	1.66	1.39	2.03
> Median	50.0 (529)	61.9 (60)	55.1 (27)	68.8 (33)	(1.08, 2.56)	(0.78, 2.49)	(1.08, 3.81)
Low-fat cakes							
Non-consumer (ref)	87.0 (921)	68.0 (66)	65.3 (32)	70.8 (34)	3.19	3.25	3.12
Consumer	13.0 (138)	32.0 (31)	34.7 (17)	29.2 (14)	(1.99, 5.10)	(1.74, 6.06)	(1.62, 6.03)
High-fat cakes							
Non-consumer (ref)	90.9 (963)	81.4 (79)	81.6 (40)	81.3 (39)	2.25	1.91	2.73
Consumer	9.1 (96)	18.6 (18)	18.4 (9)	18.8 (9)	(1.28, 3.95)	(0.89, 4.09)	(1.25, 5.95)
Fried foods							
Non-consumer (ref)	69.3 (734)	76.3 (74)	81.6 (40)	70.8 (34)	0.68	0.48	0.93
Consumer	30.7 (325)	23.7 (23)	18.4 (9)	29.2 (14)	(0.42, 1.11)	(0.23, 1.00)	(0.49, 1.77)
Fast food							
Non-consumer (ref)	42.5 (450)	41.2 (40)	44.9 (22)	37.5 (18)	1.03	0.87	1.23
Consumer	57.5 (609)	58.8 (57)	55.1 (27)	62.5 (30)	(0.68, 1.58)	(0.49, 1.55)	(0.68, 2.25)
Vegetables							
≤ Median [1] (ref)	50.1 (530)	11.3 (11)	8.2 (4)	14.6 (7)	8.33	11.45	6.53
> Median	50.0 (529)	88.7 (86)	91.8 (45)	85.4 (41)	(4.37, 15.86)	(4.06, 32.26)	(2.88, 14.78)
Fruit							
Non-consumer (ref)	26.0 (275)	32.0 (31)	18.4 (9)	45.8 (22)	0.70	1.20	0.47
Consumer	74.0 (784)	68.0 (66)	81.6 (40)	54.2 (26)	(0.44, 1.13)	(0.56, 2.57)	(0.26, 0.87)
Fungi & seaweed							
Non-consumer (ref)	65.3 (692)	41.2 (40)	34.7 (17)	47.9 (23)	2.69	3.47	2.10
Consumer	34.7 (367)	58.8 (57)	65.3 (32)	52.1 (25)	(1.76, 4.12)	(1.89, 6.36)	(1.17, 3.77)
Nuts & seeds							
Non-consumer (ref)	66.3 (702)	56.7 (55)	57.1 (28)	56.3 (27)	1.49	1.31	1.71
Consumer	33.7 (357)	43.3 (42)	42.9 (21)	43.8 (21)	(0.97, 2.29)	(0.73, 2.36)	(0.94, 3.11)

Beans & bean products							
Non-consumer (ref)	25.4 (269)	19.6 (19)	14.3 (7)	25.0 (12)	1.40	2.10	1.00
Consumer	74.6 (790)	80.4 (78)	85.7 (42)	75.0 (36)	(0.83, 2.36)	(0.93, 4.74)	(0.51, 1.96)
Red meat							
≤ Median [1] (ref)	50.0 (529)	42.3 (41)	42.9 (21)	41.7 (20)	1.32	1.24	1.40
> Median	50.1 (530)	57.7 (56)	57.1 (28)	58.3 (28)	(0.86, 2.02)	(0.69, 2.23)	(0.77, 2.54)
Poultry							
Non-consumer (ref)	64.4 (682)	69.1 (67)	65.3 (32)	72.9 (35)	0.72	0.79	0.65
Consumer	35.6 (377)	30.9 (30)	34.7 (17)	27.1 (13)	(0.46, 1.14)	(0.43, 1.46)	(0.34, 1.26)
Fish & shellfish							
Non-consumer (ref)	59.1 (626)	48.5 (47)	40.8 (20)	56.3 (27)	1.52	1.95	1.18
Consumer	40.9 (433)	51.6 (50)	59.2 (29)	43.8 (21)	(1.00, 2.32)	(1.08, 3.52)	(0.65, 2.13)
Eggs							
≤ Median [1] (ref)	50.1 (530)	39.2 (38)	34.7 (17)	43.8 (21)	1.55	1.76	1.38
> Median	50.0 (529)	60.8 (59)	65.3 (32)	56.3 (27)	(1.01, 2.38)	(0.96, 3.21)	(0.77, 2.48)
Milk & milk products							
Non-consumer (ref)	34.0 (360)	17.5 (17)	14.3 (7)	20.8 (10)	2.39	2.19	2.57
Consumer	66.0 (699)	82.5 (80)	85.7 (42)	79.2 (38)	(1.35, 4.25)	(0.95, 5.05)	(1.19, 5.53)
Sugar-sweetened beverages							
Non-consumer (ref)	89.9 (952)	90.7 (88)	85.7 (42)	95.8 (46)	0.85	1.24	0.40
Consumer	10.1 (107)	9.3 (9)	14.3 (7)	4.2 (2)	(0.41, 1.74)	(0.54, 2.87)	(0.10, 1.70)

Values are given as percentage (*n*) or OR (95% CI)

[1] Median defined according to distribution in g/1000 kcal among participants without diabetes

[2] OR (95% CI) from multivariable logistic regression, adjusted for sex (male versus female), age (<22 years versus ≥22 years), and residence status (urban versus rural)

4.4 Discussion

Individuals with T1D in China, regardless of insulin regimen, had a lower mean percent of energy from carbohydrates compared to individuals without diabetes. In addition, they had higher intakes of vegetables, fungi & seaweed, and low-fat cakes. Several distinguishing characteristics of insulin regimen groups also emerged: participants on fixed regimens had higher intakes of wheat and were less likely to consume fruit and more likely to consume high-fat cakes and dairy compared to participants without diabetes. In contrast, participants on basal-bolus regimens were less likely to consume fried foods and more likely to consume fish & shellfish compared to participants without diabetes. Together, these observations suggest that dietary modifications are common among individuals with T1D in China.

Few studies have systematically compared the dietary intakes of individuals with T1D and the general population. One study conducted in the United States between 2000 and 2002 found similar results to our study, reporting that adults with T1D had a higher mean percent of energy from fat (36.0% in males and 34.7% in females with T1D versus 33.3% and 32.3%, respectively, in controls) and protein (18.8% in males and 19.6% in females with T1D versus 18.0% and 18.9%, respectively, in controls) and a lower mean percent of energy from carbohydrates (44.0% in males and 45.9% in females with T1D versus 47.0% and 48.5%, respectively, in controls) compared to controls.[85] A similarly higher mean percent of energy from fat compared to controls has also been observed in several small samples of youth with T1D in Europe.[196,197]

In contrast to the aforementioned studies, a small study conducted in Australia between 1984 and 1995 did not find any statistically significant differences in dietary intake between adults with newly diagnosed T1D and controls despite the fact that all of the T1D participants were reportedly following fixed insulin regimens matched to a set diet.[198] Two other studies, both conducted in youth with T1D in Europe, also did not find significant differences in the macronutrient composition of the diet between participants with T1D and controls.[199,200] In our

study, most participants with T1D were on fixed insulin regimens matched to a rigid diet with respect to timing and amount of food,[188] and we observed substantial differences in dietary intake between participants with T1D and those without despite previously reporting limited nutrition education in this group of participants.[188] This result may partially stem from the fact that our sample, relative to the aforementioned European samples, was older and had longer disease durations. More research is needed to identify the underlying factors contributing to the observed dietary modifications of individuals with T1D in China.

The mean fiber intakes of participants with T1D (7.4 g/1000 kcal) and those without diabetes (8.2 g/1000 kcal) were well below the recommended level of 14 g/1000 kcal.[161] While there was no statistically significant difference between these means after adjustment for confounders, the fiber intake of participants with T1D was, on average, approximately 0.8 g/1000 kcal lower than that of participants without diabetes. Given that fiber intake is inversely associated with all-cause mortality and cardiovascular disease risk among individuals with diabetes,[201,202] identifying strategies for improving dietary fiber intake should be an important goal of future research.

Individuals with T1D in both insulin regimen groups had higher intakes of vegetables, fungi & seaweed, and low-fat cakes (including biscuits/crackers) compared to individuals without diabetes. The observation that they were more likely to consume fungi & seaweed may be the result of recommendations during diabetes education courses to eat more sugar-free foods, of which fungi are used as an example. The increased intake of low-fat cakes, which includes biscuits/crackers, likely reflects the common use of these food items to treat hypoglycemia. We observed that individuals with T1D on fixed insulin regimens were increasing their wheat product intake relative to individuals without diabetes. They also restricted their rice intake relative to individuals without diabetes, though it was not statistically significant (OR [95% CI], 0.68 [0.38, 1.23]). These observations may reflect the fact that physicians in China, when discussing the effects of carbohydrates on blood glucose, often use rice as an example. In the

absence of additional nutrition education, we hypothesize that patients may subsequently equate rice with high blood glucose and replace rice with wheat products (such as noodles or buns) for their staple food. Similarly, we observed that these individuals were more likely to consume high-fat cakes compared to individuals without diabetes, perhaps because sugar-free cakes tend to be higher in fat and patients focus on low-sugar, low-carbohydrate foods rather than the totality of nutritional information. Finally, individuals with T1D on fixed insulin regimens (but not those on basal-bolus insulin regimens) restricted fruit intake, a phenomenon also reported in the United States,[168] and again, likely the result of a carbohydrate focus rather than a healthy diet focus. Overall, the lack of physician time and dietitian involvement in T1D care in China may be contributing to patient misconceptions relating to nutrition. In-depth, qualitative research into this phenomenon may prove to be informative for future nutrition interventions in this population.

Participants with T1D on basal-bolus insulin regimens had a generally healthier diet than the other groups, consuming fewer fried foods and more fish & shellfish. They also had higher intakes of beans (typically soy-based products such as tofu) and eggs relative to individuals without diabetes, though these differences were not statistically significant (OR [95% CI], 2.10 [0.93, 4.74] and 1.76 [0.96, 3.21], respectively).These observations are consistent with the higher protein intake found in this group. Together, these results suggest that individuals with T1D in China who are on basal-bolus insulin regimens may be more motivated and/or have higher adherence to self-management recommendations, including those relating to nutrition. Participants with T1D were significantly less likely to be married or cohabitating compared to participants without diabetes even after adjustment for age: only 60% reported being married or cohabitating compared to 88% of participants without diabetes. Given epidemiological evidence linking social support with improved self-management behaviors and health outcomes,[203-205] the results of this study highlight an important barrier for individuals with T1D in China.

Participants with T1D in both insulin regimen groups had significantly lower energy intake compared to participants without diabetes. They were also more likely to be underweight and less likely to be overweight compared to individuals without diabetes: 17% of participants with T1D were underweight compared to only 3% of those without diabetes, and 10% of participants with T1D were overweight compared to 42% of those without diabetes. This observation is consistent with a study conducted in Guangdong in southern China, which reported underweight and overweight prevalences of 19.6% and 11.8%, respectively, among individuals with T1D.[26] Several factors may be underlying these results including the fact that most participants with T1D in 3CNAS reported a rigid diet with respect to timing and amount of food, including those on a basal-bolus insulin regimen,[188] and this might prevent overeating and weight gain. Furthermore, the diabetes duration in this sample was relatively long, approximately 12 years, and though 3C Study participants with self-reported advanced micro- and macrovascular complications were not eligible for 3CNAS, it is possible that the natural progression of T1D and undiagnosed complications contributed to the relatively high prevalence of underweight in this sample population.

This study focused on individuals with T1D in a large urban area in northern China. Therefore, results may not be generalizable to more rural areas or southern China where the diet differs substantially from the north. Additional challenges of this study were differences in dietary assessment methods between 3CNAS and CHNS. While interviewers from both studies were trained by staff from the China Center for Disease Control, and the 24-hour recall questionnaire and food composition tables were the same between studies, we cannot rule out that some of the differences observed between individuals with and without diabetes were the result of slight differences in dietary assessment methods rather than true differences between these populations. Related to this, dietary intake was self-reported and therefore subject to differential misclassification as individuals with T1D may be more accustomed to reporting dietary intake. Finally, participants with T1D on basal-bolus insulin regimens were more urban

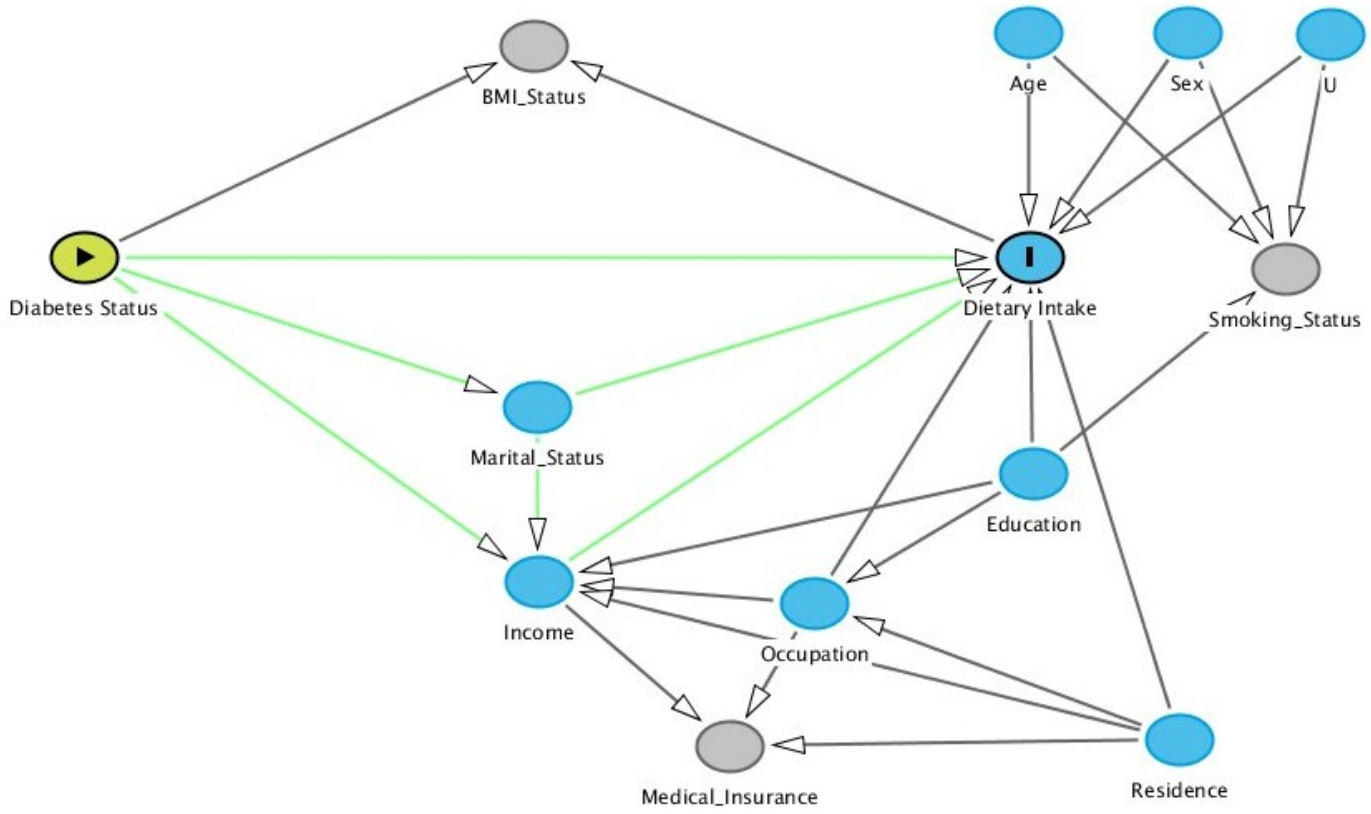
and therefore may have more modern lifestyles than the other two groups. Although we controlled for residence status in the analysis, we cannot rule out residual confounding by unmeasured correlates of a more urbanized, modern lifestyle.

Comparing the dietary intakes of individuals with T1D in China to those without diabetes allowed us to conclude that differences in observed dietary intake were the result of T1D rather than the result of cultural differences. To our knowledge, this is the first study to report on the dietary intakes of individuals with T1D relative to controls in a low- or middle-income country. One recent study reported on general dietary plans and nutritional therapy among individuals with T1D in Brazil, but to our knowledge, did not collect actual dietary intake data.[206]

The substantial differences in macronutrient content and food groups between individuals with T1D in China and those without diabetes suggest that dietary modifications are common and reflect carbohydrate-conscious nutrition recommendations for individuals with T1D. Future research should focus on the effects of these modifications on quality of life and health outcomes.

4.5 Supplemental figure

Supplemental Figure S4.1 Directed acyclic graph for relationship between diabetes status (yes or no, T1D) and dietary intake as drawn using the tool, www.dagitty.net. Body mass index (BMI) was identified as a collider. No minimal sufficient adjustment sets were identified for estimating the total effect of diabetes status on dietary intake. One minimal sufficient adjustment set was identified to estimate the direct effect of diabetes status on dietary intake: {education, income, marital status, occupation, and residence status (urban versus rural)}



CHAPTER 5: DIETARY PATTERNS ASSOCIATED WITH HBA1C AND LDL CHOLESTEROL AMONG INDIVIDUALS WITH TYPE 1 DIABETES IN CHINA

5.1 Introduction

Improvements in treatment over the past 30 years have reduced the risk of CVD and all-cause mortality among individuals with T1D;[51-53] however, CVD and mortality rates remain significantly higher among adults with T1D relative to the general population.[52,59] Furthermore, substantial geographic variation in mortality rates even among developed countries[66,67] suggests that improvements in T1D treatment have not been shared equally across the globe.

Since the completion of the landmark DCCT,[70] treatment efforts to reduce CVD and other complications among individuals with T1D have focused on intensifying SMBG and insulin dose adjustments to achieve tight glycemic control.[68,69] However, these intensive treatment regimens are uncommon in many parts of the world including China where the median number of times per day patients monitor is 0.4,[26] in stark contrast to the recommended 6-8.[68] China has the largest number of individuals with T1D in the Western Pacific Region[207] and there is some evidence to suggest that the burden of comorbidities in this population is higher than that in the United States: 2001-2002 data from two centers in China on hypertension in youth <15 years old with T1D estimated a hypertension prevalence of 24%[120] compared to 5.9% among youth 3 to 17 years old with T1D in the United States.[208] Strategies to reduce CVD and other complications in this high-risk population are urgently needed.

Dietary factors including, for example, high fiber intake,[209] are prospectively associated with reduced risk of CVD and all-cause mortality among European adults with T1D. Dietary intake may therefore represent an important point of intervention to improve health outcomes for this population. RRR has emerged over the past 10 years as a method to identify disease-specific dietary patterns.[210] The objective of this analysis was to use RRR to identify dietary patterns maximizing the explained variation in two key health indicators, HbA1c and LDL cholesterol, among individuals with T1D in China.

5.2 Methods

5.2.1 Sample population

The 3C Study was an epidemiological study of the coverage, cost, and care of T1D in China.[162] A follow-up study, 3CNAS, was conducted, on average, 1.6 ±0.2 years later and expanded the 3C Study to include detailed information on dietary intake. 3C Study participants who met the following criteria were eligible for 3CNAS: Beijing resident, ≥ 12 years old, no severe diabetes complications (i.e. advanced micro- and macrovascular complications, including nephropathy and stroke), and in-service telephone number available.

5.2.2 Data collection

Self-reported demographic and socioeconomic data were collected during the 3C Study visit. A fasting blood sample was collected by venipuncture during the 3CNAS visit and biomarkers were assessed using standardized laboratory procedures. Specifically, HbA1c was measured in whole blood with an automated high-performance liquid chromatography system (Primus Ultra^2, Trinity Biotech, Bray, Co Wicklow, Ireland). Blood samples for lipid analysis were immediately centrifuged at 2000 RPM for 15 minutes and the serum was stored at -80°C for batch analysis using an automated Hitachi-008 system (Hitachi, Chiyoda, Tokyo, Japan).

Information on insulin administration method, type, and dose, and SMBG were also collected during the 3CNAS visit. Four insulin regimens were defined as follows: (1) MDI (≥ 3 injections) that included glargine or detemir ("MDI: With basal"), (2) continuous subcutaneous infusion ("Pump"), (3) MDI with any insulin types excluding glargine and detemir ("MDI: No basal") and (4) 1-2 injections per day of any insulin types ("1-2 injections").

Dietary intake was assessed on average, beginning 3.0 ±2.8 days after the 3CNAS visit using three (two weekday and one weekend day) telephone administered 24-hour dietary recalls assisted by food records. The 24-hour recall food lists were converted into 42 nutritionally meaningful food groups by a collaborative working group that included researchers at the University of North Carolina, Chapel Hill, and the Chinese Institute of Nutrition and Food Safety.[186] Four food groups (plant oils, salt, other spices & condiments, and herbs & other functional foods) were excluded because of the measurement error associated with estimating added oil, salt, and spices, which were not the focus of this analysis. Consistent with previous RRR analyses of non-diabetic Chinese adults,[211] alcohol was excluded because it was only consumed by males. Food groups with <10% consumers (dried vegetables, organ meats, infant formula, lard & butter, candy, other high-sugar foods, sweetened dairy products, calorically-sweetened beverages, and other) were also excluded because of their lack of variability in this sample population. Where appropriate given behavioral and cultural considerations, food groups were combined. These combinations included: starchy tubers & starchy tuber products; beans and bean products; low- and high-beta carotene vegetables; fresh or canned fruit and dried fruit; low- and high-fat meat and meat products; low- and high-fat poultry; and fish and shellfish. A total of 20 food groups were considered for the RRR analysis (**Supplemental Table S5.1**). Most food groups had a large proportion of non-consumers and therefore all food groups were dichotomized for the RRR analysis. Food groups with ≥80% consumers were dichotomized as below versus above the median, and food groups with ≥10% but <80% consumers were dichotomized as non-consumers versus consumers.

5.2.3 Statistical analysis

We used RRR to identify dietary patterns maximizing the explained variation in health indicators.[210] Twenty food groups adjusted for total energy intake using the density method[189] were used as predictors. Two predefined health indicators, HbA1c and LDL cholesterol, log-transformed to improve normality, were used as responses. HbA1c and LDL cholesterol were chosen because they are well established risk factors for CVD and diabetes-related complications in individuals with T1D.[212-219] RRR produces as many factors ("dietary patterns") as there are responses, and consequently two factors were obtained. To characterize the factors, food groups with factor loadings ≥0.25 were considered. Using PLS (partial least squares) procedure in SAS software specifying method = RRR, linear functions of the 20 predictors (known as "dietary pattern scores") were derived which maximized the proportion of explained variation in the set of two responses. These dietary pattern scores were then categorized into tertiles. The explained proportion of score variation was calculated for each food group strongly associated (factor loadings ≥0.25) with the dietary patterns as the product of the standardized score parameter, the correlation coefficient with the dietary pattern score, and 100%. Results are presented in order of decreasing explained proportion of score variation.

In order to improve RRR model fit, a backwards elimination approach was used to reduce the number of predictor variables. The food group that was explained the least by the dietary patterns was eliminated first and the RRR was re-fitted. This procedure was repeated until all food groups with <5% of their variance explained by the dietary patterns, and consequently those that did not load heavily on either factor, were eliminated. Results were largely consistent compared to the full RRR model (20 predictors) with respect to food group loadings and associations with the response variables at this point, and therefore only the nine remaining predictors (rice, wheat products, high-fat cakes, beans & products, nuts & seeds,

pickled vegetables, eggs, fish & shellfish, and low-calorie beverages) were included in the final RRR.

Differences in demographic and clinical characteristics across tertiles of the dietary pattern scores were assessed using chi-square tests for categorical variables and Kruskal-Wallis tests for continuous variables. Furthermore, because sociodemographic characteristics may partially explain observed associations between the RRR-derived dietary patterns and the responses, we calculated mean values of the health indicators across the dietary pattern score tertiles with adjustment for age and household income using ANCOVA. Age and household income were chosen because these variables were independently associated (p<0.10) with both dietary intake and the risk factors (HbA1c and/or LDL cholesterol) in bivariate analyses (data not shown).

After identifying dietary patterns associated with HbA1c and LDL cholesterol, we explored independent, bivariate associations between the food groups identified as being important (factor loadings ≥0.25) in the RRR and each of these risk factors.

Values presented are mean ±SD or n (%). All statistical analyses were conducted in SAS 9.2 (SAS Institute, Cary, North Carolina).

5.3 Results

Dietary pattern 1 was characterized by low intakes of wheat products and high-fat cakes, and high intakes of beans and pickled vegetables (**Table 5.1**). These four food groups together explained 83% of the variation in the first dietary pattern score with the most important contributors being high-fat cakes (36%) and wheat products (33%). Dietary pattern 2 was characterized by low intakes of high-fat cakes, nuts & seeds, fish & shellfish, and low-calorie beverages, and high intakes of rice and eggs. These six food groups together explained 90% of the variation in the second dietary pattern score with the most important contributors being low-calorie beverages (33%) and fish & shellfish (21%).

The first RRR-identified dietary pattern explained 5.9% of the variation in HbA1c, 9.8% in LDL cholesterol, and 7.9% of the total variation in both health indicators. The second dietary pattern explained 7.1% of the variation in HbA1c, 4.2% in LDL cholesterol, and 5.7% of the total variation in both health indicators. HbA1c and LDL cholesterol were not significantly correlated in this sample (Pearson Correlation Coefficient =0.01, p=0.89).

There were few significant differences across tertiles of the dietary pattern scores in terms of sociodemographic and diabetes self-management characteristics (**Table 5.2**). Participants in the highest tertile of dietary pattern 1 score had marginally significantly longer diabetes durations (p=0.09). The significant association observed with insulin regimen was equivocal: participants in the lowest and highest tertile of dietary pattern 1 score were more likely to be on “MDI: With basal” or “pumps,” and less likely to be on “MDI: No basal” or “1-2 injections” compared to participants in the middle tertile.

Participants in the highest tertile of dietary pattern 1 score had significantly higher HbA1c (**Figure 5.1A**) and LDL cholesterol (**Figure 5.2A**) levels compared to participants in the lowest tertile: mean difference in HbA1c was one percentage point and in LDL cholesterol was 0.36 mmol/L after adjustment for age and household income. There were no significant differences in HbA1c or LDL cholesterol in either unadjusted or adjusted analyses across tertiles of dietary pattern 2 score (**Figure 5.1B and Figure 5.2B**).

In bivariate analyses estimating the association between key food groups identified in the RRR analysis and the risk factors (**Table 5.3**), only high-fat cakes were associated with HbA1c: consumers had significantly lower HbA1c compared to non-consumers (p=0.008). Consumers of wheat products had significantly lower LDL cholesterol compared to non-consumers (p=0.03), and consumers of fish & shellfish and low-calorie beverages had marginally significantly higher LDL cholesterol compared to non-consumers (p=0.08 and p=0.05, respectively).

Table 5.1 Food groups strongly associated (factor loadings ≥0.25) with the dietary patterns obtained by reduced rank regression among individuals with type 1 diabetes in China (*n*=99)

Food group	Factor loading	Explained proportion of score variation [1]	Tertile of dietary pattern score [2]			P-value [3]
			1	2	3	
Dietary pattern 1						
High-fat cakes	-0.55	36.0%				
Consumers			15 (47%)	4 (12%)	0 (0%)	<0.0001
Non-consumers			17 (53%)	29 (88%)	34 (100%)	
Wheat products	-0.57	33.2%				
Consumers			26 (81%)	20 (61%)	3 (9%)	<0.0001
Non-consumers			6 (19%)	13 (39%)	31 (91%)	
Pickled vegetables	0.39	8.4%				
Consumers			2 (6%)	8 (24%)	13 (38%)	0.009
Non-consumers			30 (94%)	25 (76%)	21 (62%)	
Beans & products	0.28	5.8%				
Consumers			11 (34%)	14 (42%)	25 (74%)	0.003
Non-consumers			21 (66%)	19 (58%)	9 (26%)	
Dietary pattern 2						
Low-calorie beverages	-0.57	32.9%				
Consumers			26 (79%)	6 (18%)	0 (0%)	<0.0001
Non-consumers			7 (21%)	28 (82%)	32 (100%)	
Fish & shellfish	-0.43	21.3%				
Consumers			25 (76%)	18 (53%)	8 (25%)	0.0002
Non-consumers			8 (24%)	16 (47%)	24 (75%)	
High-fat cakes	-0.41	18.9%				
Consumers			14 (42%)	4 (12%)	1 (3%)	0.0001
Non-consumers			19 (58%)	30 (88%)	31 (97%)	
Eggs	0.31	10.9%				
Consumers			13 (39%)	13 (38%)	24 (75%)	0.003
Non-consumers			20 (61%)	21 (62%)	8 (25%)	
Nuts & seeds	-0.26	0.8%				
Consumers			18 (55%)	16 (47%)	9 (28%)	0.09
Non-consumers			15 (45%)	18 (53%)	23 (72%)	

[1] Calculated as the product of the corresponding standardized score parameter, the correlation coefficient with the dietary pattern score, and 100%

[2] Values are given as n (%)

[3] Chi-square test comparing proportions of consumers and non-consumers of the specified food group across tertiles of the dietary pattern score

Table 5.2 Demographic and diabetes self-management characteristics according to tertiles of dietary patterns obtained by reduced rank regression among individuals with type 1 diabetes in China

	Tertile of Dietary Pattern 1 Score			P-value [1]	Tertile of Dietary Pattern 2 Score			P-value [1]
	1 *n*=32	2 *n*=33	3 *n*=34		1 *n*=33	2 *n*=34	3 *n*=32	
Age (years)	41.5 ±15.1	39.6 ±16.4	44.8 ±16.6	0.45	45.5 ± 14.5	41.3 ± 14.9	39.2 ± 18.5	0.28
Diabetes duration (years)	11.1 ±10.8	9.8 ±7.7	14.7 ±9.9	0.09	13.1 ± 10.9	12.9 ± 9.5	9.6 ± 8.4	0.31
Female								
Female	15 (47%)	13 (39%)	17 (50%)	0.67	16 (48%)	16 (47%)	13 (41%)	0.80
Male	17 (53%)	20 (61%)	17 (50%)		17 (52%)	18 (53%)	19 (59%)	
Highest level of education								
<University	9 (29%)	12 (36%)	10 (29%)		6 (18%)	12 (36%)	13 (41%)	
Junior University	5 (16%)	7 (21%)	4 (12%)	0.70	5 (15%)	5 (15%)	6 (19%)	0.25
≥University	17 (55%)	14 (42%)	20 (59%)		22 (67%)	16 (48%)	13 (41%)	
Household income (RMB/month)								
<3000	6 (19%)	8 (24%)	6 (18%)		4 (12%)	6 (18%)	10 (31%)	
3000 - <5000	8 (25%)	10 (30%)	4 (12%)	0.32	7 (21%)	7 (21%)	8 (25%)	0.52
5000 - <10 000	7 (22%)	9 (27%)	14 (41%)		11 (33%)	12 (35%)	7 (22%)	
≥10 000	11 (34%)	6 (18%)	10 (29%)		11 (33%)	9 (26%)	7 (22%)	
Marital status								
Married/cohabitating	17 (55%)	19 (58%)	22 (71%)	0.38	21 (66%)	19 (59%)	18 (58%)	0.80
Single/divorced/widowed	14 (45%)	14 (42%)	9 (29%)		11 (34%)	13 (41%)	13 (42%)	
Residency status								
Urban	27 (87%)	24 (75%)	30 (91%)	0.18	30 (91%)	26 (81%)	25 (81%)	0.44
Rural	4 (13%)	8 (25%)	3 (9%)		3 (9%)	6 (19%)	6 (19%)	
Insulin regimen								
MDI: With basal	15 (47%)	9 (27%)	17 (50%)		14 (42%)	12 (35%)	15 (47%)	
Pump	3 (9%)	0 (0%)	6 (18%)	0.03	5 (15%)	2 (6%)	2 (6%)	0.58
MDI: No basal	9 (28%)	14 (42%)	7 (21%)		8 (24%)	14 (41%)	8 (25%)	
1-2 injections	5 (16%)	10 (30%)	4 (12%)		6 (18%)	6 (18%)	7 (22%)	
SMBG								
<1 time/week	8 (25%)	15 (45%)	8 (24%)		8 (24%)	14 (41%)	9 (28%)	
1-2 times/week	10 (31%)	8 (24%)	9 (26%)	0.44	8 (24%)	9 (26%)	10 (31%)	0.36
3-6 times/week	4 (13%)	4 (12%)	4 (12%)		3 (9%)	3 (9%)	6 (19%)	
≥1 time/day	10 (31%)	6 (18%)	13 (38%)		14 (42%)	8 (24%)	7 (22%)	

Values are given as n (%) or mean ± SD

[1] Chi-square test for categorical variables and Kruskal-Wallis test for continuous variables

Table 5.3 Bivariate associations of food groups that loaded heavily (loadings ≥0.25) on the reduced rank regression-derived dietary patterns with HbA1c and LDL cholesterol in individuals with type 1 diabetes in China (*n*=99)

	HbA1c (%)	**LDL cholesterol** (mmol/L)
Beans & bean products		
Consumers	8.44 (1.72)	2.43 (0.74)
Non-consumers	8.00 (1.81)	2.37 (0.68)
P-value [1]	0.14	0.67
Pickled vegetables		
Consumers	8.57 (2.12)	2.61 (0.94)
Non-consumers	8.12 (1.65)	2.34 (0.62)
P-value [1]	0.44	0.55
Rice		
Consumers	8.29 (1.66)	2.33 (0.66)
Non-consumers	8.15 (1.89)	2.47 (0.76)
P-value [1]	0.36	0.55
Wheat products		
Consumers	8.10 (1.81)	2.25 (0.70)
Non-consumers	8.34 (1.74)	2.55 (0.70)
P-value [1]	0.37	0.03
High-fat cakes		
Consumers	7.28 (1.12)	2.24 (0.46)
Non-consumers	8.45 (1.83)	2.44 (0.75)
P-value [1]	0.008	0.41
Nuts & seeds		
Consumers	8.02 (1.62)	2.41 (0.62)
Non-consumers	8.38 (1.88)	2.39 (0.78)
P-value [1]	0.30	0.60
Eggs		
Consumers	8.52 (2.12)	2.38 (0.71)
Non-consumers	7.92 (1.28)	2.42 (0.72)
P-value [1]	0.33	0.48
Fish & shellfish		
Consumers	8.13 (1.92)	2.51 (0.69)
Non-consumers	8.33 (1.61)	2.28 (0.72)
P-value [1]	0.37	0.08
Low-calorie beverages		
Consumers	7.87 (1.39)	2.59 (0.64)
Non-consumers	8.39 (1.91)	2.31 (0.73)
P-value [1]	0.23	0.05

Values are given as mean (SD)

[1] Kruskal-Wallis test

Figure 5.1 Mean adjusted HbA1c (%) and 95% confidence intervals from analysis of covariance according to tertiles of A) reduced rank regression-derived dietary pattern 1 score and B) dietary pattern 2 score among individuals with type 1 diabetes in China (*n*=99). Adjusted for age and household income. *p<0.05 comparing 1st and 3rd tertiles

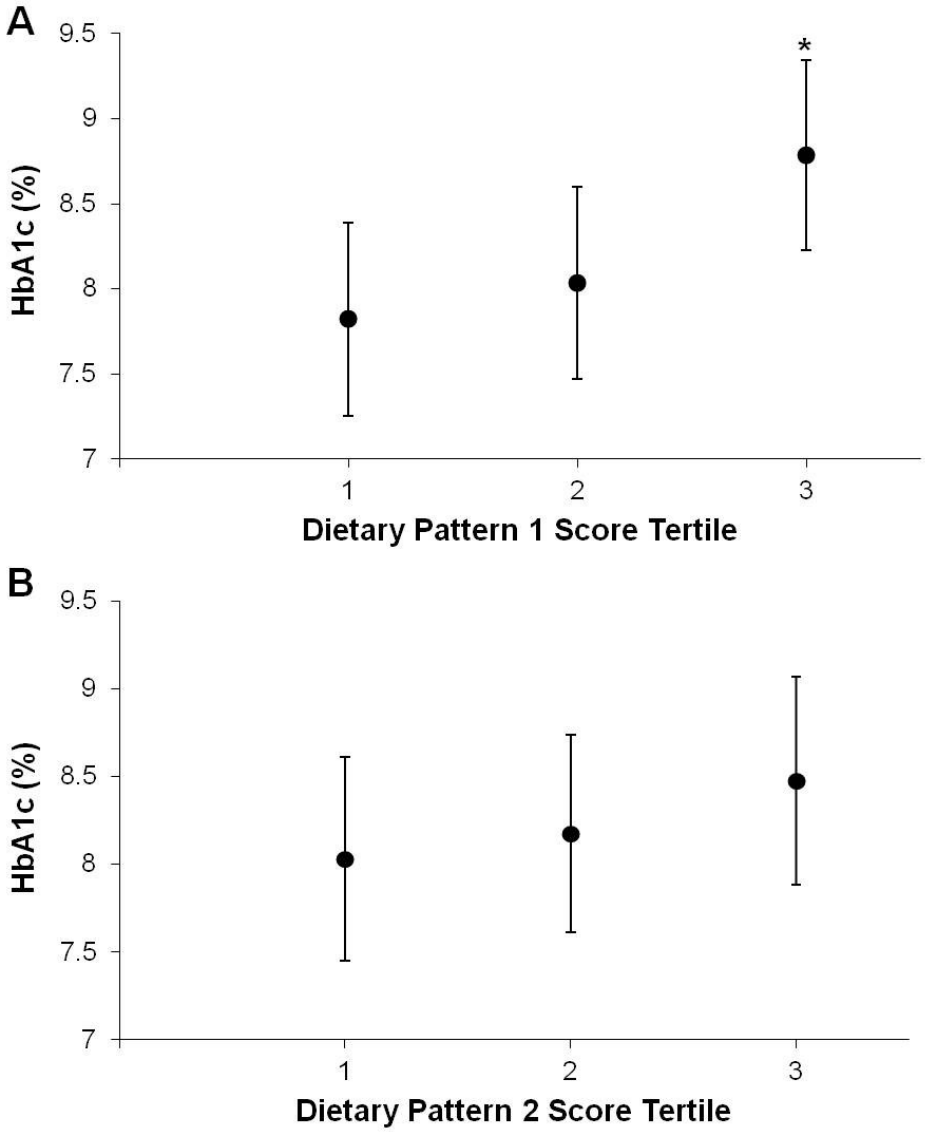
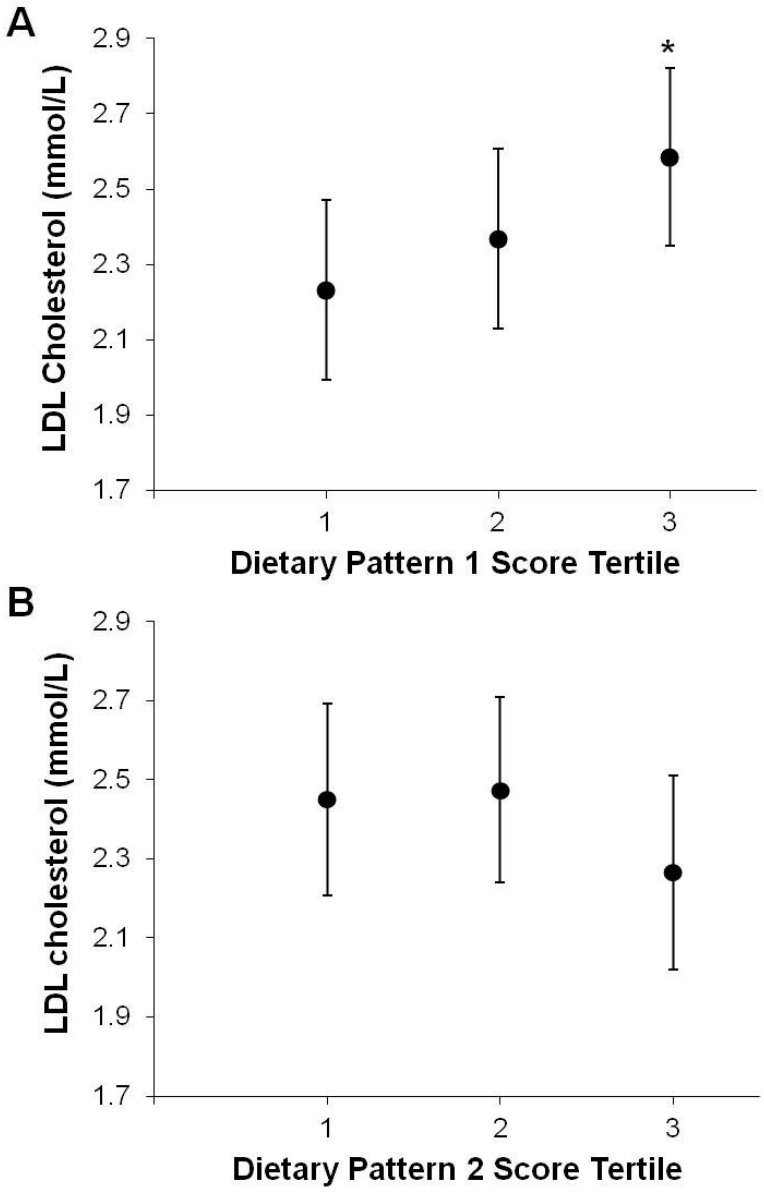


Figure 5.2 Mean adjusted LDL cholesterol (mmol/L) and 95% confidence intervals from analysis of covariance according to tertiles of A) reduced rank regression-derived dietary pattern 1 score and B) dietary pattern 2 score among individuals with type 1 diabetes in China (*n*=99). Adjusted for age and household income. *p<0.05 comparing 1st and 3rd tertiles



5.4 Discussion

We identified a dietary pattern characterized by low intakes of wheat products and high-fat cakes, and high intakes of beans & bean products and pickled vegetables that was significantly positively associated with HbA1c and LDL cholesterol in a cohort of adolescents and adults with T1D in China: the mean adjusted difference between the highest and lowest tertile of the dietary pattern score for HbA1c was one percentage point and for LDL cholesterol it was 0.36 mmol/L. In a meta-analysis of prospective cohort studies, a one-percentage point increase in HbA1c was associated with an increase in CVD risk of 18%,[220] thus this finding is clinically meaningful. Furthermore, a difference in LDL cholesterol of 0.8 mmol/L can move an individual from near optimal to borderline high risk, and therefore our observed difference in LDL cholesterol of approximately 0.4 mmol/L was also clinically important. These observations improve our understanding of dietary factors influencing CVD risk among individuals with T1D living in a country undergoing rapid changes in nutrition and health.[221,222]

Participants in the highest tertile of the dietary pattern 1 score were more likely to be consumers of pickled vegetables, which tend to be high in salt, and these participants also had higher HbA1c and LDL cholesterol levels. This is consistent with a study reporting an association between consumption of salted food and hyperlipidemia among Chinese men,[223] and a recent study linking dietary sodium prospectively with end-stage renal disease and mortality in Finnish adults with T1D.[224]

Interestingly, low intakes of high-fat cakes was an important aspect of dietary pattern 1, which was ultimately associated with poor risk factor status. Indeed, “high-fat cakes” was the only food group significantly associated with HbA1c in bivariate analyses. This observation makes sense given that nearly all T1D patients in China report having been told to limit their sweet intake (for example, desserts, non-diet sodas, and candy), and “sugarless” products are increasingly available at food retailers in China. Individuals that adhere to recommendations may choose sugarless cakes that are high in fat over low-fat cakes that are high in sugar. While

not statistically significant, a greater proportion of low-fat cake consumers were in the highest tertile of dietary pattern 1 (and therefore had lower high-fat cake intakes): 45% compared to 26% in the lowest tertile of dietary pattern 1. Together, these observations may explain the inverse association between high-fat cake consumption and HbA1c in this analysis.

In contrast to a small (*n*=12) crossover dietary intervention trial of a soy diet in young adults with T1D and hyperfiltration (defined as glomular filtration rates >120 mL/min/1.73m^2),[225] and a meta-analysis of intervention trials in adults without T1D,[226] which both found a soy-based diet high in isoflavones reduced LDL cholesterol, we found that a dietary pattern characterized by high bean & bean product (tofu) intakes was associated with higher LDL cholesterol and HbA1c. This result was unexpected, though it is important to consider that only 5.8% of the variability in the dietary pattern score was explained by this food group. More research is needed to understand the effects of bean & bean product intake on health in this population.

To our knowledge, only one study has derived dietary patterns using RRR in a population of individuals with T1D.[227] Using data from the SEARCH for Diabetes in Youth Study, a dietary pattern characterized by high intakes of eggs, sweetened coffee and tea, sweetened soda/fruit-flavored drinks, diet soda, potatoes, and high-fat meat, and low intakes of sweets/desserts and low-fat dairy was positively associated with markers of CVD risk (LDL cholesterol, triglycerides, systolic blood pressure, HbA1c, C-reactive protein, and waist circumference).[227] The differences observed between this dietary pattern and the dietary pattern derived in our analysis are likely the result of a combination of factors including different sample populations (different continent of residence, age, and disease duration), different response variables (disease biomarkers), and different predictor variables (due to cultural differences in dietary intake). Nonetheless, the similarities are worth mentioning here, particularly the high intakes of eggs, which was an important food group in both studies. Evidence relating egg consumption to CVD risk is equivocal: while a recent meta-analysis found that egg consumption is related to increased risk of coronary heart disease among adults with T2D (relative risk [95%

confidence interval] comparing highest and lowest egg intake 1.54 [1.14, 2.09]), there was no association among non-diabetic adults.[228] More research on dietary patterns in diverse populations is needed to improve our understanding of the effects of foods and beverages on disease outcomes.

The objective of RRR is not to describe dietary patterns that reflect either dietary recommendations or cultural patterns described in the literature, but rather to identify dietary patterns important in the development of disease. Nonetheless, an important challenge of interpreting this analysis is that the dietary patterns identified by RRR do not necessarily represent patterns of foods and beverages actually eaten together in the sample population. Furthermore, this study was cross-sectional and we cannot rule out reverse causality: the process of recording and recalling dietary intake could differentially affect reporting between those at high-risk and those at low-risk of CVD. However, purposeful dietary misreporting may be uncommon in China.[153] In our study, these biases were addressed by using interviewers who were not the participants' healthcare providers and training them to use a standardized protocol and neutral probes,[159] as well as emphasizing in conversations with participants that we were interested in understanding what individuals with T1D usually eat and that it was important that they not change their dietary habits. Another limitation of this study is the small sample size, which limits the generalizability of our findings. However, this is the largest sample of individuals with T1D in a developing country for which comprehensive dietary data are available, and therefore these results provide invaluable insight into potential areas for future research.

In summary, a dietary pattern was identified that is strongly related to two established risk factors for serious, chronic complications of T1D. These findings provide support for development of behavioral strategies to prevent complications including CVD in adolescents and adults with T1D in China.

5.5 Supplemental tables

Supplemental Table S5.1 Food groups consumed by individuals with type 1 diabetes in China included in the reduced rank analysis

Food group	Examples of foods included	Consumers n (%)
Rice	Rice	94 (95%)
Wheat products	Noodles, buns (*baozi*), breads (*shaobing*)	98 (99%)
Low-fat cakes	Cakes with <15 g fat/100 g cake such as fruit cakes, “Royal style” cakes, sesame seed cookies, *sachima*, and soda biscuits	31 (31%)
High-fat cakes	Cakes with ≥15 g fat/1000 g cake such as “Mooncakes”, walnut cookies (*taosu*), pastries	19 (19%)
Deep-fried foods	Deep-fried dough sticks (*youtiao*)	23 (23%)
Corn & products	Fresh corn, corn grits, corn flour	45 (45%)
Tubers & products	Potato, cassava, lotus root, starchy root flours and noodles	58 (59%)
Beans & products	Soybean, kidney bean, broad bean, soybean curd (*tofu*)	80 (81%)
Nuts & seeds	Walnuts, peanuts, sesame seeds	43 (43%)
Vegetables	Carrot, tomato, broccoli, bok choi, radishes, eggplant	99 (100%)
Pickled vegetables	Preserved radish, preserved cabbage	23 (23%)
Fruit	Apples, peaches, watermelon, bananas, lychee, dates	65 (66%)
Fungi & seaweed	Mushrooms, wood ear fungus, kelp	57 (58%)
Meat & products	Beef, mutton, pork, sausages	93 (94%)
Poultry	Chicken, duck	29 (29%)
Eggs	Chicken eggs, quail eggs	91 (92%)
Fish & shellfish	Carp, shrimp	51 (52%)
Milk & products	Liquid milk, powdered milk, yogurt, cheese	82 (83%)
Fast food	Chicken fillet burger (KFC); French fries (KFC); frozen dumplings; instant noodles; breakfast cereals	60 (61%)
Teas & coffee	Coffee, Green tea, Jasmine tea	32 (32%)

CHAPTER 6: CHALLENGES

Several challenges were faced in conducting 3CNAS and are divided into two broad categories: 1) challenges relating to data collection and 2) challenges relating to data analysis. Within data collection, getting institutional review board (IRB) approval from our collaborating institution in China (Peking University Health Science Center) was the first barrier to moving forward on the project. Difficulties were also encountered with recruitment, dietary intake assessment via telephone interview, and converting the 24-hour recall food lists into nutrients. In regards to data analysis, the small sample size, selection bias, and the dietary pattern analysis were key areas requiring additional consideration. Each of these challenges is discussed in detail in the sections that follow.

6.1 Data collection

6.1.1 Institutional Review Board approval

In September 2013, Tufts University issued a statement that a study published in the *American Journal of Clinical Nutrition* in August 2012 in which researchers fed children in Hunan province, China, genetically modified rice ("golden rice") had violated Federal rules governing human research.[229] Tufts' IRB concluded that the Principal Investigator of the study had not provided sufficient evidence that the study had been reviewed by an ethics review board in China; some of the consent forms had not been obtained prior to the study start; some of the dates on the consent forms had been changed; some of the consent forms were inappropriately signed; and none of the consent forms included the phrase, "genetically modified."[229]

Given this situation, it was not surprising that we ran into difficulties getting IRB approval from our collaborating institution in China as we began the process in the fall of 2012. Although our study was only observational, it involved children (<18 years old) and the Peking University Health Science Center IRB required a full board review. Furthermore, written consent (participants ≥18 years old) or written assent and parent permission (participants <18 years old) was required, even for the Relative Validity Study, which simply involved completing two 24-hour recalls (one over the telephone and one in-person at the hospital). The process was particularly baffling because there were no clear guidelines as to what qualified for expedited review or when oral consent would be acceptable. Thus, we could not anticipate the IRB's comments and prepare our application accordingly. Ultimately, to prevent any further delays in study start (we began the IRB application process in November 2012, and still had not received approval from Peking University by January 2013), we decided to split the study into three distinct parts: 1) Adult Relative Validity Study, 2) Adolescent Relative Validity Study, and 3) Main Study in Adults and Adolescents. The Adult Relative Validity Study received approval from Peking University by expedited review at the end of January 2013, while the Adolescent Relative Validity Study and Main Study in Adults and Adolescents required full board review at the end of February 2013 (delayed due to Spring Festival). Following this meeting, the Peking University IRB asked our permission to share the Chinese versions of our consent forms with other researchers; these forms are now available as a template for scientists in China, a small but important contribution to the future protection of human research subjects and efficiency of the application process.

6.1.2 Recruitment

6.1.2.1 Following up with 3C Study participants

A common barrier to all longitudinal follow-up studies is not being able to contact participants. 3CNAS was designed as a follow-up study to the 3C Study because of efficiency (it would have been time consuming to recruit participants directly from the outpatient clinic as was done in the 3C Study), and because it will allow researchers to look at *change* in key variables such as HbA1c. However, a large proportion of participants originally enrolled in the 3C Study did not provide a telephone number (especially the adolescents) or the telephone number they did provide was no longer in service. Of *n*=443 Beijing 3C Study participants ≥12 years old, we were not able to contact *n*=233 (52.6%) due to lack of in-service telephone number. Therefore, approximately one-fifth of participants were lost to follow up simply because their telephone numbers were no longer in service. Future studies could include additional contact information, for example, telephone numbers for relatives or employers, to improve researchers' ability to stay in contact with participants.

6.1.2.2 Type 1 diabetes stigma

Another significant barrier to recruitment was the stigma associated with T1D in China. Recent results of the second Diabetes Attitudes, Wishes and Needs (DAWN2) study indicated that 19.1% of participants from China reported being discriminated against because of their diabetes, compared to 10.6% of participants from the United States.[230] However, the majority of DAWN2 participants had T2D,[230] an increasingly common disease,[112] whereas T1D remains relatively rare.[101] We therefore suspect that the proportion of individuals with T1D who are discriminated against is much higher: as with many relatively rare diseases in China (for example, epilepsy),[231] individuals who are diagnosed with T1D are considered 'monsters' by

society. One parent of a child with T1D told us: 'type 1 diabetes in China is not like in the U.S. because there are so few people with it here and if anyone finds out that my daughter has it they will think she is strange.'

Structural discrimination—institutional practices that result in disadvantage for stigmatized groups—by schools and employers is pervasive in China. For example, there is a government regulation stating that individuals with 'severe endocrine and metabolic diseases' should not be admitted to universities or junior colleges,[232] or employed by the government. As a result, individuals hide their diabetes in order to 'save face' and gain acceptance to schools, or government employment; a coping strategy similar to that observed among individuals with schizophrenia and AIDS in China.[233,234] One man with T1D told us that he does not use his government medical insurance card and pays for all of his diabetes care out-of-pocket because he does not want his name associated with the disease.

While designing 3CNAS, we were not aware of the severity of the stigma associated with T1D in China or the general population's lack of trust in doctors conducting medical research (perhaps due to recent reports of doctors accepting bribes from pharmaceutical companies).[235] Looking ahead to future research, integration of study visits with semi-annual check-up visits for T1D may improve response rates. However, this would require an expanded recruitment and enrollment period as well as inclusion of many data collection sites (e.g. including all hospitals where patients receive their usual care).

6.1.3 Dietary assessment

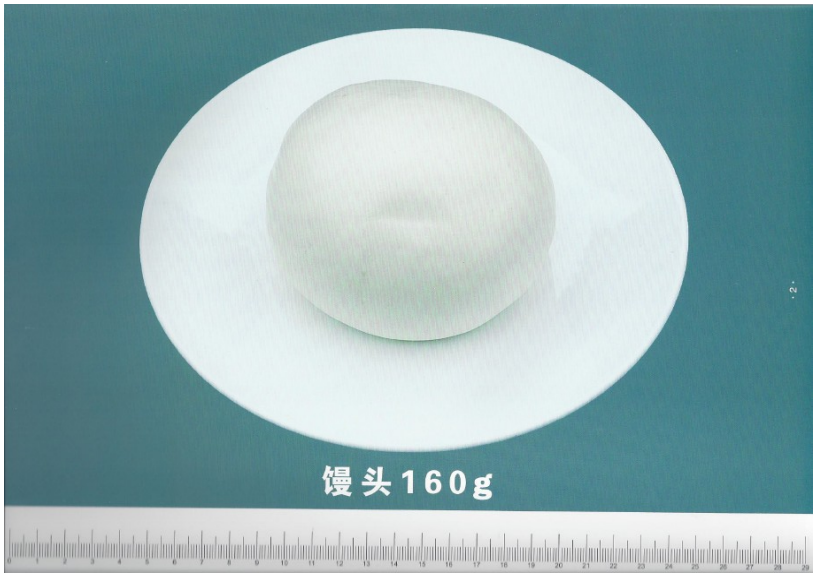
The severe stigma associated with T1D in China also precluded our ability to go to the participants' houses in order to collect dietary data, as has been done in other studies in China.[186] Because it would have been burdensome for participants to travel to the hospital on three separate occasions to complete the three 24-hour recalls required to estimate usual

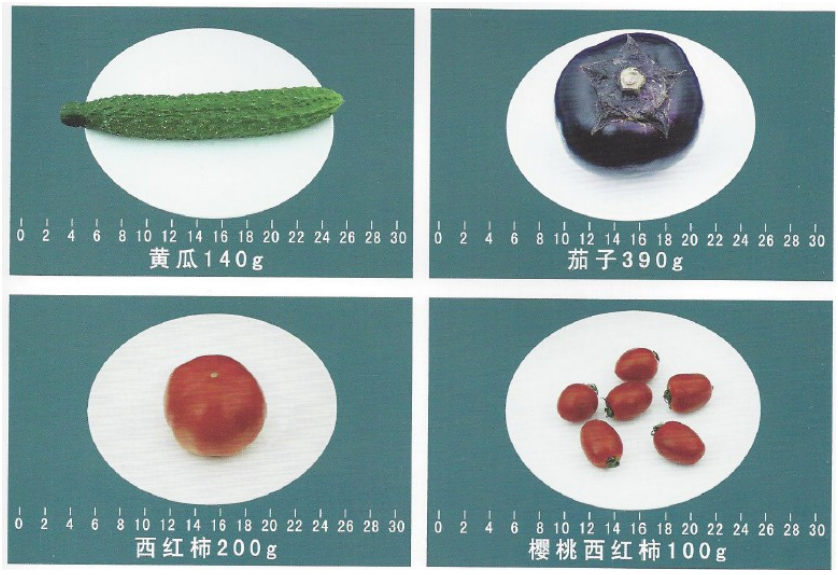
dietary intake for the sample population,[236] we had to administer the 24-hour recalls via telephone interview. A critical strength of this study was that we assessed the relative validity of this administration method against in-person administration in a subset of participants prior to beginning data collection for the larger cohort.

One of the biggest difficulties and likely sources of measurement error in 3CNAS and in most observational studies of dietary intake is estimation of portion sizes.[237] What is a "typical" portion size for any given food varies between countries, within countries, and over time. Therefore, it was essential that we integrate discussion (in Mandarin, the participants' native language) of culturally appropriate food models and pictures (**Figure 6.1**) into the in-person visit with a trained clinical dietitian. While two-dimensional food pictures have been shown to be as helpful as three-dimensional food models in estimating portion sizes in 24-hour recalls,[238] portion size estimates based off of food pictures appear to be more accurate (e.g. closer to weighed portion sizes) when there is greater concordance between the food picture and the actual food consumed.[239] This is why it was essential to develop a food picture guide specific to the diets of participants in northern China.

An added difficulty with estimating portion sizes in China was the fact that "family style" meals, in which food is directly consumed from a common dish, were common. This rendered ineffectual the plate diagrams typically used to estimate portion sizes in Western settings. To overcome this barrier, we asked participants to estimate what proportion of the total recipe they consumed.

Figure 6.1 Examples of culturally appropriate portion size picture guides from book given to 3C Nutrition Ancillary Study participants in their Introductory Packet





Related to this, given the limited scope of the Chinese Food Composition Tables,[151,152] we had to probe for each ingredient of complex recipes. Because the focus of this study was not salt, and because of the inherent errors in estimating spices added to recipes, we did not probe specifically for these ingredients. However, we did probe specifically for oil (type and amount), other sauces (e.g. soy sauce), vegetables, starches (e.g. wheat noodles), and proteins (e.g. pork, soybean curds). This was especially difficult when participants consumed food outside the home and did not directly observe the food preparation. This challenge is not limited to our study, and will be an important area to address in future dietary assessments in rapidly developing countries such as China where food consumed away from home is increasingly common.[240]

6.1.4 Conversion of food lists into nutrients

The 2009 Chinese Food Composition Tables[151] contain approximately 1500 different food items, compared to over 18,000 food items contained in the University of Minnesota Nutrition Coordinating Center's Nutrition Data System for Research.[241] The direct implication of this limited range of options was that we had to develop a set of rules for entering codes associated with each food reported by participants (the codes were then used to determine the nutrient composition of the corresponding food). For example, several participants reported consuming a newly formulated product, whole-wheat *mantou* (bun), for which there was no food code. After consulting with two Chinese nutrition specialists, we decided to use the food code for "standard wheat *mantou*" for any whole-wheat *mantou* and "average *mantou*" for any non-whole-wheat *mantou*. Other examples of substitutions included: "chicken broth" for "fish broth," "peanut oil" for "chili oil," "beef tenderloin" for "beef backstrap," and "raisin" for "dried cranberry."

Another limitation of the Chinese Food Composition Tables[151,152] was that they did not include separate codes for "raw" and "cooked" for all foods. Therefore all vegetable portion sizes that were reported as cooked had to be converted to raw, and all rice portion sizes reported as

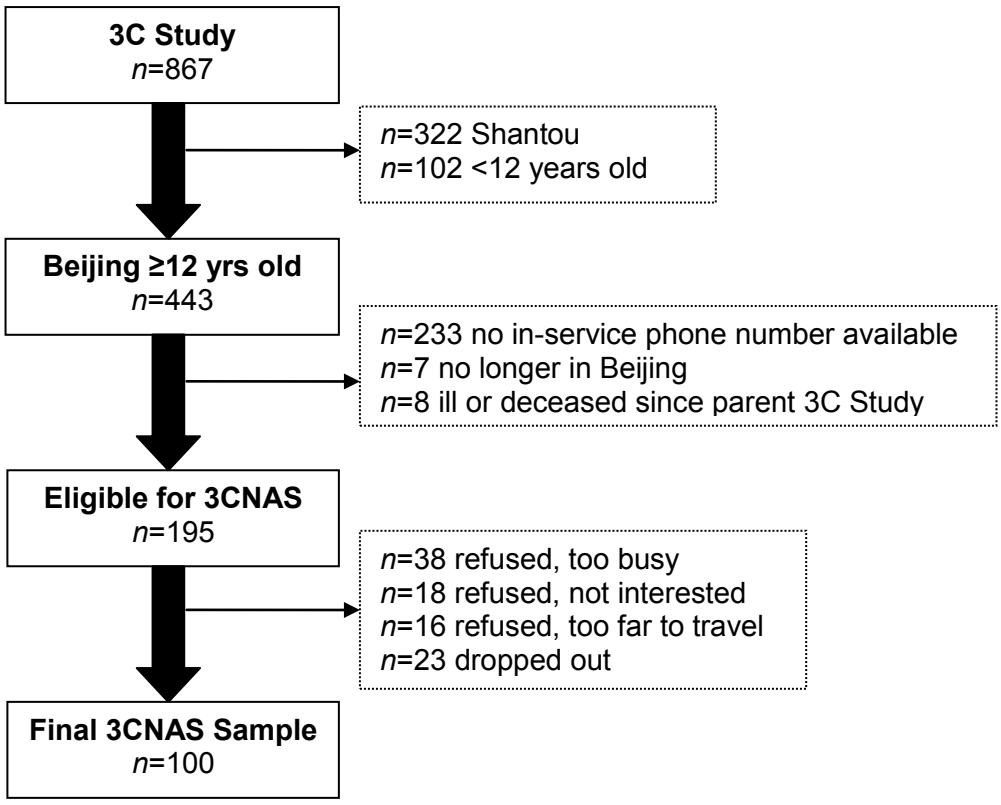
uncooked (grains without water) had to be converted to cooked (with water). While this was a time consuming task that assumed constant cooked: uncooked ratios across participants, it had the advantage of allowing us to directly compare food group intakes in absolute amounts (grams) between participants.

6.2 Data analysis

6.2.1 Small sample size

In the proposal for 3CNAS, we assumed an enrollment rate of approximately 50% and a sample size of *n*=54 <18 years old and *n*=100 ≥18 years old. Despite the integration of several elements to improve study enrollment (e.g. recruiting from hospital telephone, 20 RMB travel reimbursement + 50 RMB mobile phone gift card + test results as an incentive for adults, and additionally a glucometer for adolescents), the final sample size was only *n*=10 <18 years old and *n*=90 ≥18 years old, for reasons discussed previously (**Section 6.3**) and summarized in **Figure 6.2**. Several implications of this small sample size for data analysis are discussed in detail in the sections that follow.

Figure 6.2 Participant flow in the 3C Nutrition Ancillary Study



6.2.1.1 Implications for subgroup analyses within 3CNAS

The proposed data analysis plan for 3CNAS involved stratification of all results by age: <22 years versus ≥22 years. The age of 22 years was chosen as a cut-point after preliminary recruitment results indicated that it would be difficult to achieve an adequate sample size with a cut-point of 18 years, and because at the age of 22 years in China, young adults tend to move out of their parents' house and transition into independent living; a very important period for diabetes self-management as responsibility shifts entirely to the patient with T1D. However, even with this new cut-point, the sample size was small for the younger age group: only *n*=14 participants were <22 years old, hence, we did not stratify results by age.

Another important effect modifier of interest was insulin regimen because dietary recommendations for T1D management are specific to an individual's insulin regimen and differ between flexible, basal-bolus regimens and fixed regimens.[195] While we evaluated four insulin regimen categories (MDI: With basal, Pump, MDI: No basal, and 1-2 injections) for the analyses presented in **Chapter 3**, we combined "MDI: With basal" with "Pump" and "MDI: No basal" with "1-2 injections" to create two categories for **Chapter 4** (Basal-bolus and Fixed) to improve power and interpretability of results (ISPAD nutrition recommendations, for example, focus on "conventional" or fixed insulin regimens versus basal-bolus including pumps).[195] A larger sample size would have improved our ability to detect differences in effect across these important subgroups, and the fact that significant effects were observed despite the relatively small sample size suggests strong differences warranting further research.

A specific example of insulin regimen as an effect modifier was explored as a sensitivity analysis to the dietary exposure-cardiometabolic risk factor outcome analyses presented in **Chapter 5** (RRR). This particular sensitivity analysis was conducted because we hypothesized that participants with less intensive insulin regimens (e.g. 1-2 injections/day) may be more vigilant about following prescribed eating plans and more reliant on diet to control their diabetes, and therefore we may see a stronger association in these participants relative to participants on

more intensive insulin regimens (e.g. pumps). However, after excluding participants with 1-2 injections/day, the bivariate associations between the food groups and health outcomes (HbA1c and LDL cholesterol) were the same except that the association between fish & shellfish and LDL cholesterol was no longer marginally significant (p=0.08 when all participants were included, p=0.21 after exclusion of participants on 1-2 injections/day). It was interesting that results remained after adjustment with only slight attenuation. This could be because participants with MDI but no basal were also relying heavily on diet (because we did not exclude all participants not using basal, only those on 1-2 injections/day without basal). Alternatively, it may indicate that being on a less intensive insulin regimen does not influence underlying diet-disease relationships. Taking into account the totality of our 3CNAS analyses, we suspect that all participants regardless of insulin regimen are depending on diet more heavily than in high-income countries such as the United States. Stratification by insulin regimen would have been a more appropriate method to answer this question than exclusion, but the limitation of a small sample size precluded our ability to conduct such an analysis.

6.2.1.2 Implications for comparing 3CNAS to SEARCH for Diabetes in Youth

Because of the differences in age distribution between the final 3CNAS sample and the SEARCH for Diabetes in Youth cohort study, we were not able to compare the dietary intakes of individuals with T1D in China with the dietary intakes of individuals with T1D in the United States as originally proposed. Results of such a comparison would not only improve our understanding of diabetes care in China relative to diabetes care in the United States, but also inform personalized chronic disease care for Asian Americans via integration of sociocultural context. The relatively small number of Asians with T1D in the United States precludes our ability to study this group: among T1D cases incident in 2002-2003 (n=1902 total) in SEARCH, only n=56 (2.9%) were Asian.[242,243] Thus, this would have been an ideal context for developing

population-specific guidelines. Given that few other large cohort studies of T1D have dietary data (e.g. T1D Exchange), additional primary data collection may be needed before these important questions can be addressed.

6.2.2 Selection bias

The collapse of the commune-supported Cooperative Medical System in 1982 and the subsequent privatization of 'barefoot doctors' (a.k.a. 'village doctors') has created a substantial gap in access to care between urban and rural areas in China.[244,245] Indeed, preliminary analysis of the 3C Study has revealed large urban-rural disparities in care with more urban areas experiencing improvements in SMBG and insulin regimens over the past 10 years while treatment remains substandard in more rural areas.[125] This has important implications for the external validity or generalizability of our results, which are based on a largely urban sample and therefore may not be applicable to rural T1D populations. We attempted to address this limitation by expanding our in-person visits to include a hospital in Pinggu District at the extreme eastern end of Beijing, a more rural area. A total of n=16 participants living in Pinggu who previously declined to participate in 3CNAS because it was 'too far to travel,' agreed to participate when visits were held at the hospital in Pinggu. Combined with the n=3 participants living in Pinggu who agreed to travel to Peking University People's Hospital (where all other visits were held), nearly 20% of our sample was from this relatively rural District of Beijing.

In order to understand the degree to which our sample was comparable to participants that 1) were eligible and 2) refused to participate or dropped out, we conducted a sensitivity analysis, the results of which are presented in **Table 6.1**. Compared to participants who refused to participate or dropped out, our sample was older and more likely to be married or cohabitating (versus single, divorced, or widowed) (all p<0.05). Compared to Beijing 3C Study participants ≥12 years old who were not eligible due to not having a phone number in service, no longer living in Beijing, or being ill or deceased since the parent 3C Study, our sample was

older, more likely to be married or cohabitating, more likely to be retired or unemployed or never worked, less likely to be a student, and more urban (all $p<0.05$).

Table 6.1 External validity of 3C Nutrition Ancillary Study

	3CNAS *n*=100	**Refusals and Drop-outs** [1] *n*=95	**Not Eligible** [2] *n*=248	**P-value** [3]	**P-value** [4]
Age (years)	40.1 (16.2)	32.0 (16.8)	26.3 (15.2)	0.001	<0.001
Diabetes duration (years)	10.2 (9.7)	9.8 (10.4)	8.9 (10.3)	0.78	0.27
Male	54 (54%)	41 (43%)	113 (46%)	0.13	0.15
Residence					
Urban	82 (85%)	74 (79%)	168 (69%)	0.30	0.003
Rural	15 (15%)	20 (21%)	77 (31%)		
Highest level of education					
<University	32 (32%)	35 (37%)	104 (42%)	0.79	0.09
Junior University	16 (16%)	15 (16%)	47 (19%)		
≥University	51 (52%)	45 (47%)	95 (39%)		
Household income (RMB/month)					
<3000	20 (20%)	27 (28%)	78 (31%)	0.05	0.18
3000 - <5000	23 (23%)	23 (24%)	48 (19%)		
5000 - <10,000	30 (30%)	34 (36%)	69 (28%)		
≥10,000	27 (27%)	11 (12%)	53 (21%)		
Occupation					
Worker (non-government)	31 (31%)	25 (27%)	64 (26%)	0.06	<0.001
Worker (government)	17 (17%)	13 (14%)	14 (6%)		
Student	17 (17%)	33 (35%)	113 (46%)		
Farmer	7 (7%)	5 (5%)	8 (3%)		
Retired/unemployed	28 (28%)	17 (18%)	45 (18%)		
Marital status					
Married/cohabitating	58 (60%)	40 (44%)	85 (34%)	0.02	<0.001
Single/divorced/widowed	38 (40%)	51 (56%)	163 (66%)		

Values are given as mean (SD) or n (%)

[1] Eligible participants that refused to participate or dropped out before the in-person visit

[2] 3C Study participants residing in Beijing and ≥12 years old who were not eligible due to not having a phone number in service, no longer living in Beijing, or being ill or deceased since the parent 3C Study

[3] Chi-square test (categorical variables) or ANOVA (continuous variables) comparing 3CNAS sample to Refusals and Drop-outs

[4] Chi-square test (categorical variables) or ANOVA (continuous variables) comparing 3CNAS sample to those Not Eligible

6.2.3 Dietary pattern analysis

Dietary pattern analysis is an emerging method used to capture holistic dietary exposures in nutritional epidemiology studies.[210] Because dietary patterns allow nutrient interactions, some have argued that they better represent dietary intake and improve prediction of disease. Especially in the case of international studies, dietary patterns have the additional advantage that they do not rely on food composition databases, which assume that the nutrient composition of foods is constant and that the data provided by laboratory analyses are accurate and reflect current food composition.

There are also several criticisms and limitations of dietary pattern analysis. Subjectivity can be introduced when, for example, in principal component analysis, one must decide the number of factors to retain and the criteria for retention (such as eigenvalue cut-points) and whether to use rotation (and if so, what type of rotation). Furthermore, it is difficult (and often impossible) to determine the underlying biological and physiological mechanisms responsible for the observed effects. This is an especially important challenge for RRR, the dietary pattern analysis technique used in 3CNAS, because the association observed with the biomarkers is the result of the specific combination of dietary factors, not any one dietary factor. This is where nutrient-based or food group-based analyses are useful for testing specific hypotheses relating to the contribution of certain dietary components to disease outcomes.

There were several challenges specific to the RRR analysis used in 3CNAS discussed in detail in the sections that follow: 1) specification of predictor variables (food groups), 2) selection of predictor variables (food groups), and 3) selection of response variables (biomarkers).

6.2.3.1 Specification of predictor variables

Most dietary pattern analyses are conducted in large cohort studies that used food frequency questionnaires to collect dietary data. However, we used 24-hour recalls to collect

dietary data. One important implication of this was that we had several food groups with very few consumers, and therefore the distribution of the food group intake in the sample was non-normally distributed. To our knowledge, only one other dietary pattern analysis has encountered and addressed this problem, a study conducted using CHNS data.[246]

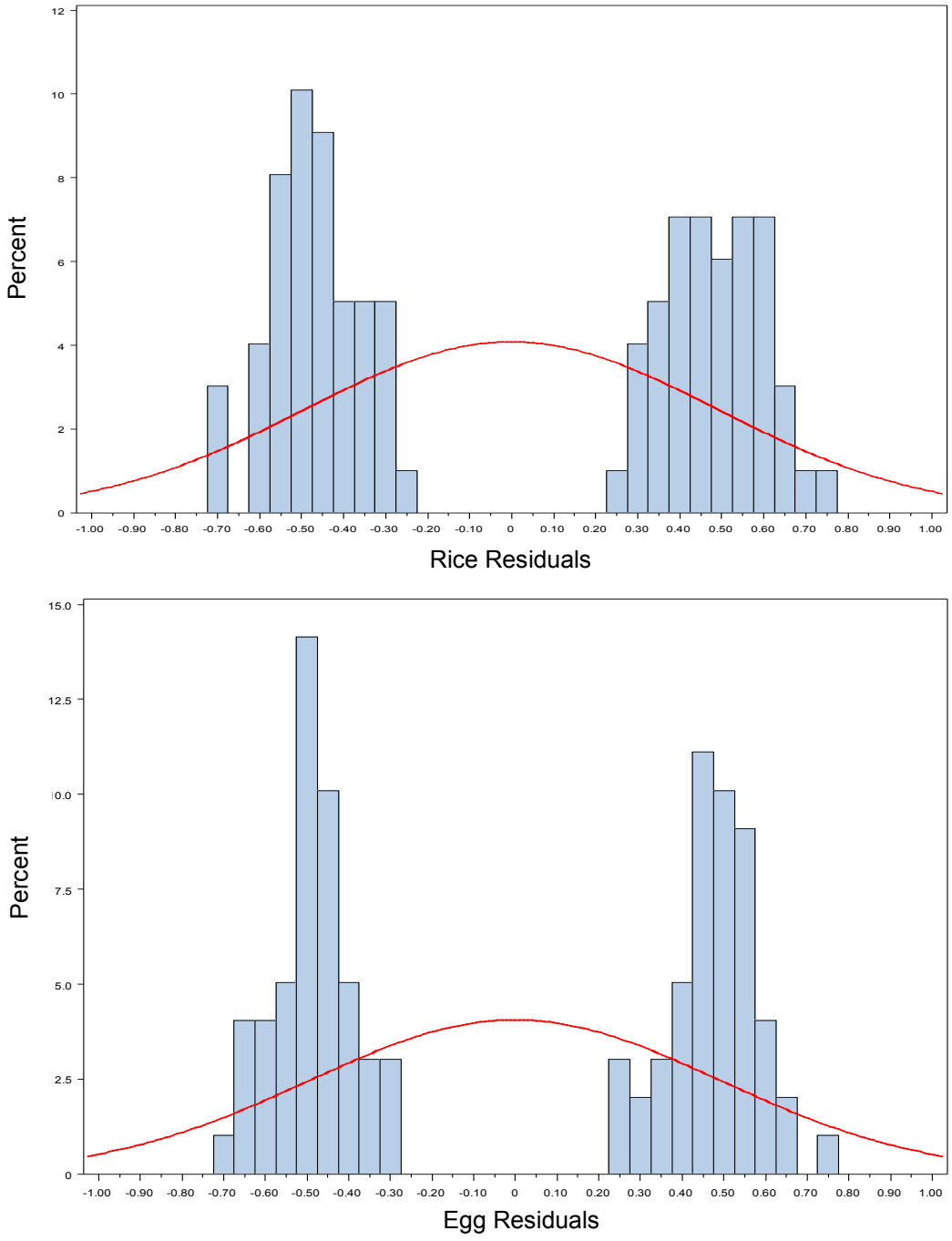
The Pearson's correlation matrix used in RRR was robust to modeling one binary and one continuous variable, though using a mixed set of predictors (e.g. binary and continuous food groups) would have been difficult as it would have required two different correlation matrices. With these considerations in mind, we decided to specify all of the predictor variables (food groups) as binary variables, keeping the response variables (biomarkers) continuous.

Another important issue when specifying the predictor variables was adjustment for energy intake. Two approaches are generally used to adjust for energy intake in RRR: 1) specify food groups as energy densities or 2) calculate residuals.[247,248] For continuous variables, the residuals are the amount consumed not explained by the variables included in the residual model (e.g. total energy intake), and for dichotomous variables, the residuals can be defined as the difference between the consumption predicted by the variables included in the residual model (e.g. total energy intake, and in some cases, other confounding variables) and the actual (0 or 1) consumption. The difficulty with the latter of these is that the resulting residuals are continuous, but their distribution is often closer to bimodal than normal.

To verify this in our dataset, we used a series of logistic regression models to estimate the predicted probability of being a consumer of the food group (food groups with <80% consumers) or being a consumer above the median of the food group (food groups with ≥80% consumers) given energy (continuous, kcal/day), age (continuous, years), and income (categorical). The residuals were then calculated as the difference between the observed value for the food group (0 or 1) and the predicted probability (between 0 and 1) estimated by the logistic regression model. As predicted, the distribution of the residuals for all food groups was

bimodal (**Figure 6.3**). It was therefore determined that this approach would not work for RRR, which requires continuous predictor variables to be normally distributed.

Figure 6.3 Examples of bimodal distribution of residuals calculated for two food groups: a) rice and b) eggs



6.2.3.2 Selection of predictor variables

Another challenge, also stemming from the small sample size, was reducing the number of predictors (food groups) because factor analysis requires a sample size of 10-30 per predictor variable, with the range primarily reflecting level of communality between predictor variables and number of factors to be determined.[249] Overdetermined factors (e.g. factors that exhibit high loadings on at least 3-4 variables and simple structure) are a goal of factor analysis, particularly in this study as sample size may have less impact on the quality of results when factors are highly overdetermined.[249]

Given our sample size of n=99 and n=2 factors (RRR produces as many factors as there are response variables), we could have, at the most, 10 predictor variables (food groups) and still meet these sample size considerations. We used a backwards elimination procedure to reduce the number of predictor variables. The food group that was explained the least by the dietary patterns was eliminated first and the RRR was re-fitted. This procedure was repeated until all food groups with <5% of their variance explained by the dietary patterns, and consequently those that did not load heavily (≥0.25) on either factor, were eliminated. Results were largely consistent compared to the full RRR model (20 predictors) with respect to food group loadings and associations with the response variables at this point (**Table 6.2**). Particularly for the first dietary pattern, results were robust: there was very little change in the factor loadings from 20 food groups to 9 food groups. The results for the second dietary pattern were different in that the sign (positive versus negative) of key food groups "flipped." However, the direction of the associations with the response variables also "flipped," thus the interpretation was consistent. There were a couple of minor differences for the second dietary pattern, namely that high-fat cakes and nuts & seeds loaded more heavily when food groups were eliminated, but these food groups were close to the cutpoint of 0.25 when 20 food groups were included.

Table 6.2 Factor loadings for food groups that loaded heavily (factor loading ≥0.25) on dietary patterns derived using reduced rank regression after backwards elimination of food groups

	All food groups (20)	Drop fungi (19)	Drop fungi + fruit (18)	Drop fungi + fruit + veges (17)	Drop fungi + fruit + veges + poultry (16)	Drop fungi + fruit + veges + poultry + corn (15)	Drop fungi + fruit + veges + poultry + corn + meat (14)
Dietary Pattern 1							
Negative loadings							
High-fat cakes	-0.60	-0.61	-0.61	-0.61	-0.61	-0.61	-0.62
Wheat products	-0.44	-0.40	-0.40	-0.42	-0.42	-0.42	-0.42
Positive loadings							
Pickles	0.34	0.31	0.32	0.33	0.33	0.33	0.33
Beans & products	0.31	0.32	0.32	0.32	0.32	0.32	0.32
Eggs	0.25	0.27	0.27	0.27	0.27	0.27	0.27
Dietary Pattern 2							
Negative loadings							
Wheat products	-0.33	-0.38	-0.38	-0.37	-0.37	-0.38	-0.38
Rice	-0.25	-0.25	-0.25	-0.25	-0.25	-0.25	-0.26
Positive loadings							
Low-calorie beverages	0.55	0.56	0.56	0.56	0.56	0.57	0.57
Fish & shellfish	0.44	0.45	0.45	0.45	0.46	0.46	0.46

Table 6.2 Continued

	Drop fungi + fruit + veges + poultry + corn + meat + tubers (13)	Drop fungi + fruit + veges + poultry + corn + meat + tubers + dairy (12)	Drop fungi + fruit + veges + poultry + corn + meat + tubers + dairy + fried foods (11)	Drop fungi + fruit + veges + poultry + corn + meat + tubers + dairy + fried foods + fast food (10)	Drop fungi + fruit + veges + poultry + corn + meat + tubers + dairy + fried foods + fast food + low-fat cakes (9)
Dietary Pattern 1					
Negative loadings					
High-fat cakes	-0.60	-0.59	-0.54	-0.55	-0.55
Wheat products	-0.48	-0.51	-0.56	-0.57	-0.57
Positive loadings					
Pickles	0.35	0.37	0.38	0.39	0.39
Beans & products	0.31	0.30	0.27	0.27	0.28
Eggs	0.25				
Dietary Pattern 2					
Negative loadings					
Wheat products	-0.32	-0.27			
Eggs		-0.26			
Rice	-0.25	-0.25			
Teas & coffee			-0.54	-0.56	-0.57
Fish & shellfish			-0.41	-0.42	-0.43
High-fat cakes			-0.40	-0.40	-0.41
Nuts & seeds			-0.25	-0.26	-0.26
Positive loadings					
Teas & coffee	0.57	0.57	0.56		
Fish & shellfish	0.45	0.44	0.45		
High-fat cakes	0.25	0.31			
Eggs			0.30	0.30	0.31
Rice					0.25

6.2.3.3 Selection of response variables

Because of the small sample size (*n*=99 with biomarker data available), only two response variables could be selected. The number of response variables used throughout the RRR/dietary pattern literature varies from two[250] up to seven.[251] Prior to beginning the RRR analysis, all biomarkers assessed during the 3CNAS visit (e.g. HbA1c, HDL cholesterol, LDL cholesterol, total cholesterol, and triglycerides) were carefully considered for inclusion as response variables. By focusing on HbA1c and LDL cholesterol, we improved the translational potential of this analysis as these are two commonly measured biomarkers in clinical practice, and they are commonly reported throughout the scientific literature.

HbA1c was chosen given unequivocal evidence from the DCCT that HbA1c is a strong predictor of future diabetes complications.[70] Specifically, intensive glycemic control in the DCCT significantly decreased rates of microvascular (retinopathy and nephropathy) and neuropathic complications in patients with T1D.[70] The relationship between HbA1c and CVD is less clear, but data from long-term follow-up of the DCCT cohort suggests that participants who were randomized to the intensive glycemic control arm had a lower risk of nonfatal myocardial infarction, stroke, and cardiovascular disease death compared to those in the standard arm.[214]

LDL cholesterol was chosen because, according to the ADA Standards of Medical Care (2014), the first priority of dyslipidemia therapy in patients with T1D is to lower LDL cholesterol to <2.60 mmol/L.[68] Furthermore, LDL cholesterol is a well established risk factor for cardiovascular disease and diabetes-related complications in individuals with T1D.[212-219] While HDL cholesterol and triglycerides would have been interesting to explore, the ADA does not provide targets for these risk factors, except for severe hypertriglyceridemia (>11.2 mmol/L), for which it recommends immediate pharmacological therapy (fibric acid derivative, niacin, or fish oil).[68] Finally, though BMI would have been an interesting response variable to evaluate, it was measured, on average, 1.6 years prior to dietary intake during the 3C Study visit.

CHAPTER 7: IMPLICATIONS AND FUTURE DIRECTIONS

In 2006, T1D was proposed as a "tracer condition" for international benchmarking of healthcare systems, used to identify potential problems and to stimulate discussion about what can be done to address them.[252,253] The reason for this is that optimal management of T1D requires surveillance, collaborative healthcare teams, access to essential medicines, education that promotes patient empowerment, and continuity of care,[253] and these are also critical components of optimal management for other chronic diseases (e.g. HIV/AIDS, T2D, and hypertension). Therefore, in completing 3CNAS, not only were the specific aims addressed, but also valuable information was learned that can be used to inform research into health systems strengthening in China. This chapter will first discuss the substantial gap that remains in our understanding of the burden of T1D in China, and then describe the implications of 3CNAS in the larger context of improving care for T1D in China and translating observations to other low- and middle-income countries.

7.1 Improving type 1 diabetes surveillance in China

We do not know the current burden of T1D in China. The most recent T1D incidence rate reported in the IDF Diabetes Atlas for China is from the WHO DIAMOND project, conducted between 1990 and 1999.[22] Not only is this estimate severely outdated, it only covers children <15 years of age.[22] Given recent evidence suggesting that the peak age of onset of T1D may be 10 years later in China compared to Caucasian populations,[254] we suspect that previous estimates of incidence are significantly underestimating the population burden of T1D.

In addition, the incidence rate estimates from the WHO DIAMOND project varied from 0.1 cases per 100,000 person-years in Zunyi to 4.5 cases per 100,000 person-years in Wuhan, only 700 miles away.[100] Given that China is also largely ethnically homogenous (91.5% Han ethnicity),[255] this large range in incidence rates is somewhat unexpected and could be the result of variation in methodologies across sites or genetic heterogeneity in T1D susceptibility (e.g. HLA alleles) within the Han Chinese population. While studies have supported differences in susceptibility (e.g. prevalence of high-risk HLA alleles and association between HLA alleles and diabetes autoantibodies) between the Han Chinese population and Caucasian populations,[256-258] there is limited research on differences within the Han Chinese population.

To address this significant gap in knowledge, a National Type 1 Diabetes Registry project was started this year by researchers from the Guangdong Type 1 Diabetes Mellitus Translational Medicine Study and will include 10 cities across China. Modeled after the U.S.-based SEARCH study,[33] the Chinese Registry project should provide valuable information on the incidence of T1D in the years to come. Additional research on age of onset, presenting symptoms, and prevalence of insulin autoantibody positivity and HLA alleles will further improve our understanding of the etiology of T1D in the Chinese population.

7.2 Improving type 1 diabetes care in China

7.2.1 Summary of key 3CNAS results

This is the first study to evaluate T1D self-management, including the integration of insulin regimen, SMBG, and dietary intake, in a low- or middle-income country. A key result was that diabetes education, particularly as relates to nutrition, is severely limited in China. Fewer than half of participants had “ever” met with a dietitian and only 18% had attended a diabetes education session in the past 12 months that covered nutrition. Nutrition therapy for T1D in this sample typically involved matching fixed insulin doses to a diet that was rigid with respect to amount and timing, rather than an individualized approach that allows a flexible insulin-dosing

regimen to match variable food intake, as recommended by the American and European Diabetes Associations. An effect of this self-management approach was that participants with T1D had a significantly lower mean percentage of energy from carbohydrates and higher mean percentage of energy from fat and protein compared to a similar cohort of individuals without diabetes. Several distinguishing characteristics of insulin regimen groups also emerged: when compared to individuals without diabetes, participants on fixed regimens tended to substitute wheat products for rice intake and restrict fruit, while those on basal-bolus regimens had healthier diets characterized by lower fried food intakes and higher fish & shellfish intakes. Finally, we identified a dietary pattern characterized by high intakes of wheat products and low-sugar (high-fat) cakes, and low intakes of beans & bean products and pickled vegetables that was significantly associated with lower HbA1c and LDL cholesterol. Together, these results highlight an important need for nutrition counseling for individuals with T1D in China that is consistent with current clinical practice guidelines to promote health and reduce risk for both acute and chronic complications of diabetes.

7.2.2 Gaps that remain in addressing 3CNAS specific aims

The key limitation of 3CNAS that we were not able to overcome and that will need to be addressed in future research is generalizability (e.g. external validity). While we made every effort to enroll participants from a more rural district of Beijing (Pinggu), this area was still peri-urban. Furthermore, we only enrolled participants from Beijing, and language, cultural norms, dietary intake, physical activity, and the prevalence of CVD risk factors (for example, blood pressure and obesity) differ significantly in northern versus southern China.[259-262] Therefore, our results may not be generalizable to the entire Chinese T1D population, but only to the northern, urban Chinese T1D population. Future research should expand to include more rural and southern populations of individuals with T1D in China to determine if the lack of nutrition

education and carbohydrate counting is universal and if similar dietary patterns predictive of cardiometabolic risk are uncovered.

Another gap that remains, which will require longitudinal data from a larger cohort of individuals with T1D to address, is the predictors of HbA1c in China. Bivariate analyses in our sample indicated that high intakes of low-sugar (high-fat) cakes were significantly associated with lower HbA1c. However, perhaps due to the cross-sectional study design, the small sample size, or limited variability in HbA1c, few other factors (e.g. insulin regimen, SMBG frequency, nutrition education, nutrition therapy, or other dietary factors) were consistently, statistically significantly associated with glycemic control. It is interesting that, despite having severely outdated self-management practices, the mean HbA1c of our sample (8.2 ±1.8%) was lower than that reported for the T1D Exchange in the United States (8.3 ±1.5%).[263] Indeed, the HbA1c recently reported for a large sample of children and adults with T1D in Guangdong Province in southern China, 36.2% of whom were on 1-2 injections/day, was also similar to that reported in the United States (median, Q1-Q3: 8.4%, 7.0-10.2%).[26]

One hypothesis explaining this observation may be that the later age at onset in the Chinese cohorts correlates with less rapid beta cell destruction, as has been seen in European cohorts.[27,264] The median (25^{th} percentile, 75^{th} percentile) age of onset in our sample was 28.4 years (17.9 years, 40.8 years). Alternative hypotheses may relate to the strict dietary management of T1D observed in Chinese patients, improved insulin sensitivity (a substantial proportion of individuals with T1D in the United States and Europe have insulin resistance),[265-268] genetics, or interactions between these factors. More research is needed to understand predictors of HbA1c in China. One study that may begin to answer these questions is the 30-year Study, led by researchers at Peking University People's Hospital and modeled after the Joslin 50-year Medalist Study.[269,270] Extensive survey data and a blood sample for risk factor assessment and DNA analysis will be collected in approximately 100 patients in China who have had T1D for at least 30 years.

7.2.3 Next research questions

The following section seeks to address the question: in addition to expanding 3CNAS to other sites throughout China and exploring predictors of HbA1c, what other research questions remain to be answered relating to T1D care in China?

7.2.3.1 Improving training for healthcare providers

We found that fewer than half of participants had "ever" met with a dietitian and only 18% had attended a diabetes education session in the past 12 months that covered nutrition. Interestingly, 56% of participants who had been taught carbohydrate counting were taught by physicians while only 30% were taught by dietitians, 5% by diabetes educators, and 3% by nurses. Participants who had been taught carbohydrate counting by dietitians were nearly twice as likely to report sometimes using it (26%) compared to participants who had been taught by physicians (14%). Together, these results suggest that dietitians can be as effective as physicians at nutrition counseling, but are rarely part of the healthcare team. Furthermore, despite the fact that nutrition is a critical component of T1D self-management, it is rarely part of ongoing diabetes education. Severely limited time with physicians in outpatient departments, an absence of certified diabetes educators, lack of dietitian involvement in care, and overall deficiencies in T1D nutrition therapy training are likely the main factors underlying these observations.

To date, no studies have been published regarding the impact of physician education on process and patient outcomes for diabetes in China. However, a Cochrane review recently summarized the literature regarding the effect of continuing education meetings and workshops and found that educational meetings, particularly mixed interactive and didactic meetings, can improve professional practice, health outcomes, and simple behaviors.[271] Specific to diabetes care, several studies have also supported positive effects of provider education. For example,

an intervention in Louisiana found that providing physicians with performance reports and scientific literature regarding the validity of HbA1c testing along with personal contact by a knowledgeable colleague regarding the importance of HbA1c testing significantly improved the frequency and values of HbA1c in patients with T2D.[272] A short (7 hour), small group continuing education program in Canada significantly improved provider knowledge and self-reported practice relating to national clinical practice guidelines for diabetes, though the impact of the program declined after 1 year.[273] Similarly, an intervention in an outpatient clinic in Texas consisting of two lectures and a quality assurance announcement at a staff meeting significantly improved compliance with foot examination recommendations for diabetes patients.[274] Finally, a 1-year intervention in South African physicians consisting of quarterly interactive training sessions significantly decreased the average number of clinic visits and increased the consultation times relative to the control group, though HbA1c did not differ significantly between groups.[275]

A project is currently underway that will improve our understanding of the impact of physician education on process and patient outcomes for diabetes in China. CIDE is an innovative program started in 2010 to provide specialty training for 500 endocrinologists using a train-the-trainer approach.[115] The program is taught by a collective faculty from the WHO International Diabetes Center, the Mayo Clinic, and the Chinese Diabetes Society, and is based on Staged Diabetes Management, developed by the Park Nicollet International Diabetes Center.[276] Preliminary results presented at the World Diabetes Congress in December 2013 showed significant improvements in healthcare provider diabetes knowledge pre- and post-training (mean test score increased from 74% to 86%).[115] Although the program briefly covers T1D, it is largely based on T2D and gestational diabetes. A T1D-specific curriculum emphasizing nutrition therapy is under development and will be implemented using existing CIDE infrastructure.

In addition to physician education, there is also scientific evidence to support the effectiveness of mid-level providers such as nurses in providing care for chronic diseases. A recent systematic review of 28 studies comparing the effectiveness of care provided by nurses to care provided by doctors in patients with chronic diseases found no significant differences in the need for a repeat consultation, improvements in physical functioning, attendance at follow-up visits, or attendance at an emergency department after receiving care.[277] Furthermore, they reported that dissatisfaction with care was significantly lower when care was provided by nurses compared to when care was provided by doctors.[277] Specific to diabetes, the use of mid-level providers to cover an increased frequency of visits was associated with more successful weight loss among adults with pre-diabetes,[278] and when mid-level providers led DSME in a study of youth with T1D in Pakistan, significant improvements in HbA1c were reported.[279]

Along the lines of integrating mid-level providers into healthcare teams, a Gillings Innovative Labs proposal is being developed by a team of researchers at UNC, Chapel Hill in collaboration with Peking University People's Hospital, with the aim of advancing collaborative care in China. The ultimate goal of the proposal is to identify ways to incorporate nutrition more effectively as part of T1D self-management and patient education in China.

7.2.3.2 Stigma and psychosocial issues

From my observations interacting with participants as part of 3CNAS and talking with physicians who regularly see patients with T1D in China, I hypothesize that the stigma associated with T1D in China underlies many of the psychosocial issues faced by patients; however, there is currently no data on this topic. Several small studies have reported the prevalence of depressive symptoms in youth with T1D in China,[280-283] but only one was published in English, reporting a prevalence of 17.6% in Hunan Province.[282] Given data from elsewhere in the world, we have reason to believe that the prevalence of depression in

individuals with T1D in China is substantially higher than the general population: a systematic review of studies conducted in the United States in Europe reported a pooled prevalence of clinical depression of 12.0% for individuals with T1D compared to 3.2% for controls.[284] We do not know the prevalence of discrimination or diabetes-related distress in individuals with T1D in China. While the DAWN2 study collected data on psychological well-being, diabetes-related distress, diabetes empowerment, family support, and discrimination, only 16% of the sample had T1D and results were not published according to diabetes type.[230]

Dr. Brock Chisholm, the first Director-General of the WHO, famously proposed the notion that there can be 'no health without mental health.'[285] This is especially true for diabetes as comorbid depression is associated with poor glycemic control (stronger in youth than adults), diabetes complications, increased healthcare costs, and early mortality.[286] A significant barrier to improving T1D care in China is access to mental healthcare. There is a shortage of mental health professionals in China, particularly trained nurses and especially in under-developed western areas.[287] In 2011, nationally, there were 1.53 psychiatrists per 100,000 population, 0.18 psychologists per 100,000 population, and 2.65 psychiatric nurses per 100,000 population (compared to global averages of 1.27, 0.30, and 5.80, respectively).[288] In additional to the challenge of limited personnel, the Chinese mental health system continues to focus on 'psychosis management'[287] rather than mental wellbeing integrated into community health systems and multidisciplinary healthcare teams. As a result, the majority of mental healthcare is provided in psychiatric hospitals, and the government funding structure for mental health is still primarily based on psychiatric hospital beds rather than care received from personnel.[287]

Data on discrimination and mental health among individuals with T1D in China is extremely limited. Addressing this issue will therefore require quantitative data on prevalence of experienced discrimination, depression, and other psychosocial outcomes, and qualitative data on acceptability of interventions (for example, peer-support groups). In regards to clinical T1D care, healthcare providers in China, particularly physicians, must begin to take a holistic rather

than biomedical approach to disease management recognizing that the salience of stigma confounds disease management. Counseling on coping skills should be an integral component of care. Researchers can also play a role by expanding the scope of interventions to consider the psychosocial realities of T1D in China.

7.2.3.3 Improving access to and use of glucose monitoring supplies

Several studies in the United States and Europe have found a significant correlation between increased frequency of SMBG and improved glycemic control (e.g. lower HbA1c), in all age groups and across insulin regimens (e.g. basal-bolus and fixed).[263,289-292] In our sample of individuals with T1D in China, the frequency of SMBG was abysmal: 31% of participants reported testing <1 time *per week or never*. Given some evidence from the United States that patients tend to overestimate self-reported frequency of SMBG compared to meter-downloaded frequency of SMBG (by, on average, approximately 1 test/day) due to social desirability bias,[263] an even greater proportion of our participants may have fallen into this category of <1 time per week or never. In the United States, <1% of patients with T1D reported testing <1 time *per day*.[263]

An example of the rarity of blood glucose testing in China was encountered in 3CNAS: as part of the standard protocol for a fasting blood draw in individuals with T1D, we did a finger-prick blood glucose test at the beginning of the 3CNAS in-person visit. This blood glucose test was discussed in the written consent document, and several participants questioned the need for such a test during the consent process; testing was such a rare activity that it seemed odd to them to test prior to the blood draw. Indeed, very few participants had tested prior to coming to the in-person visit, after an overnight fast.

The factors underlying this low frequency of SMBG in China have not been explored, but may relate to the fact that testing strips are expensive and not covered by insurance. Given that

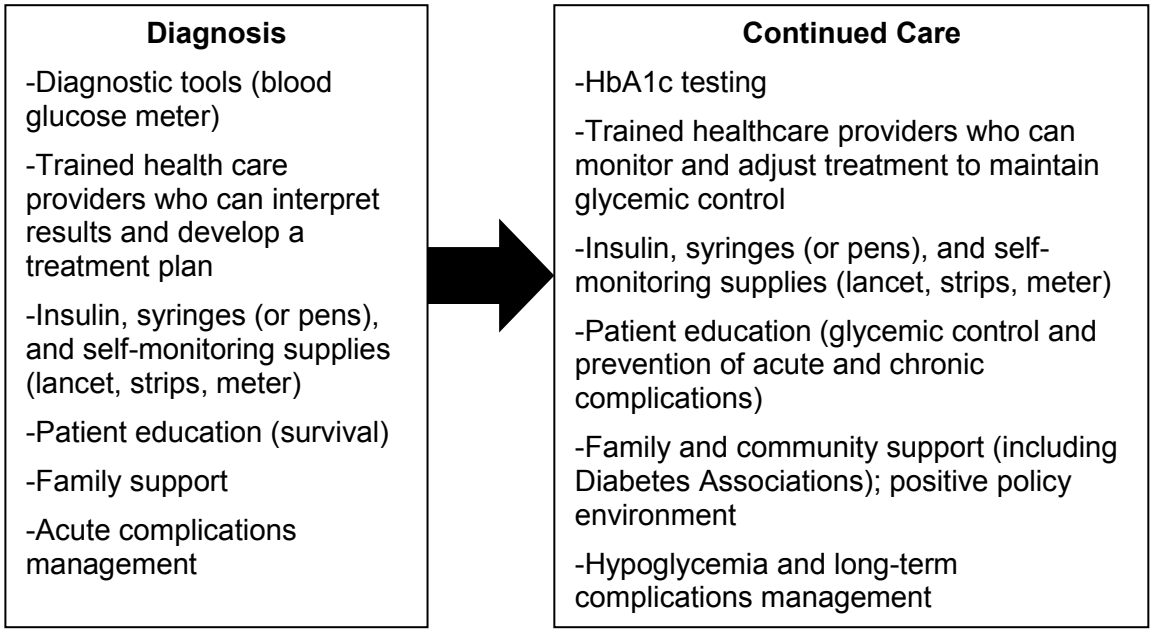
SMBG is a critical component of flexible, basal-bolus self-management of T1D, barriers to SMBG will need to be addressed before patients can be advised to follow such regimens. A positive deviance analysis of individuals with T1D in China who do achieve recommended SMBG frequencies could be informative.

7.3 Translating results to type 1 diabetes in other resource-limited settings

3CNAS is unique relative to other T1D studies in that it evaluated individual-level self-management approaches. There is very limited research on T1D care from other resource-limited regions of the world and the vast majority has focused on access to insulin and cost of care.[114,293-295] While insulin is the first priority for patients with T1D, it is not sufficient; there is a significant difference between access to medicine and access to treatment.[296] We therefore started 3CNAS knowing very little about T1D care, and ended up learning much more than the originally proposed aims; this knowledge will be integral to framing research that follows, in China and around the world.

In 2013, the IDF published a "Pocketbook for Management of Diabetes in Childhood and Adolescence in Under-resourced Countries."[297] The Pocketbook focuses on "survival education" such as management of DKA and initiation of insulin therapy, and provides detailed flow charts for both "Recommended Care" and "Limited Care."[297] Only one page of the 56-page document covers nutritional management; only one bullet covers approaches used to estimate carbohydrates.[297] While hypoglycemia and management of complications are touched on in the Pocketbook, only limited guidance is provided and focuses on the components of a "Standard Screening Regimen."[297] As T1D care continues to improve in these settings and acute complications (e.g. DKA) are managed, the issues of preventing hypoglycemia and long-term complications (e.g. CVD and kidney disease) become increasingly important. An overview of this shift in focus of T1D care is provided in **Figure 7.1**.

Figure 7.1 Overview of basic needs for type 1 diabetes in resource-limited settings



The IDF's Life for a Child program, established in 2000, attempts to address many of these aspects of care and is currently providing assistance to over 14,000 children in 46 countries, ranging from 1835 children in Bangladesh and 1424 in Pakistan to one child in Papua New Guinea.[298] Diabetes centers established by Life for a Child aim to provide insulin (24.4% of direct funds), syringes (2.0% of direct funds), SMBG equipment (33.8% of direct funds), HbA1c testing (11.9% of direct funds), diabetes education (8.7% of direct funds), and technical support for health professionals (3.4% of direct funds).[299] While these centers provide "comprehensive clinical feedback" according to the IDF's website,[298] no data on in-country diabetes care is published in the Annual Report for Life for a Child.[300] In the Annual Report, the IDF estimates that "up to 80,000 children with diabetes are in need of assistance,"[300] but do not define "assistance" or provide any information regarding how they came to that estimate. Clearly, there is a need for improved monitoring of this vast network of diabetes centers caring for individuals with T1D in low- and middle-income countries.

Other organizations involved in T1D care in resource-limited settings include Insulin for Life[301] and the International Insulin Foundation,[302] which developed the Rapid Assessment Protocol for Insulin Access (RAPIA),[303] a multi-level assessment of healthcare systems designed to provide stakeholders (e.g. national Ministries of Health and Diabetes Associations) recommendations for action. Of note, RAPIA is now being field tested as a possible method for investigating access to care for all chronic diseases.[304] The International Insulin Foundation has completed RAPIA assessments in seven countries (Vietnam, Philippines, Mali, Mozambique, Zambia, Nicaragua, and Kyrgyzstan).[295,305-308] Similar to our study, RAPIA assessments in Vietnam and the Philippines found that patients had inadequate education due to several factors including lack of trained staff, lack of involvement of healthcare providers other than physicians, and lack of materials adapted to sociocultural context.[305] By collecting individual-level data, our study was also able to evaluate associations of this inadequate education with self-management practices, diet, and glycemic control. These results will be informative as countries begin to focus attention not only on service delivery (e.g. RAPIA), but also the experiences of patients (e.g. 3CNAS).

7.4 Concluding remarks

It is clear from the limited literature discussed above that more data on current T1D care practices are urgently needed from low- and middle-income countries to inform country-specific guidelines, resource allocation, and future research. The key issues documented in individuals with T1D in China are not "T1D issues," but rather chronic disease issues. Infrequent nutrition education provided largely by physicians with limited time rather than trained dietitians in conjunction with limited SMBG has resulted in a lack of empowerment to adapt disease self-management practices to patient preferences and cultural norms. Individuals with T1D in China therefore adhere to strict dietary regimens, deviating from the dietary intakes of the general population in China. As the prevalence of chronic diseases, including T1D, increases in China

and other rapidly developing countries, use of mid-level providers such as dietitians in continued care and patient education to improve self-management practices will be essential to reduce healthcare costs and prevent morbidity and mortality. Looking ahead to the future, coordinated action by multiple stakeholders informed by scientific research will be required in order to produce meaningful improvements in the treatment of individuals with T1D in China and around the world, ultimately leading to better physical and emotional health outcomes.

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