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What protects against pre-diabetes progressing to diabetes? Observational study of integrated health and social data

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ABSTRACT

Aims: To examine the incidence of type 2 diabetes in people with newly diagnosed prediabetes and the factors that protect against this progression.
Methods: The study population was 14,043 adults with pre-diabetes enrolled in a primary health organization in the upper North Island of New Zealand. Glycated hemoglobin (HbA1c) and body mass index (BMI) were linked to government health, census and social datasets in the Statistics New Zealand Integrated Data Infrastructure. Adults with a first diagnosis of pre-diabetes between 2009 and 2017 (HbA1c in range 5.9–6.6% [41–49 mmol/-mol]) were followed-up for type 2 diabetes incidence. Cox regression was used to examine protective factors and adjust for potential confounding.
Results: Cumulative diabetes incidence was 5.0% after three years. Progression was greater in younger adults, men, people with higher HbA1c, greater BMI and a more recent diagnosis. Progression was lower in people treated with metformin, and Indigenous language speakers. Higher progression rates for Māori (Indigenous population) and Pacific peoples (migrants to New Zealand) were related to higher baseline HbA1c.
Conclusions: This is the first study to identify Indigenous language as a protective factor against diabetes, and results confirm obesity as a key target for population prevention. People with identified risk factors should be prioritized for pre-diabetes interventions.

1. Introduction

Pre-diabetes (intermediate hyperglycemia) is a predictor of progression to type 2 diabetes mellitus [1–5] and an independent risk factor for cardiovascular disease [6]. Globally, rates of obesity, pre-diabetes and diabetes have increased and it is projected that >470 million people will have pre-diabetes by 2030 [7]. A quarter of adults in New Zealand had

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pre-diabetes in 2008/09 and 7% had diabetes (using the 2010 American Diabetes Association criteria) [8].

Rates of progression from pre-diabetes to diabetes internationally range from around 2–18% per year but previous studies have generally measured progression by a glucose based test (fasting glucose or oral glucose tolerance test) and many of these studies are under trial conditions [1–5]. HbA1c has become an acceptable and common first-line test for diagnosis of pre-diabetes and diabetes internationally [9] yet progression of pre-diabetes defined by HbA1c has rarely been studied. Improved understanding of how new HbA1c criteria impact on diabetes risk is needed. Accurate pre-diabetes progression rates are important for planning and monitoring interventions to prevent diabetes in people with pre-diabetes.

Evidence is building for the benefits of intensive diet and lifestyle and other novel interventions for pre-diabetes. Trial evidence suggests that structured lifestyle changes (physical activity and diet), BMI reduction and treatment with metformin are important for protecting against pre-diabetes progression [4,10]. An understanding of risk by age, sex, socioeconomic position (SEP) and ethnicity is important to help target programs to the right population groups and to monitor their success over time. Furthermore there are concerns about using pre-diabetes as a singular category if rates of pre-diabetes progression are low, or the risk of diabetes is no different from people with a combination of other risk factors [7]. For these reasons it is important to determine pre-diabetes progression, and do so using HbA1c testing.

Differences in diabetes incidence by ethnicity are common internationally [11–14], however more information is required to identify the key policy levers and interventions to address ethnic disparities. For example, the highest rates of diabetes in adult New Zealanders are among Indian and Pacific peoples (24%) [15,16]. Māori – the Indigenous population in New Zealand – also experience a disproportionate share of obesity and diabetes (16%) compared to European peoples (6%) [15]. Little has been done to implement interventions that effectively curb the growing tide of obesity worldwide, particularly for indigenous and minority populations. Such inaction in the face of need has been recognized as institutionalized racism [17].

In New Zealand, regular HbA1c testing has become more widespread since 2002 as part of a broader cardiovascular risk assessment (CVRA) – making a cohort study of progression from pre-diabetes to diabetes using routine data possible. CVRAs are recommended at least once every five years, and more frequently for people at the higher risk. The eligible age for CVRA is 55–74 years old for European/Other women; 45–74 years old for European/Other men and Māori, Pacific or Indian Subcontinent women; and 35–74 years old for Māori, Pacific or Indian men. In June 2016, CVRA coverage was 90% nationally and 92% within the studied primary care population [18]. Individuals who are 75 years or older are recommended ongoing annual cardiovascular review. These settings allow a study HbA1c defined pre-diabetes and its progression.

The aim of this study was to first, examine the incidence of diabetes in an ethnically-diverse primary care population with newly diagnosed pre-diabetes; and second, to quantify the factors that protect against progression to diabetes, with an emphasis on non-clinical as well as clinical factors. The question posed in this paper was developed in response to issues raised as part of an Indigenous community co-design project that used the He Pikinga Waiora Implementation Framework [19]. The framework is a participatory approach to developing and implementing interventions that places Māori knowledge and self-determination at the center and then integrates systems thinking to enhance effectiveness, sustainability and improve health equity.

2. Methods

2.1. *Primary care cohort*

A primary health organization in New Zealand with practices in Auckland (primarily), Waikato and Whanganui and an enrolled population of 130,000 was selected as the source population, given its diversity with 16% who identified as Māori, 14% Pacific, and 35% Asian (using Statistics New Zealand classifications). Asian and Pacific peoples had a greater representation than in the overall New Zealand population (15% Māori, 7% Pacific, 12% Asian, 2013 census). Eligible individuals were aged 25 years and older, with a first-time reported diagnosis of pre-diabetes (glycated hemoglobin [HbA1c] in range 5.9–6.6% [41–49 mmol/mol]), and at least one subsequent HbA1c test result. In a cohort study design, individuals were followed up from the time they were first diagnosed with pre-diabetes (baseline) to determine whether they got type 2 diabetes (HbA1c 6.7%+/≥50 mmol/mol). We used HbA1c for diabetes diagnosis because it was the recommended first-line test for diagnosis of type 2 diabetes during the study period and was likely to be available for everyone who developed diabetes during the study period HbA1c criteria differed from those of the American Diabetes Association who recommend a lower but overlapping range (HbA1c between 5.7 and 6.4% [39–47 mmol/-mol]) [9]. The WHO does not offer any recommendation on HbA1c criteria for pre-diabetes, but defines diabetes similarly to the ADA with a HbA1c of 6.5% (48 mmol/mol) or more [20].

Individuals were excluded if they had a pre-existing diagnosis of diabetes recorded in primary care HbA1c test records or in the Ministry of Health Virtual Diabetes Register (that predicts who has diabetes based on algorithms run across hospital, pharmaceutical and outpatient records) [21,22]. Women were excluded if they had a hospital admission with a diagnosis of hyperglycemia or diabetes in pregnancy, because pregnancy related hyperglycemia was not the focus of this study.

Ethical approval was awarded by the Otago Human Ethics Committee (HD16/002, 20th September 2016). Patients enrolled in the Primary health organisation sign to agree to the use of their health information for research as approved by an ethics committee.

2.2. *Data*

There were three sources of variables that were linked: variables recorded in primary care records, health-related variables recorded in national datasets held by the Ministry of Health, and socio-demographic variables held in other national datasets in the Statistics New Zealand Integrated Data Infrastructure (IDI). The IDI is a government-led research database of administrative, survey and non-government data.

Linkage was achieved by deterministically linking the primary care data to health data in the IDI [23] using the national health index (NHI) number (99.7% of records were successfully linked). The health data in the IDI were then probabilistically linked to the IDI spine by Statistics New Zealand in the September 2017 refresh, using common variables such as name, age and sex (85% of health records were linked). The IDI spine is a central list of individual records of people who have ever been a resident, and this list is comprised using tax records, visa information and birth records [24]. The 2013 census data was also probabilistically linked to the IDI spine. Supplementary Fig. S1 outlines a flow diagram outlining linkage between datasets. These linked datasets were used to create the following variables.

HbA1c test results and BMI measures were generated from primary care records. BMI records were selected if recorded in the five years before baseline or 30 days after, and were categorized into standardized groupings. Extreme BMI measures were excluded (e.g. <10 kg/m^2 and >1 m, or >100 kg/m^2 and <1 m).

Ministry of health datasets were used to identify antidepressant use (five years prior to baseline), most recent primary care consultation at baseline, existing diabetes and other chronic conditions (within the five years prior to baseline), metformin treatment during follow-up (pharmaceutical dataset), bariatric surgery, and hospital admission with diabetes/hyperglycemia in pregnancy.

IDI summary tables draw on multiple datasets and were used to identify basic demographic information; age (ten year groups), sex, ethnicity (self-identified ethnicity from the 2013 census if available otherwise it was taken from health or other datasets; individuals were allowed to identify with one or more groups termed here total ethnicity), New Zealand deprivation index (small area index of socioeconomic position [25]) and mobility (number of small residential areas someone has lived in the five years prior to baseline).

Personal income quintiles were extracted from Inland Revenue Department (tax) summary tables (with data up to the third quarter of 2015, excludes self-employed and investment income). The 2013 census was used for indicators of highest qualification, equivalised household income (quintiles based on national income pattern), household crowding (Canadian National Occupancy Standard), labor force status, home ownership, smoking status and te reo speaking (Indigenous Māori language). The te reo association was tested across all ethnic groups and an interaction term was used to test if this association varied by Māori/non-Māori. Variables of interest were informed by discussions with primary care practitioners and researchers, including a Māori health provider.

2.3. *Analyses*

The pre-diabetes study population and key variables were described including the pattern of missing data. Estimates of diabetes prevalence at 3 years post-diagnosis were produced using Kaplan Meier survival analysis for each ten year age group and by sex, ethnicity, baseline HbA1c, education, deprivation, household income and time period. These analyses were done on the full available dataset.

Proportional hazards (Cox) regression models were used to estimate the association between variables of interest and pre-diabetes progression. Analyses were run on the 'non-missing dataset' that had no missing data on education, personal income or deprivation. These SEP variables were the only variables in the full model that had missing data. A univariate analysis model was run for each of the variables of interest. Second, the same models were run with adjustment for age and sex. Third, additional adjustment was made for prioritized ethnicity (mutually exclusive groups prioritized by Māori, Pacific, Asian then non-Māori/Pacific/Asian termed European/Other), education, personal income, neighborhood deprivation, and baseline HbA1c. For the association between metformin and pre-diabetes progression, further models were run with additional adjustment for BMI (Table S5). Analyses of census risk factors were limited to the group of people with pre-diabetes that was diagnosed after the census (5th of March 2013) to avoid reverse causality (with the one exception of highest qualification which was not expected to change during the study period).

A sensitivity test was done to assess the effect of excluding records with missing SEP data. A model with adjustment for age, sex, ethnicity (prioritized to create mutually exclusive groups) and HbA1c was run for each variable of interest on the full set of available data. The same model was run on the restricted non-missing dataset used in the above regression analyses. Model results were compared to assess the possible extent of selection bias. All analysis was done using SAS [26].

3. Results

14,043 individuals with pre-diabetes met the inclusion criteria, from a total of 65,802 individuals with at least one HbA1c record. The study group was followed up for a total of 432,645 person months to calculate diabetes incidence. Regression analyses were carried out on the two-thirds of individuals (n = 9222) in the 'non-missing dataset'.

3.1. *Pre-diabetes population*

The study population was a relatively deprived subset of the New Zealand population with a high proportion of Asian (41%) and Pacific peoples (16%), and 13% who identified as Māori (Table 1). One quarter of individuals had missing data for each of education and personal income, and three-quarters for BMI.

3.2. *Diabetes incidence*

The cumulative incidence of diabetes was 4.95% (95%CI 4.53–5.42) at three years. This figure was 1.04% (0.88–1.23) at one year, 2.99% (2.69–3.32) at two years, 7.65% (7.00–8.35) at four years and 9.45% (8.52–10.48) at five years. Three-year cumulative diabetes incidence demonstrated different progression rates by age, ethnicity, HbA1c, BMI, equivalised household income and time period (Table 2). Progression was 5.8% for men and in women it was 4.2%. Diabetes incidence for Māori was 7.5%, Pacific 7.6%, Asian 6.0% and European 4.9%.

Table 1 – A description of the study primary care population of adults 25+ years old with pre-diabetes, 2009–2017.

		Men	Women
Population	n	6624	7419
Developed diabetes	n	354 (5.3%)	276 (3.7%)
Person-months follow-up	Sum	204,174	228,471
	Mean	30.8	30.8
Complete data*	Total	4311 (65%)	4911 (66%)
Ethnicity (multiple response)	Māori	789 (12%)	990 (13%)
	Pacific	1107 (17%)	1149 (15%)
	Asian	2649 (40%)	3150 (42%)
	European	2301 (35%)	2535 (34%)
Age (%)	25–34 years	411 (6%)	525 (7%)
	35–44 years	1188 (18%)	1011 (14%)
	45–54 years	1743 (26%)	1794 (24%)
	55–64 years	1683 (25%)	2043 (28%)
	65 + years	1599 (24%)	2049 (28%)
BMI at baseline (%)	<25	378 (6%)	513 (7%)
	25–30	627 (9%)	489 (7%)
	30–35	408 (6%)	390 (5%)
	35–40	168 (3%)	237 (3%)
	40+	126 (2%)	207 (3%)
	Missing	4920 (74%)	5586 (75%)
Glycated hemoglobin at baseline, HbA1c (mmol/mol)	41	2094 (32%)	2304 (31%)
	42	1551 (23%)	1740 (23%)
	43	1074 (16%)	1149 (15%)
	44	708 (11%)	825 (11%)
	45	435 (6.6%)	516 (7%)
	46	309 (4.7%)	351 (4.7%)
	47	192 (2.9%)	255 (3.4%)
	48	153 (2.3%)	150 (2%)
	49	108 (1.6%)	126 (1.7%)
Personal income quintile (tax records, 5 years)	Lowest Income	1059 (16%)	1278 (17%)
	Second Income	1113 (17%)	1338 (18%)
	Middle Income	852 (13%)	1521 (21%)
	Fourth Income	1122 (17%)	1251 (17%)
	Highest Income	1533 (23%)	864 (12%)
	Missing	948 (14%)	1161 (16%)
NZ Deprivation Index (2013) quintile in area of residence at baseline	Least deprived	732 (11%)	792 (11%)
	Second deprived	1104 (17%)	1104 (15%)
	Middle deprived	1251 (19%)	1425 (19%)
	Fourth deprived	1689 (25%)	1929 (26%)
	Most deprived	1719 (26%)	2040 (27%)
	Missing	129 (2%)	129 (2%)
Education (census)	No qualification	1170 (18%)	1443 (19%)
	School qualification	2589 (39%)	2895 (39%)
	Tertiary qualification	1035 (16%)	1158 (16%)
	Missing	1833 (28%)	1926 (26%)
Time Period	2009–2013	3717 (56%)	4116 (55%)
	2014–2017	2907 (44%)	3306 (45%)
Metformin	Treated	228 (3.4%)	318 (4.3%)
	Not treated	6396 (96.6%)	7098 (95.7%)

Notes: All numbers are random rounded to base three to meet Statistics New Zealand confidentiality requirements. Percentages are a proportion of the total numbers of men and women in the study.

* These individuals had complete data on age, sex, ethnicity, personal income (tax), deprivation index, education and HbA1c.

3.3. *Protective factors: Multivariable analyses*

Cox regression model estimates adjusted for age, sex, ethnicity, SEP and HbA1c are presented in Table 3 with separate models for each variable of interest. Women experienced one-third lower (RR 0.67 CI:0.54–0.82) progression rates than men. By age, the highest progression rates were in 35–44 year olds, who had nearly three times higher diabetes incidence

than 65+ year olds, who had the lowest progression rates. After adjusting for HbA1c status, rates of progression were similar by ethnicity, however before adjusting for HbA1c and SEP, Māori had 1.49 (1.07–2.07) and Pacific had 1.46 (1.09–1.97) times greater progression than European/Other whereas progression in Asian people was more similar to European/Other (RR 1.05 CI:0.81–1.36).

There was a strong protective association between speaking te reo (Indigenous language) and progression to diabetes (RR 0.31 CI:0.12–0.81). Sensitivity tests suggested that this result was only partially affected by missing data bias. We tested whether the association with te reo was any more or less protective for Māori than non-Māori, but there was no evidence ($p = 0.975$) of any interaction. Power for this test was limited because the number of non-Māori who were fluent in te reo was low.

Glycated hemoglobin at baseline was strongly ($p < 0.001$) and independently associated with progression to diabetes with a clear dose-response relationship (RR 55.6 CI:33.3–90.9 for HbA1c 49 vs 41 mmol/mol). BMI was independently associated ($p = 0.033$) with progression to diabetes with a dose-response relationship (RR 3.68 CI:1.39–9.72 comparing 40+ vs <25 kg/m^2). There was weak ($p = 0.067$) evidence that smoking (RR 1.52 CI:1.01–2.30) and ex-smoking (RR 1.42 CI:0.98–2.07) were associated with greater diabetes incidence compared to never smoking. The impact of missing data suggests the risk of ex-smoking may be less than is reported here (Appendix 1: sensitivity analysis).

There was no evidence that chronic health conditions at baseline, home ownership, household crowding, rurality, mobility, primary care access and personal income were associated with pre-diabetes progression. Although tertiary education and full-time and part-time work appeared to be protective, there was no statistical evidence of an association with these factors.

Metformin treatment was associated with an 88% decreased progression to diabetes (RR 0.12 CI:0.02–0.85) (Table S5). In sensitivity analyses, missing data on SEP and BMI shifted results but each in opposite directions.

4. Discussion

After three years 5% of people with pre-diabetes had developed diabetes, but this varied significantly by age, sex, HbA1c, ethnicity, Indigenous language, BMI, smoking (weaker evidence) and metformin treatment.

Progression rates in the current study were generally lower than that found by earlier studies [1–5] (2.5–18% at one year) particularly in trials (5.8–18.3% at one year). This may be partially due to the higher coverage of HbA1c testing in this contemporary primary care cohort, which may have resulted in a healthier study population however this does not seem to be the full picture. A 2006 trial in India had a slightly higher average baseline HbA1c than this study (44.3 vs 42.9 mmol/mol) and high progression rates (18% per year in control group) [3] whereas a 2017 observational study in Japan had similar progression rates to this study (2.5% per year) and a much lower baseline HbA1c (38 mmol/mol) [5]. Pre-diabetes was defined in our study with an HbA1c test with criteria of 5.9–6.6% [41–49 mmol/mol] when most previous studies have defined pre-diabetes using a glucose based test (or both) [1–5]. It is likely that differences in definitions influence rates of progression but further studies using HbA1c in contemporary primary care population would help to understand the extent of this.

Three year, progression rates varied from 1% at a baseline HbA1c of 5.9% (41 mmol/mol, after 3 years) to 40% with a HbA1c of 6.6% (49 mmol/mol) (considered diabetes using ADA criteria). This reflects the biological continuum of glycemic status and the challenge of selecting criteria for diagnosis of diabetes. At the lower end of the spectrum there is a concern that pre-diabetes might be a target for over medicalization and treatment (especially with an absence of other risk factors), when the risks of diabetes and cardiovascular complications are likely to be low. The pre-diabetes spectrum of HbA1c is a way of targeting diabetes prevention activities and is important for the evaluation of these interventions.

Progression was greater in men and in the 35–44 year old age group, independent of baseline HbA1c. Progression rates appeared to be greater in sex-ethnicity groups that were younger than the CVRA HbA1c screening age cut-offs. This means that people tested at younger ages are likely to be at higher risk, compared to age groups where more people (90+ %) are screened, and more people already have diabetes. Furthermore, younger people with prediabetes are likely to be on a faster trajectory to diabetes than older people who get prediabetes.

Māori and Pacific peoples had greater progression rates than New Zealand European peoples, but this result was completely attenuated by adjusting for HbA1c. This is because Māori and Pacific peoples had higher baseline HbA1c levels than other ethnic groups. SEP factors such as tertiary education, employment and household crowding were protective but did not remain statistically significant after adjusting for ethnicity and HbA1c. Study results appear to reflect the different HbA1c distribution (normoglycaemia, pre-diabetes and diabetes) by ethnicity and SEP. Higher HbA1c at diagnosis may also be related to the slightly lower HbA1c testing rates (or less frequent tests) in Māori (88%, 2018) and Pacific (90%) than European (92%) and greater barriers to accessing primary health care [27].

A cultural protective factor was the evidence of an association between speaking te reo (Indigenous language, with 87% of te reo speakers being Māori) and 19 to 88% lower progression to diabetes, independent of age, sex, income, education, deprivation, ethnicity and HbA1c. This finding suggests that language and cultural identity are positive for health, particularly in Indigenous communities. This is the first known study to examine a relationship between diabetes and Indigenous language, and results are consistent with the protective association found between traditional language and suicide [28].

BMI was strongly independently associated with progression, as has been demonstrated elsewhere [29]. Similarly, smoking was found to increase progression of pre-diabetes to diabetes (weak evidence), consistent with several studies [30,31] but not all [32]. BMI and smoking are both important targets for population prevention of diabetes. Metformin

Table 2 – Kaplan Meyer type 2 diabetes incidence estimates (percentage of people with pre-diabetes who had HbA1c ≥ 50 - mmol/mol at 3 years) with 95% confidence intervals, in 25+ year olds, 2009–2017.

Variable	Category	Incidence diabetes at three years, percent (95% CI)	
		Men	Women
Total	All	5.84 (5.18–6.58)	4.15 (3.63–4.75)
Age	25–34 years	7.32 (4.50–11.8)	3.91 (2.07–7.32)
	35–44 years	8.03 (6.22–10.3)	5.04 (3.56–7.12)
	45–54 years	6.68 (5.39–8.27)	5.92 (4.71–7.43)
	55–64 years	4.98 (3.88–6.39)	3.66 (2.80–4.77)
	65 + years	4.18 (3.16–5.54)	2.84 (2.10–3.85)
Ethnicity (multiple response)	Māori	7.52 (5.46–10.3)	4.96 (3.52–6.98)
	Pacific	7.55 (5.87–9.69)	5.47 (4.12–7.24)
	Asian	5.95 (4.91–7.19)	4.26 (3.44–5.27)
	European	4.92 (3.96–6.12)	3.25 (2.51–4.21)
Glycated hemoglobin (mmol/mol)	41	1.09 (0.63–1.89)	0.71 (0.38–1.31)
	42	1.72 (1.09–2.72)	1.10 (0.62–1.92)
	43	3.12 (2.03–4.78)	2.54 (1.61–4.00)
	44	6.28 (4.45–8.84)	2.85 (1.73–4.68)
	45	8.58 (6.00–12.2)	5.70 (3.71–8.69)
	46	20.3 (15.4–26.5)	10.8 (7.53–15.4)
	47	23.1 (16.8–31.2)	19.0 (14.2–25.1)
	48	40.5 (31.7–50.6)	33.1 (24.9–43.1)
	49	43.6 (32.8–56.3)	37.7 (28.0–49.3)
BMI (kg/m^2)	<25	2.98 (1.43–6.17)	1.09 (0.46–2.61)
	25–29	4.82 (3.04–7.59)	4.34 (2.09–8.89)
	30–34	7.38 (3.78–14.2)	3.57 (1.68–7.52)
	35–39	20.2 (11.0–35.3)	7.32 (3.97–13.3)
	40+	15.1 (8.06–27.3)	17.8 (10.7–28.8)
	Missing	5.52 (4.82–6.32)	3.87 (3.32–4.51)
Equivalised household income (census)	Lowest	5.35 (3.69–7.74)	4.87 (3.23–7.30)
	Second	5.17 (3.17–8.39)	4.26 (2.77–6.53)
	Middle	6.04 (3.64–9.93)	3.05 (1.40–6.59)
	Fourth	5.10 (3.09–8.35)	2.76 (1.47–5.18)
	Highest	3.22 (1.48–6.95)	3.26 (1.70–6.24)
	Missing	6.11 (5.30–7.04)	4.29 (3.64–5.05)
NZ Deprivation Index (2013) quintile at baseline	Lowest	4.48 (2.89–6.92)	3.53 (2.25–5.52)
	Second	4.37 (3.09–6.16)	3.50 (2.31–5.28)
	Middle	5.19 (3.85–6.97)	3.88 (2.82–5.34)
	Fourth	6.67 (5.37–8.27)	4.00 (3.07–5.20)
	Highest	6.72 (5.41–8.34)	4.53 (3.57–5.75)
Education (census)	No qualification	4.93 (3.62–6.69)	4.55 (3.46–5.98)
	School Qualification	5.98 (4.97–7.19)	3.82 (3.05–4.77)
	Tertiary qualification	4.36 (3.05–6.22)	3.24 (2.15–4.85)
	Missing	5.96 (5.14–6.91)	4.09 (3.43–4.86)
Time period (year)	2009–2013	5.60 (4.87–6.44)	3.87 (3.29–4.54)
	2014–2017	7.09 (5.31–9.42)	6.09 (3.66–10.1)

Note: No age standardization.

treatment resulted in a large 92% reduction in progression. The direction of this finding is consistent with randomized trial evidence [33] however the magnitude was greater than expected. The 3.9% of people selected for metformin treatment may have been less likely to get diabetes for other reasons; they were being treated for polycystic ovary syndrome or they were also receiving other lifestyle interventions. Justification for metformin treatment at lower levels of HbA1c requires stronger evidence for reduced cardiovascular disease and other complications.

4.1. *Strengths and weaknesses*

This study links nearly a decade of contemporary primary care data (2009–2017) from a diverse primary care population to a national research data base of integrated administrative and survey data (IDI) to create a pre-diabetes cohort study. Our results are relevant to countries where HbA1c screening is increasingly being used.

We were able to adjust and examine for many factors, however unmeasured factors may have confounded some of

Table 3 – Proportional hazards/Cox multivariate regression models comparing the relative incidence of type 2 diabetes (rate ratio) for each variable of interest, 25+ year olds.

Variable of interest	Comparison	Unadjusted models		Age and sex adjusted models		Age, sex, SEP,[†,‡] HbA1c[§] & ethnicity[‖] adjusted models	
		Rate ratio	p	Rate ratio	p	Rate ratio	p
Sex	Females vs Males	0.64 (0.53–0.79)	<0.001	0.66 (0.54–0.81)	<0.001	0.67 (0.54–0.82)	<0.001
Age group	35–44 vs 25–34 years old	1.72 (1.03–2.91)	<0.001	1.66 (0.98–2.79)	<0.001	1.55 (0.92–2.63)	<0.001
	45–54 vs 25–34 years old	1.55 (0.93–2.57)		1.52 (0.92–2.53)		1.31 (0.79–2.19)	
	55–64 vs 25–34 years old	0.93 (0.55–1.57)		0.93 (0.55–1.56)		0.77 (0.45–1.31)	
	65–99 vs 25–34 years old	0.73 (0.43–1.24)		0.72 (0.43–1.23)		0.54 (0.31–0.94)	
Prioritized ethnicity[‖]	Māori vs European/Other	1.71 (1.24–2.37)	<0.001	1.49 (1.07–2.07)	0.012	0.95 (0.68–1.34)	0.321
	Pacific vs European/Other	1.78 (1.34–2.38)		1.46 (1.09–1.97)		0.85 (0.63–1.17)	
	Asian vs European/Other	1.25 (0.97–1.59)		1.05 (0.81–1.36)		0.76 (0.58–1.00)	
Total ethnicity[‖]	Māori vs non-Māori	1.40 (1.05–1.86)	0.023	1.34 (1.00–1.79)	0.048	1.09 (0.81–1.48)	0.559
	Pacific vs non-Pacific	1.48 (1.16–1.90)	0.002	1.33 (1.04–1.71)	0.025	0.96 (0.74–1.25)	0.766
	Asian vs non-Asian	0.97 (0.79–1.19)	0.750	0.86 (0.70–1.07)	0.173	0.82 (0.64–1.03)	0.092
Te reo language (census)[*] n = 5997	Te reo vs No te reo	0.71 (0.29–1.72)	0.446	0.72 (0.30–1.75)	0.464	0.31 (0.12–0.81)	0.017
Time period	2014–2016 vs 2009–2013	1.12 (0.86–1.45)	0.401	1.10 (0.85–1.42)	0.478	1.39 (1.07–1.81)	0.012
Glycated hemoglobin at baseline, HbA1c (mmol/mol)[¶]	42 vs 41	2.01 (1.19–3.39)	<0.001	2.03 (1.20–3.42)	<0.001	2.03 (1.20–3.42)	<0.001
	43 vs 41	2.91 (1.72–4.93)		2.91 (1.72–4.93)		2.92 (1.72–4.95)	
	44 vs 41	4.78 (2.88–8.00)		5.08 (3.06–8.47)		5.13 (3.08–8.55)	
	45 vs 41	7.75 (4.65–12.8)		8.20 (4.95–13.7)		8.20 (4.93–13.7)	
	46 vs 41	15.9 (9.80–26.2)		17.2 (10.5–27.8)		17.5 (10.8–28.6)	
	47 vs 41	22.7 (13.9–37.0)		24.4 (14.9–40.0)		23.8 (14.5–38.5)	
	48 vs 41	41.7 (25.0–66.7)		41.7 (25.6–71.4)		43.5 (27.0–71.4)	
	49 vs 41	52.6 (31.3–83.3)		52.6 (32.3–90.9)		55.6 (33.3–90.9)	
BMI at baseline[*] (kg/m^2) n = 2265	25–29 vs <25	1.24 (0.54–2.83)	<0.001	1.18 (0.52–2.71)	<0.001	1.18 (0.51–2.75)	0.033
	30–34 vs <25	2.16 (0.98–4.77)		2.04 (0.92–4.51)		1.50 (0.61–3.69)	
	35–39 vs < 25	3.69 (1.64–8.27)		3.36 (1.48–7.61)		2.34 (0.90–6.12)	
	40 + vs < 25	6.36 (2.91–13.9)		5.69 (2.56–12.6)		3.68 (1.39–9.72)	
Antidepressant use	Yes vs No (5y prior to baseline)	1.16 (0.87–1.56)	0.304	1.22 (0.91–1.63)	0.187	1.24 (0.92–1.68)	0.164
AMI	AMI vs None	1.64 (0.88–3.08)	0.122	1.73 (0.92–3.26)	0.091	1.40 (0.74–2.66)	0.298
Cancer	Cancer vs None	0.71 (0.32–1.59)	0.406	0.84 (0.38–1.89)	0.681	0.82 (0.36–1.84)	0.626
CHD	CHD vs None	1.24 (0.74–2.07)	0.420	1.35 (0.80–2.28)	0.255	1.14 (0.67–1.93)	0.626
COPD	COPD vs None	0.78 (0.40–1.51)	0.462	0.95 (0.49–1.86)	0.891	0.77 (0.40–1.50)	0.444
Gout	Gout vs None	1.48 (1.00–2.21)	0.052	1.39 (0.93–2.08)	0.106	1.20 (0.80–1.80)	0.390
Stroke	Stroke vs None	0.57 (0.14–2.27)	0.422	0.66 (0.17–2.67)	0.564	0.48 (0.12–1.94)	0.304
TBI	TBI vs None	0.61 (0.09–4.29)	0.617	0.65 (0.09–4.65)	0.672	0.66 (0.09–4.72)	0.675
Smoking (census)[*] n = 5805	Ex-Smoker vs Never Smoker	1.50 (1.06–2.12)	<0.001	1.55 (1.09–2.21)	0.002	1.42 (0.98–2.07)	0.067
	Smoker vs Never Smoker	2.06 (1.43–2.96)		1.83 (1.27–2.65)		1.52 (1.01–2.30)	

Table 3 – (Continued)

Variable of interest	Comparison	Unadjusted models		Age and sex adjusted models		Age, sex, SEP,[†,‡] HbA1c[§] & ethnicity[‖] adjusted models	
		Rate ratio	p	Rate ratio	p	Rate ratio	p
Metformin	Treated vs Not	0.17 (0.06–0.46)	0.001	0.18 (0.07–0.48)	0.001	0.08 (0.03–0.21)	<0.001
Own home (census)[*] n = 5310	Yes vs No	0.72 (0.54–0.98)	0.034	0.77 (0.57–1.05)	0.099	0.94 (0.69–1.30)	0.727
Household Crowding (census)[*] n = 5649	Yes vs No	1.59 (1.12–2.25)	0.010	1.46 (1.02–2.08)	0.038	1.08 (0.74–1.57)	0.684
Mobility in the last five years	2 vs 1 meshblocks	1.07 (0.84–1.36)	0.186	0.99 (0.78–1.26)	0.608	1.01 (0.79–1.29)	0.535
	3 vs 1 meshblocks	1.39 (1.03–1.87)		1.20 (0.89–1.63)		1.21 (0.90–1.64)	
	4+ vs 1 meshblocks	1.11 (0.79–1.55)		0.97 (0.69–1.36)		0.92 (0.65–1.30)	
Time since most recent primary care visit at baseline n = 8067	6–12 vs <6 months	1.15 (0.82–1.61)	0.586	0.95 (0.68–1.34)	0.380	0.93 (0.66–1.31)	0.272
	12+ vs <6 months	0.87 (0.53–1.41)		0.71 (0.43–1.16)		0.67 (0.41–1.10)	
Residence (census)[*] n = 6033	Urban vs Rural	0.76 (0.31–1.86)	0.554	0.71 (0.29–1.74)	0.458	0.75 (0.30–1.90)	0.547
Equivalised Household Income quintile (census)[*,†] n = 5112	Lowest vs Highest	1.32 (0.77–2.27)	0.262	1.38 (0.80–2.38)	0.161	0.89 (0.51–1.56)	0.288
	Second vs Highest	1.14 (0.65–2.02)		1.13 (0.64–2.00)		0.87 (0.49–1.55)	
	Middle vs Highest	0.82 (0.44–1.52)		0.80 (0.43–1.48)		0.56 (0.30–1.04)	
	Fourth vs Highest	0.89 (0.48–1.64)		0.90 (0.49–1.67)		0.77 (0.42–1.43)	
Personal Income quintile previous five years (tax records)[†]	Lowest vs Highest	1.13 (0.82–1.56)	0.076	1.45 (1.05–2.01)	0.108	1.33 (0.96–1.84)	0.212
	Second vs Highest	0.88 (0.63–1.22)		1.28 (0.91–1.80)		1.10 (0.78–1.54)	
	Middle vs Highest	1.00 (0.72–1.37)		1.35 (0.97–1.88)		1.11 (0.80–1.54)	
	Fourth vs Highest	1.34 (1.00–1.80)		1.46 (1.08–1.96)		1.37 (1.02–1.84)	
Labor Force Status (census)[*,†] n = 6033	Unemployed vs Full-time	1.45 (0.82–2.54)	0.454	1.56 (0.88–2.73)	0.022	1.19 (0.67–2.13)	0.179
	Not in Workforce vs Full-time	1.01 (0.75–1.37)		1.64 (1.16–2.33)		1.43 (1.01–2.02)	
	Part-time vs Full-time	0.80 (0.47–1.37)		0.99 (0.58–1.69)		0.92 (0.53–1.57)	
Education (census)[†]	School qualification vs None	1.02 (0.81–1.29)	0.283	0.90 (0.71–1.14)	0.029	1.09 (0.86–1.39)	0.246
	Tertiary qualification vs None	0.82 (0.61–1.11)		0.66 (0.49–0.90)		0.34 (0.22–0.53)	

Each column for each variable of interest represents a separate model. All models are run on the non-missing dataset, maximum = 9222.

[*] There were additional missing data for these variables however the study population was consistent across the row. Furthermore all analyses on census variables; te reo, smoking, urban, crowding, home ownership, household income, workforce status variables were limited to people who got pre-diabetes after the March 2013 census to avoid reverse causality.

[‡] SEP variables used were personal income in the previous five years (tax records), 2013 deprivation index at baseline residence, and highest qualification.

[†] The models for these socioeconomic position (SEP) variables of interest in the SEP adjusted models were not adjusted for SEP (instead only ethnicity was added to the model).

[§] HbA1c was adjusted using HbA1c as a continuous variable, and as HbA1c squared.

[‖] The models for ethnicity variables of interest in the ethnicity adjusted models were not adjusted for ethnicity (instead only SEP was added to the model).

[¶] The models for HbA1c variable of interest in the HbA1c adjusted model were adjusted for age, sex, ethnicity, and SEP only.

our results, such as diet or physical activity, sleep and stress, hypertension and hypercholesterolemia. These factors however are unlikely to have caused any confounding for the more distal social factors that were examined. Furthermore, the impact of renal function, hepatic function and inflammatory status on progression was not investigated because this data is likely to be incomplete; and nor was the impact of medications such as ACE-inhibitors, Angiotensin II receptor blockers, diuretics, corticosteroids, statins or estroprogestins that may affect glucose homeostasis.

This study focuses on the engaged primary care population. We excluded people who were not enrolled in primary care or who had only one recorded HbA1c test. If unenrolled or infrequently tested individuals have higher rates of prediabetes progression, study progression may be underestimated. Also it is possible that despite frequent use of HbA1c as a first-line test for type 2 diabetes, some people may have been diagnosed via oral glucose tolerance tests and not have been HbA1c tested (at least until later follow-up). This may have slightly underestimated prediabetes progression.

This study had complete data on key variables such as age, sex, ethnicity and HbA1c. However, there was missing data for BMI, personal income and education. This is for two possible reasons; one, there were no available records (BMI, census records); or two, an individual's health record could not be probabilistically linked to the IDI spine, or the spine record could not be probabilistically linked to the census record. However, 98% of non-Māori and 97% of Māori health records were linked to the spine (linkage rates are lower for older people and Asian and Pacific peoples), and 94% of census data were linked to the IDI spine. The impact of missing SEP data was examined by sensitivity analysis but did not appear to have a major impact on key findings (Supplementary Table S4).

4.2. *Implications*

Public health solutions are required to prevent the rising tide of diabetes and address its structural drivers, including the obesogenic environment and tobacco control policy. More is needed at multiple levels; from limiting access to profit making and health negative industries to indigenous and socioeconomically deprived environments to increasing access to health protective factors at Indigenous community, family and individual levels. Ethnic inequities in diabetes progression represent both a range of unaddressed systems and structural problems and unmet need for healthcare. Under the United Nations Declaration on the Rights of Indigenous Peoples, member states are obliged to take the necessary steps to ensure indigenous people's full rights to health are met. Te reo findings here suggest the importance of cultural connectedness for health and are encouraging for more advanced research in this area to be developed.

Lifestyle interventions can reduce pre-diabetes progression and prioritizing more intensive intervention by age, sex, ethnicity, HbA1c, and BMI has the potential to improve cost-effectiveness [34]. The manner in which lifestyle interventions are developed appears to be as important as the content included [19]. Further research on the effectiveness and cost-effectiveness of pre-diabetes interventions by level of HbA1c would help determine how future lifestyle interventions should be targeted. More research is needed on the health impact at lower HbA1c levels given the low rates of progression shown here.

4.3. *Conclusions*

This contemporary study of a pre-diabetes cohort from a well screened primary care population demonstrated lower rates of diabetes progression than expected. Indigenous language, lower BMI and never smoking were protective against pre-diabetes progression and are targets for prevention policies. Groups at high risk of diabetes identified by age, sex, ethnicity, HbA1c and BMI could be considered for prioritization of pre-diabetes interventions.

Author contributions

AT led this study, drafted the article and takes the role of guarantor. AT, JO, NS and TB contributed to the conception and design of the paper. AT, RJ, JO, NS and BMA contributed to acquisition of the data. AT and TB contributed to the analysis. All authors contributed to interpretation of data, reviewed the article for critical academic content and gave approval of the final draft. The authors declare no conflicts of interest.

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The results in this paper are not official statistics. They have been created for research purposes from the Integrated Data Infrastructure (IDI), managed by Statistics New Zealand. The opinions, findings, recommendations, and conclusions expressed in this paper are those of the author(s), not Statistics NZ, or the University of Otago. Access to the anonymised data used in this study was provided by Statistics NZ under the security and confidentiality provisions of the Statistics Act 1975. Only people authorized by the Statistics Act 1975 are allowed to see data about a particular person, household, business, or organization, and the results in this paper have been confidentialised to protect these groups from identification and to keep their data safe. Careful consideration has been given to the privacy, security, and confidentiality issues associated with using administrative and survey data in the

IDI. Further detail can be found in the Privacy impact assessment for the Integrated Data Infrastructure available from www.stats.govt.nz.

The results are based in part on tax data supplied by Inland Revenue to Statistics NZ under the Tax Administration Act 1994. This tax data must be used only for statistical purposes, and no individual information may be published or disclosed in any other form, or provided to Inland Revenue for administrative or regulatory purposes. Any person who has had access to the unit record data has certified that they have been shown, have read, and have understood section 81 of the Tax Administration Act 1994, which relates to secrecy. Any discussion of data limitations or weaknesses is in the context of using the IDI for statistical purposes, and is not related to the data's ability to support Inland Revenue's core operational requirements.

Conflict of interest

None.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2018.12.003.

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