Increased Diabetes Incidence in Greek and Italian Migrants to Australia

How much can be explained by known risk factors?

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OBJECTIVE — The aims of the study were to determine whether Greek or Italian migrants to Australia have an elevated incidence of type 2 diabetes compared with Australian-born individuals and to what extent any differences can be explained by known risk factors.

RESEARCH DESIGN AND METHODS — This was a prospective study of 34,097 men and women aged 40–69 years born in Greece, Italy, Australia, or New Zealand who were free from diabetes at baseline. For all self-reported cases of diabetes at the 4-year follow-up, a confirmation of diagnosis was sought from medical practitioners. Of these, anyone for whom there was no evidence against a diagnosis of type 2 diabetes was considered a case subject.

RESULTS — Follow-up was completed by 29,331 (86%) participants, and 334 case subjects were identified. The cumulative incidence of type 2 diabetes among Greek (2.6%) and Italian (2.4%) migrants was more than three times that in Australian-born (0.7%) individuals. After adjusting for age only, the odds ratios (ORs) for being of Greek and Italian origin compared with Australian origin were 3.8 (95% CI 2.9–5.0) and 3.3 (2.6–4.3), respectively. The only known risk factor for type 2 diabetes that materially affected these ORs was BMI. After adjusting for BMI and age, the ORs for being of Greek and Italian origin, respectively, were 2.4 (1.8–3.2) and 2.0 (1.5–2.6).

CONCLUSIONS — Greek and Italian migrants to Australia have a more than three times greater incidence of type 2 diabetes than Australian-born individuals, and this is only partly explained by BMI. Although weight control will remain important for these high-risk groups, identification of other risk factors is required.

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Migrants from Greece and Italy to Australia have higher mortality from type 2 diabetes (1) and approximately a twofold-higher prevalence than the Australian-born population (2–4). However, differences in mortality and prevalence could result from differences in survival of people with diabetes as well as differences in incidence. It is not clear to what extent the higher diabetes mortality and prevalence in Greek and Italian migrants reflect higher incidence or to what extent known risk factors can explain any increased incidence in southern European migrants.

Understanding why people of southern European origin are at high risk for type 2 diabetes is important, not only from the perspective of furthering our knowledge of diabetes risk factors in general, but also to inform interventions specific to this potentially high-risk group, which comprised ~6% of Australians age >65 years in 2000 (5).

Our aims were to determine whether people born in Greece or Italy have an elevated incidence of type 2 diabetes compared with the Australian-born individuals and to what extent any differences could be explained by known risk factors for type 2 diabetes, using data from the Melbourne Collaborative Cohort Study (MCCS).

RESEARCH DESIGN AND METHODS

— The MCCS was a prospective cohort study of 41,528 people (17,049 men) aged 27–75 years at baseline (99.3% were 40–69 years) and included 5,425 migrants from Italy and 4,535 from Greece or Macedonia. Recruitment occurred from 1990 to 1994. The Cancer Council Victoria's Human Research Ethics Committee approved the study protocol. Subjects gave written consent to participate and for the investigators to obtain access to their medical records.

Diabetes prevalence at baseline was calculated in 38,385 people after excluding 3,018 people born in the U.K. or Malta and 125 who could not be classified for glucose tolerance. For analyses of incidence, we also excluded subjects with self-reported diabetes at baseline, subjects whose measured plasma glucose at baseline was consistent with diabetes, and subjects who did not report diabetes at baseline but later reported a date of diabetes diagnosis before baseline. Subjects with heart attacks or angina were excluded because their reported diets were not representative of the cohort (e.g., they had low intakes of saturated fat), and we were unsure when they changed their diets. Other exclusions included people with reported energy intakes above or below the top or bottom 1% of the sex-specific distributions, subjects with missing data on alcohol consumption (as alcohol intake was used in calculating nutrient intakes), and subjects with missing

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values for baseline risk factors. These exclusions left 34,097 subjects for analyses of incidence.

Baseline glucose measurement

Blood was collected into 15-ml sodium heparin vacutainers. Immediately thereafter, a 0.5-ml aliquot was transferred into an Eppendorf tube and spun for 30 s in a Kodak Statspin centrifuge. Plasma glucose was measured using a Kodak Ektachem analyzer (Rochester, NY), which is based on the enzyme-catalyzed (glucose oxidase) reaction of glucose with molecular oxygen. For the 68% of participants who were fasting, plasma glucose values of ≥ 7.8 mmol/l were considered to represent diabetes, and for those who were not fasting, diabetes was defined as a value ≥ 11.1 mmol/l, which was consistent with the World Health Organization criteria that were current at the time (6).

Measurement of risk factors

A structured interview schedule was used to obtain information on potential risk factors at baseline, including country of birth, smoking, alcohol consumption, physical activity for recreation or exercise (walking, vigorous and less vigorous exercise), education, history of diabetes in first-degree relatives, and weight change in the past 5 years. Current alcohol intake was calculated in grams/day and categorized according to 1992 National Health and Medical Research Council of Australia criteria (7). Education was classified as "primary school or less," "some high or technical school," "completed high school or technical school," "some study toward degree/diploma," and "degree/diploma." Smoking was categorized as never, former, and current.

Standard methods were used to measure height, weight, and waist and hip circumferences, from which BMI and waist-to-hip ratio (WHR) were calculated. Resistance and reactance were measured using a bioelectrical impedance analyzer (BIA-101A; RJL Systems, Detroit, MI) and were used to calculate fat mass and fat-free mass (8).

Dietary information was collected using a 121-item food frequency questionnaire (FFQ), specifically developed for use in the MCCS (9), to reflect the intakes of the different country-of-birth groups. The FFQ results were used to calculate intakes of 29 common nutrients, 33 individual fatty acids, 5 carotenoids (all continuous), and 29 food groups (cate-gorical). Nutrients contributed by alcoholic beverages were also included.

Follow-up and ascertainment of diabetes

Incident cases of diabetes were identified from a questionnaire mailed to participants ~4 years after baseline with the last being diagnosed in 1998. If the questionnaire was not returned, it was completed by telephone when possible. Participants were asked, "Has a doctor ever told you that you have had diabetes?" Those who responded in the affirmative were asked to provide the year of diagnosis. Confirmation of the diagnosis and the type of diabetes was sought from doctors nominated by participants.

Statistical analysis

Logistic regression was used to determine how much of the association between country of birth and incidence of diabetes was explained by known risk factors, including age, sex, physical activity, weight change, education level, smoking status, alcohol intake, family history of diabetes, BMI, WHR, and dietary factors. Because the incidence of diabetes was low, the odds ratios (ORs) from the models are approximately equal to cumulative incidence ratios.

To identify possible dietary risk factors, each dietary intake variable for which there was a priori evidence of an association with diabetes risk (energy, fats, fiber, carbohydrate, sugar, magnesium, cereal-based foods, meat, fats/oils, vegetables, and fruit) was included separately in a model with all other covariates except BMI and WHR. Dietary variables that were associated with diabetes and had distributions by country of birth that were consistent with higher risk in Greek and Italian migrants were considered for inclusion in the next step of the analysis. Only white bread met these criteria and was included in combination with energy intake.

Next, forward stepwise regression was used to identify a parsimonious set of risk factors. Variables were added sequentially; at each step, the variable selected had the smallest P value. The process stopped when all remaining variables had a P value for entry to the model of at least 0.1. Smoking status, weight change, and country of birth were treated as categorical variables, and all other variables were treated as continuous.

Finally, variables were dropped se-quentially from this "full" model. At each step, the effect on the ORs of the country-of-birth terms was examined by temporarily dropping each variable singly. The variable that had the least impact on the country of birth ORs was then removed permanently from the model. Age was purposely retained in the model throughout this process.

To further clarify the role of BMI in the elevated diabetes risk observed in migrants, we also computed a model including the interaction of BMI as a continuous variable with country of birth, along with the other covariates in the "full" model. From this model, the estimated cumulative incidence of diabetes was calculated by country of birth for specific values of BMI for men and women separately, using the sex-specific mean values for age, WHR, and intakes of alcohol, white bread, and energy and assuming there was no family history of diabetes.

RESULTS

Baseline prevalence

At baseline, 2.9% of the Australian-born participants and 9.8 and 9.5% of Greek and Italian migrants, respectively, were classified as having diabetes. Most participants already knew they had diabetes; only 21, 15, and 15%, respectively, of Australian-, Greek-, and Italian-born participants classified as having diabetes were newly identified from blood glucose measurements (χ^2 test, $P \leq 0.001$).

Response to follow-up questionnaire

A total of 29,331 people (86% of eligible participants) completed the follow-up questionnaire on diabetes. People who completed follow-up had similar levels of baseline risk factors for type 2 diabetes compared with those who did not complete follow-up: BMI (mean of 26.7 vs. 27.2 kg/m^2), age (54.3 vs. 54.5 years), and fasting plasma glucose (5.5 vs. 5.5 mmol/l). Eighty-seven percent of women and 85% of men completed follow-up. Greek-born participants (80%) were slightly less likely to complete follow-up than Australian (87%)- or Italian (86%)-born individuals. The average length of follow-up was 4.4 years in Greek and Italian migrants and 4.0 years in the Australian-born participants.

Incidence of diabetes

A total of 422 (1.4%) participants reported a diagnosis of diabetes after base-

Table 1—*Distribution of risk factors for type 2 diabetes by country of birth*

	Australia	Greece/Macedonia	Italy
n	22,463	2,988	3,880
Medians			
Age (years)	54	54	56
25th–75th percentile	46–62	48–60	49–62
Height (cm)	165.5	160.4	159.6
25th–75th percentile	159.8–173.0	154.2–167.5	153.5–166.5
Weight (kg)	70.9	73.9	73.1
25th–75th percentile	62.2–80.9	65.6–82.1	64.9–81.3
BMI (kg/m^2)	25.5	28.2	28.4
25th–75th percentile	23.2–28.2	25.9–30.9	25.9–31.1
Waist (cm)	82.0	89.0	89.6
25th–75th percentile	73.2–92.0	80.0–96.4	81.2–97.0
Hip (cm)	100.0	102.1	102.3
25th–75th percentile	95.0–105.0	97.2–107.7	97.5–108.0
WHR	0.81	0.86	0.86
25th–75th percentile	0.75–0.90	0.79–0.93	0.80–0.93
Waist/height ratio	0.49	0.55	0.56
25th–75th percentile	0.45–0.54	0.50–0.59	0.51–0.60
Fat-free mass (kg)*	43.4	44.4	44.4
25th–75th percentile	39.0–55.1	38.9–54.6	39.0–54.2
Fat mass (kg)*	24.3	26.7	25.9
25th–75th percentile	19.4–30.1	21.9–32.7	21.0–31.9
Body fat content (%)*	35	37	36
25th–75th percentile	29–41	31–44	30–43
Percentages			
Moderate to high alcohol intake (%)	14.0	5.8	14.0
No physical activity (%)	17.6	35.9	35.3
Current female smoker (%)	8.7	6.7	6.0
Current male smoker (%)	10.5	22.4	20.6
Family history of diabetes (%)	16.4	16.5	25.8
Female (%)	62.7	57.4	57.4
Increased weight in last 5 years (%)	24.4	21.8	23.9
No secondary school (%)	3.3	69.5	61.2
Top quartile of white bread	28.1	50.3	58.6
Top quartile of whole-meal bread	24.8	15.3	12.1

*Some missing values (Australia, *n* = 22,381; Greece, *n* = 2,969; Italy, *n* = 3,871).

line. Of 368 people for whom there was a response from their doctor, 277 (75%) were confirmed as having type 2 diabetes. Of the people identified as case subjects, the percentages with confirmed type 2 diabetes were 86, 78, and 82% for Australian-, Greek-, and Italian-born individuals, respectively. Thus, it was unlikely that major differences in misclassification of new cases would account for the differences observed in incidence rates. Because the proportion confirmed was high, those for whom the doctor did not know the type or diabetes status were considered to be case subjects, as were those for whom no response was available because the doctor could not be found or did not complete the questionnaire. Subjects whose doctors reported that they had type 1 diabetes (*n* = 11), had IGT (*n* = 2), or did not have diabetes (*n* = 75) were classified as non–case subjects, along with those who did not report diabetes at the follow-up. This left 334 case subjects and 28,997 non–case subjects.

There were 162 case subjects among the Australian-born individuals (cumulative incidence 0.7%), 78 (2.6%) in Greek migrants, and 94 (2.4%) in Italian migrants. Table 1 shows that all measures of obesity (body weight, BMI, WHR, waist circumference, hip circumference, fat mass, and fat mass as percentage of body mass) were greater in migrants, but migrants were shorter than the Australian-born individuals and had similar fat-free mass. Migrants were less likely to be women, were more likely to report no physical activity, were more likely to be current smokers (men only), had less education, and ate white bread more frequently compared with the Australian-born individuals. Italian migrants were more likely to report a family history of diabetes, and Greek migrants consumed less alcohol than the Australian- or Italian-born individuals.

Education, weight change over the last 5 years, physical activity, and smoking were not included in the "full" model from the initial forward stepwise regression. Age, family history of diabetes, WHR, BMI, and frequency of white bread intake were all positively associated with risk of diabetes, whereas alcohol intake demonstrated an inverse association. Men had a lower incidence than women.

Table 2 shows that after adjustment for all other risk factors in the "full" model, the ORs in the migrants were approximately two times higher than that in the Australian-born individuals. Removing variables from the model had little impact on either OR until BMI was removed (Table 2). With adjustment for age only, the ORs in Greek and Italian migrants
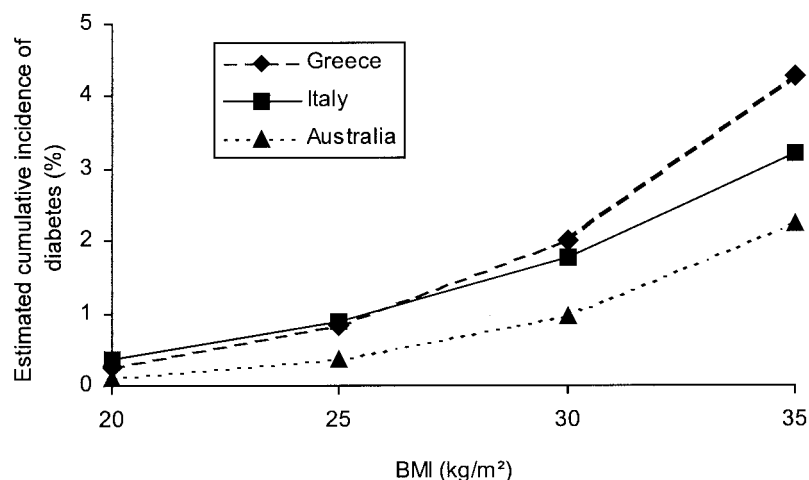
Table 2—*Effect on ORs for country of birth of removing variables sequentially from a logistic regression model predicting type 2 diabetes incidence*

	Greece	Italy
Full model*	2.1 (1.6–2.8)	1.7 (1.3–2.3)
Remove sex	2.1 (1.6–2.7)	1.7 (1.3–2.3)
Remove white bread and kilojoules	2.1 (1.6–2.8)	1.8 (1.4–2.3)
Remove alcohol	2.3 (1.7–3.0)	1.8 (1.4–2.3)
Remove family history	2.2 (1.7–2.9)	1.9 (1.4–2.4)
Remove lnWHR	2.4 (1.8–3.2)	2.0 (1.5–2.6)
Remove lnBMI, adjusted for age only	3.8 (2.9–5.0)	3.3 (2.6–4.3)

Data are OR (95% CI). ORs for Greek- and Italian-born individuals compared with Australian-born individuals. *The full model contains all variables listed in the table; these were sequentially removed from the model, as indicated, until only age remained. ln, log-transformed variable.

Figure 1—*Estimated cumulative incidence of type 2 diabetes by BMI according to country of birth in men with no family history of diabetes and with mean values for age and WHR and intakes of alcohol, white bread, and energy.*

compared with Australian-born individuals were 3.8 and 3.3, respectively (Table 2), indicating that BMI explained almost 50% of the excess relative risk of diabetes observed in southern European migrants. Substituting glycemic index for white bread made little difference to our findings. Repeating the analyses with cases restricted to those confirmed as type 2 diabetes by the doctor also made no substantive difference to our findings.

There was little evidence for an interaction between country of birth and BMI in the "full" model ($P = 0.14$). Figure 1 illustrates the relationship between estimated cumulative incidence of type 2 diabetes by BMI for each country-of-birth group in men, adjusting for other variables in the "full" model, including the interaction term. The incidence among migrants is higher than in Australian-born individuals across a range of BMI values. The results for women were similar, although the cumulative incidence was lower (data not shown).

CONCLUSIONS — The baseline prevalence and the cumulative incidence of type 2 diabetes were more than three times higher in migrants born in Greece or Italy than in the Australian-born individuals. Higher BMI in the migrants was responsible for approximately one-half the excess relative risk in incidence, whereas other risk factors for diabetes, including WHR and diet, had little impact on the remaining excess relative risk. Our findings of a more than threefold higher incidence in the Greek- and Italian-born individuals is consistent with the higher prevalence observed in Australian cross-sectional studies (2–4).

The high response rate in our study and the small differences between respondents and nonrespondents should minimize response bias. The 10% longer follow-up period among Greek and Italian migrants would have contributed only a small part of their excess incidence. Unlike some studies of diabetes incidence (10,11), we measured blood glucose at baseline and excluded those whose levels were consistent with diabetes.

At follow-up, doctors confirmed the diagnosis of type 2 diabetes for 75% of the self-reported cases. This compares favorably with the results from the Iowa Women's Health Study in which, in a validation substudy, diagnosis was confirmed in only 64% of self-reported cases (11). Some incident cases would have been missed because we did not screen participants at follow-up, but underascertainment of cases would not affect the results if not associated with the exposure (12). Case subjects who would have been diagnosed on the basis of isolated postchallenge hyperglycemia at baseline would have been missed, which possibly contributed to our low prevalence of undiagnosed diabetes. The slightly lower proportion of undiagnosed cases at baseline among migrants indicates that surveillance may be higher in this group and could have contributed marginally to their higher incidence. The responses from doctors indicated that only 46 of the 334 cases had a postchallenge glucose value, and of these, only 11 had no other glucose value. Thus, our incidence rates were unlikely to be greatly elevated by people who would have been diagnosed with diabetes at baseline due to isolated postchallenge hyperglycemia.

Imperfect measurement of known risk factors for diabetes may have limited our ability to explain the differences in risk of diabetes by country of birth. The questions on physical activity obtained no information about duration of activity, sedentariness, or about incidental forms of physical activity, such as gardening and household chores, which might have explained some of the increased risk in migrants. The difficulties of obtaining accurate information on diet (13) and alcohol consumption (14) are well known, and the quality of the information may have varied by country of birth.

A number of different measures of body size and shape were available from the MCCS. The combination of BMI and WHR was chosen to cover both overall and abdominal obesity. However, BMI does not differentiate between lean and fat mass, and WHR cannot distinguish between subcutaneous and visceral abdominal fat, the latter of which may be most relevant to insulin resistance (15). The inability of our obesity measures to fully explain differences in diabetes risk may be partly due to them not accurately reflecting differences in metabolically important adipose tissue. The bioimpedance-based estimates of fat and fat-free mass did not appear to be stronger predictors of type 2 diabetes incidence than BMI and WHR.

Despite the strength of the association between obesity and type 2 diabetes, differences in obesity have not fully explained differences in prevalence of type 2 diabetes observed in other studies where distinct ethnic groups live in similar environments. For example, Stern et al. (16) found that Mexican Americans had elevated prevalence of type 2 diabetes com-

pared with Anglo-Americans, even adjusting for obesity. No other risk factors were included in the analysis, but it was suggested that dietary composition, physical activity, and genetic susceptibility could contribute to the differences observed (16). Similar results were observed among village women in coastal Papua New Guinea (17). However, there was no evidence in a comparison of diabetes prevalence across 11 European centers to suggest that Italians in Italy are a particularly high-risk group (18). No comparable data were available for Greece. Thus, a genetic susceptibility to diabetes in Greek and Italian migrants is unlikely to explain all the excess risk.

Several lines of evidence suggest that early growth restriction leads to an increased risk of diabetes and that the adverse effect of low birth weight is enhanced by adult obesity (19). It is possible that early growth restriction among the Greek and Italian migrants could contribute to the increased risk of type 2 diabetes. Adult height, which is a crude marker of early nutritional status within a population (20), was lower in the Greek- and Italian-born individuals than in the Australian-born individuals.

In conclusion, we have observed that even after accounting for higher BMI and WHR, Greek and Italian migrants in the MCCS experienced type 2 diabetes incidence rates approximately two times higher than those seen in Australian-born men and women. Our results also highlight the need for further research to identify other risk factors accounting for the unexplained excess of diabetes in Greek- and Italian-born Australians.

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