# A New Zealand Linkage Study Examining the Associations Between A1C Concentration and Mortality

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**OBJECTIVE** — To examine associations between A1C concentration and mortality in a New Zealand population.

**RESEARCH DESIGN AND METHODS** — During a Hepatitis Foundation screening campaign for hepatitis B (1999–2001), participants were offered A1C testing. The participants were anonymously linked to the national mortality collection to 31 December 2004. Hazard ratios (HRs) and 95% CIs adjusted for age, ethnicity, smoking, and sex were estimated using Cox regression.

**RESULTS** — There were 47,904 participants (71% Mâori, 12% Pacific, 5% Asian, and 12% other). A1C measurements were categorized as <4.0% ($n = 142$), 4.0 to <5.0% (reference category; $n = 12,867$), 5.0 to <6.0% ($n = 30,222$), 6.0 to <7.0% ($n = 2,669$), and ≥7.0% ($n = 1,596$); there were also 408 participants with a previous diabetes diagnosis. During the follow-up period, 815 individuals died. In those without a prior diabetes diagnosis, there were steadily increasing HRs from the A1C reference category to the highest category (≥7.0%; HR 2.36 [95% CI 1.72–3.25]). As well as all-cause mortality, A1C was associated with mortality from diseases of the circulatory system; endocrine, nutritional, metabolic, and immunity disorders; and other and unknown causes. Mortality was also elevated in those with a prior diabetes diagnosis (5.19 [3.67–7.35]), but this was only partially explained by their elevated A1C levels.

**CONCLUSIONS** — This is the largest study to date of A1C levels and subsequent mortality risk. It confirms previous findings that A1C levels are strongly associated with subsequent mortality in both men and women without a prior diabetes diagnosis.

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A1C reflects overall blood glucose levels over a period of 2–3 months and is used to monitor diabetes treatment (1–3). As the level of A1C is not affected by recent meals and does not require a fasting blood sample, it is a possible alternative to fasting plasma glucose and 2-h postload plasma glucose for preliminary screening for undiagnosed diabetes (1,2,4–6). A1C is also associated with other risk factors for cardiovascular disease and diabetes, including low birth weight (7).

Only a few prospective studies have examined the associations between A1C among subjects initially free of diabetes and subsequent risk of mortality (8–12). Each of these studies found associations with subsequent mortality. A1C levels have also been associated with mortality in patients with type 1 diabetes (13) and nondiabetic chronic kidney disease (14) and with incident cardiovascular disease (15).

The largest prospective study to date is the Norfolk component of the European Prospective Investigation into Cancer and Nutrition; this involved 4,662 men and 5,570 women aged 45–79 years (9,10). They had an A1C measurement during 1995–1997 and were followed to January 2003. An increase of 1% in A1C was associated with a 26% increase in risk of death independent of age, blood pressure, serum cholesterol, BMI, and cigarette smoking. This effect remained after people with known diabetes, an A1C concentration ≥7%, or a history of cardiovascular disease were excluded (10). Moreover, A1C levels appeared to explain most of the excess mortality risk of diabetes and to be a continuous risk factor through the whole population distribution. Khaw et al. (9) concluded that the predictive value of A1C for total mortality was greater than that previously documented for cholesterol concentration, BMI, and blood pressure. The study also found similar patterns for cardiovascular disease events.

Here, we report the findings on the relationship between A1C levels and subsequent mortality in the participants in a New Zealand population-based screening program.

## RESEARCH DESIGN AND METHODS

The methods of the survey have been described previously (16). Between 1999 and 2001, free hepatitis B screening was offered in the lower half of the North Island of New Zealand. The program was targeted at non-European (predominantly Mâori, Pacific, and Asian) adults. Participants were recruited through caravans located in public places such as shopping malls. All participants who reported that they did not have diabetes were offered an A1C measurement as an additional test at the same time as the hepatitis B test. For the A1C measurements, all of the samples were analyzed in an International Accreditation New Zealand–accredited laboratory using a standardized Bio-Rad Assay and Variant analyzer.

**Table 1—*Characteristics of 47,904 participants included in the study***

| | | A1C levels | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | All | <4.0% | 4.0 to <5.0% | 5.0 to <6.0% | 6.0 to <7.0% | ≥7.0% | Prior diabetes diagnosis | P value* |
| Total | 47,904 (100) | 142 (0.3) | 12,867 (26.9) | 30,222 (63.1) | 2,669 (5.6) | 1,596 (3.3) | 408 (0.9) | |
| Sex | | | | | | | | |
| Male | 21,280 (44.4) | 60 (42.3) | 5,251 (40.8) | 13,774 (45.6) | 1,186 (44.4) | 825 (51.7) | 184 (45.1) | <0.001 |
| Female | 26,624 (55.6) | 82 (57.8) | 7,616 (59.2) | 16,448 (54.4) | 1,483 (55.6) | 771 (48.3) | 224 (54.9) | |
| Ethnicity | | | | | | | | |
| European and other | 5,844 (12.2) | 17 (12.0) | 2,463 (19.1) | 3,172 (10.5) | 110 (4.1) | 65 (4.1) | 17 (4.2) | <0.001 |
| Mâori | 33,753 (70.5) | 99 (69.7) | 8,520 (66.2) | 21,745 (72.0) | 1,949 (73.0) | 1,116 (69.9) | 324 (79.4) | |
| Pacific | 5,904 (12.3) | 8 (5.6) | 1,208 (9.4) | 3,877 (12.8) | 457 (17.1) | 311 (19.5) | 43 (10.5) | |
| Asian | 2,403 (5.0) | 18 (12.7) | 676 (5.3) | 1,428 (4.7) | 153 (5.7) | 104 (6.5) | 24 (5.9) | |
| Age (years) | | | | | | | | |
| 0–30 | 15,866 (33.1) | 76 (53.5) | 6,228 (48.4) | 9,257 (30.6) | 215 (8.1) | 81 (5.1) | 9 (2.2) | <0.001 |
| 31–40 | 13,788 (28.8) | 36 (25.4) | 3,929 (30.5) | 8,990 (29.8) | 525 (19.7) | 257 (16.1) | 51 (12.5) | |
| 41–50 | 10,143 (21.2) | 21 (14.8) | 1,914 (14.9) | 6,912 (22.9) | 718 (26.9) | 482 (30.2) | 96 (23.5) | |
| ≥51 | 8,107 (16.9) | 9 (6.3) | 796 (6.2) | 5,063 (16.8) | 1,211 (45.4) | 776 (48.6) | 252 (61.8) | |
| Smoking status | | | | | | | | |
| Never smoker | 16,876 (35.2) | 57 (40.1) | 4,796 (37.3) | 10,203 (33.8) | 996 (37.3) | 664 (41.6) | 160 (39.2) | <0.001 |
| Ex-smoker | 5,211 (10.9) | 11 (7.8) | 1,371 (10.7) | 3,124 (10.3) | 386 (14.5) | 243 (15.2) | 76 (18.6) | |
| Current smoker | 19,191 (40.1) | 43 (30.3) | 4,702 (36.5) | 12,949 (42.9) | 904 (33.9) | 469 (29.4) | 124 (30.4) | |
| Unknown | 6,626 (13.8) | 31 (21.8) | 1,998 (15.5) | 3,946 (13.1) | 383 (14.4) | 220 (13.8) | 48 (11.8) | |

Data are frequency (%). *P value of the association between A1C level and explanatory variable.

Ethnicity was self-identified, as is standard in New Zealand health research (17). Participants who reported more than one ethnicity were classified using the standard system of prioritization, in which participants who identify as Mâori are classified as Mâori (even if they also recorded other ethnicities); of the remainder, those who identify as Pacific are classified as Pacific, and so on. When ethnicity was not reported in the hepatitis B program records, the participant was assigned their ethnicity as recorded in the National Health Index (NHI) database. (The NHI is a unique identifier used in the New Zealand Public Health system.) Smoking data were self-reported at the time of the blood sampling for the A1C measurement.

Although participants who reported having diabetes were not offered an A1C test, it was nevertheless found that 408 participants had previously been diagnosed with diabetes; these were identified from hospitalizations or general practice prescriptions for insulin, an oral hypoglycemic, or a home glucose-monitoring kit. These were included in the analysis as a separate category (none had A1C levels of <4%, 4 had A1C levels of 4.0 to <5.0%, 40 had A1C levels of 5.0 to <6.0%, 71 had A1C levels of 6.0 to <7.0%, and 293 had A1C levels of ≥7.0%).

We have examined the subsequent risk of mortality to the end of 2004 in these participants by linkage to the national mortality collection data held by the New Zealand Health Information Service. Linkage was performed using the NHI identifier. Follow-up extended from the date of the A1C measurement to the date of death or to 31 December 2004 (in those who had not died before that date).

All analyses were conducted using Stata, version 8.2 (Stata, College Station, TX). Preliminary analyses involved standard $\chi^2$ tests (18) to compare the A1C distributions (excluding those with a prior diabetes diagnosis) by sex, ethnicity, age, and smoking status. Cox proportional hazards regression was used to model the mortality hazard ratios (HRs). The numbers were very small in the <4% category, so the 4.0 to <5.0% category was used as the reference, with the exception of the analyses for "endocrine, nutritional and metabolic and immunity disorders" (ICD-9 240–279), for which there were no deaths in this category, and therefore the 5.0 to <6.0% category was used as the reference. All models were adjusted for age (as a continuous variable), self-reported smoking status, sex, and ethnicity (Mâori, Pacific, Asian, and other). We performed tests for heterogeneity and found no statistically significant interactions by sex, ethnicity, or smoking status. As noted above, this survey was added on to a population-based screening survey for hepatitis B. A total of 5.4% of participants tested positive for the hepatitis B surface antigen, and adjustment for hepatitis B status made no difference to the study findings. For simplicity, the unadjusted estimates are therefore presented.

**RESULTS** — A1C measurements were obtained for 48,673 subjects. Of these, 769 (1.6%) did not appear to be correctly matched to the NHI database (e.g., dates of birth of >366 days difference between the hepatitis and NHI databases or a date of death before the date of the A1C test). All analyses are therefore based on the remaining 47,904 participants. As shown in Table 1, there was a slight overall preponderance of female subjects but an excess of male subjects in the high (≥7.0%) A1C category. Overall, 71% were Mâori, 12% were Pacific, 5% were Asian, and 12% had other ethnicities. Pacific and Asian people were overrepresented in the high (≥7.0%) A1C category. The mean age was 38 years. The median A1C level was 5.2%; 91.0% of the subjects (excluding those with diagnosed diabetes) had levels of A1C <6%, while 5.6% had moderately elevated levels (6.0 to <7.0%) and 3.4% had highly elevated levels (≥7.0%).

The median follow-up period was 4.4 years (range 2 days to 5.3 years). During

the follow-up period, 815 participants died. For mortality (Table 2), there were steadily increasing HRs from the A1C reference category (4.0 to <5.0%; HR 1.0) to the highest category (≥7.0%; HR 2.36 [95% CI 1.72–3.25]). Among those without a previous diabetes diagnosis, the highest HR was observed in participants with the lowest A1C concentrations (<4.0%; 2.90 [0.91–9.19]), although this figure was based on only three deaths and was of marginal statistical significance. Table 2 also shows the mortality findings by sex, ethnicity, age, and smoking status. In general, these subgroup analyses yielded similar findings to the overall analyses, and for the highest levels (≥7.0%) of A1C, the HRs in each subgroup were similar to those for all study participants combined. The exception to the overall pattern of increasing HRs with increasing A1C levels was the data for Pacific participants, in which mortality showed no association with A1C levels; however, the numbers involved were low and the CIs for the HRs were consistent with those for all study participants combined. For the participants with A1C concentrations of <4.0%, all three deaths occurred in male subjects, and the association was statistically significant (4.53 [1.41–14.63]).

Table 3 shows the findings for specific causes of death. As expected, A1C was strongly associated with mortality from "endocrine, nutritional and metabolic and immunity disorders." (The 47 deaths in this category included 38 classified as diabetes; 18 of 19 deaths in the highest A1C category and 19 of 20 deaths in those with a prior diabetes diagnosis were classified as diabetes.) A1C was strongly associated with deaths from diseases of the circulatory system (particularly ischemic heart disease). There were weaker associations with deaths from cancer and other and unknown causes.

When A1C was analyzed as a continuous variable (not shown in tables) adjusted for sex, ethnicity, age, and smoking status, the HR associated with a 1% increase in A1C level in those without diabetes was 1.16 (95% CI 1.11–1.21), representing an increase in mortality of 16% for each 1% increase in A1C level. However, in those with a prior diabetes diagnosis, A1C (analyzed as a continuous variable) was, in general, not associated with their subsequent risk of death (HR 0.98 [95% CI 0.86–1.12]). The reason for this was that the association of A1C with mortality was not monotonically increas-

Table 2—HRs showing the association between A1C levels and mortality in a New Zealand population-based sample by sex, ethnicity, and smoking status

| Deaths | n | <4.0% n | <4.0% HR (95% CI) | 4.0 to <5.0% n | 4.0 to <5.0% HR (95% CI) | 5.0 to <6.0% n | 5.0 to <6.0% HR (95% CI) | 6.0 to <7.0% n | 6.0 to <7.0% HR (95% CI) | ≥7.0% n | ≥7.0% HR (95% CI) | Prior diabetes diagnosis n | Prior diabetes diagnosis HR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Total* | 815 | 3 | 2.90 (0.91–9.19) | 82 | 1.0† | 449 | 1.33 (1.05–1.70) | 129 | 2.12 (1.58–2.85) | 87 | 2.36 (1.72–3.25) | 65 | 5.19 (3.67–7.35) |
| Gender‡ | | | | | | | | | | | | | |
| Males | 471 | 3 | 4.53 (1.41–14.63) | 49 | 1.0† | 261 | 1.29 (0.94–1.77) | 66 | 1.87 (1.26–2.78) | 55 | 2.49 (1.65–3.75) | 37 | 5.29 (3.35–8.36) |
| Females | 344 | 0 | § | 33 | 1.0† | 188 | 1.35 (0.92–1.98) | 63 | 2.41 (1.53–3.78) | 32 | 2.11 (1.26–3.53) | 28 | 4.98 (2.91–8.52) |
| Ethnicity‖ | | | | | | | | | | | | | |
| European and other | 55 | 1 | 20.71 (2.55–167.97) | 12 | 1.0† | 34 | 1.10 (0.54–2.22) | 4 | 2.31 (0.68–7.88) | 4 | 2.56 (0.71–9.19) | 0 | § |
| Māori | 689 | 2 | 2.34 (0.57–9.59) | 61 | 1.0† | 378 | 1.44 (1.09–1.90) | 112 | 2.29 (1.65–3.19) | 77 | 2.71 (1.90–3.85) | 59 | 5.64 (3.86–8.24) |
| Pacific | 59 | 0 | § | 8 | 1.0† | 29 | 0.63 (0.27–1.43) | 12 | 1.06 (0.39–2.84) | 5 | 0.53 (0.16–1.75) | 5 | 2.68 (0.77–9.28) |
| Asian | 12 | 0 | § | 1 | 1.0† | 8 | 2.04 (0.24–17.07) | 1 | 0.55 (0.02–14.62) | 1 | 1.70 (0.10–29.73) | 1 | 13.27 (0.66–265.17) |
| Smoking status¶ | | | | | | | | | | | | | |
| Never smoker | 271 | 2 | 5.74 (1.33–24.79) | 21 | 1.0† | 142 | 1.61 (1.01–2.58) | 49 | 3.00 (1.75–5.14) | 32 | 2.97 (1.67–5.29) | 25 | 6.55 (3.55–12.08) |
| Ex-smoker | 121 | 0 | § | 11 | 1.0† | 65 | 1.31 (0.67–2.54) | 19 | 1.49 (0.67–3.29) | 14 | 2.04 (0.89–4.70) | 12 | 3.45 (1.43–8.29) |
| Current smoker | 294 | 0 | § | 36 | 1.0† | 179 | 1.13 (0.78–1.64) | 34 | 1.55 (0.93–2.56) | 26 | 1.88 (1.10–3.23) | 19 | 5.28 (2.92–9.54) |
| Unknown | 129 | 1 | 5.37 (0.70–41.37) | 14 | 1.0† | 63 | 1.45 (0.80–2.64) | 27 | 2.96 (1.45–6.06) | 15 | 2.95 (1.34–6.49) | 9 | 5.95 (2.37–14.93) |

* Adjusted for age, sex, ethnicity, and smoking status. †Reference category. ‡Adjusted for age, ethnicity, and smoking status. §Not calculated due to zero deaths. ‖Adjusted for age, sex, and smoking status. ¶Adjusted for age, sex, and ethnicity.

**Table 3—HRs for the association between A1C levels and mortality in a New Zealand population-based sample by cause of death**

| Site (ICD-9) | | A1C levels | | | | | | | | | | | Prior diabetes diagnosis | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | | <4.0% | | 4.0 to <5.0% | | 5.0 to <6.0% | | 6.0 to <7.0% | | ≥7.0% | | | | |
| | n | n | HR (95% CI)* | n | HR (95% CI)* | n | HR (95% CI)* | n | HR (95% CI)* | n | HR (95% CI)* | | n | HR (95% CI)* |
| All deaths | 815 | 3 | 2.90 (0.91–9.19) | 82 | 1.0† | 449 | 1.33 (1.05–1.70) | 129 | 2.12 (1.58–2.85) | 87 | 2.36 (1.72–3.25) | | 65 | 5.19 (3.67–7.35) |
| All cancers (140–239) | 262 | 0 | ‡ | 26 | 1.0† | 154 | 1.10 (0.72–1.68) | 44 | 1.50 (0.90–2.48) | 23 | 1.29 (0.72–2.30) | | 15 | 2.35 (1.22–4.53) |
| Endocrine, nutritional & metabolic, and immunity disorders (240–279) | 47 | 0 | ‡ | 0 | ‡ | 6 | 1.0† | 2 | 1.79 (0.35–9.18) | 19 | 27.17 (10.20–72.39) | | 20 | 90.36 (33.42–244.33) |
| Diseases of circulatory system (390–459) | 280 | 1 | 3.95 (0.53–29.51) | 20 | 1.0† | 151 | 1.43 (0.89–2.30) | 54 | 2.46 (1.44–4.19) | 32 | 2.44 (1.37–4.35) | | 22 | 4.75 (2.53–8.92) |
| Ischemic heart disease (410–414) | 166 | 1 | 6.26 (0.81–48.13) | 13 | 1.0† | 91 | 1.27 (0.71–2.30) | 26 | 1.75 (0.88–3.49) | 23 | 2.55 (1.26–5.16) | | 12 | 3.89 (1.72–8.77) |
| Other and unknown causes | 226 | 2 | 4.53 (1.09–18.85) | 36 | 1.0† | 138 | 1.41 (0.96–2.06) | 29 | 2.52 (1.47–4.31) | 13 | 1.86 (0.95–3.65) | | 8 | 3.88 (1.72–8.74) |

*Adjusted for age, sex, ethnicity, and smoking status. †Reference category. ‡Not calculated due to zero deaths.

ing in this group (i.e., it did not always increase as the level of A1C increased); the proportion who died was 12.5% (5 of 40) in those with A1C levels of 5.0 to <6.0%, 25.4% (18 of 71) in those with levels of 6.0 to <7.0%, and 14.3% (42 of 293) in those with levels of ≥7.0%. Overall, a prior diabetes diagnosis was strongly associated with risk of death (3.35 [2.58–4.34]; this differs from the estimate of 5.19 given in Table 2, which involved a comparison with those without diabetes with an A1C of 4.0 to <5.0%, whereas the comparison here is with all those without diabetes), but this risk reduced somewhat (2.46 [1.86–3.26]) when adjusted for A1C. If the adjustment was conducted using A1C as a categorical rather than a continuous variable (to allow for the nonlinear association between A1C and mortality), the HR in those with a prior diabetes diagnosis reduced to 2.44 (95% CI 1.82–3.26).

## CONCLUSIONS

Before discussing the findings of this study, several limitations should be acknowledged. The main limitation is the lack of anthropometric data and information on other cardiovascular risk factors. The short follow-up time of this study meant that we could not restrict the analyses to the cases diagnosed at least two years after the A1C test to eliminate subjects with undetected disease at the time of the blood test. Therefore, we cannot exclude the possibility that diabetes at the time of the A1C test might have led to elevated glucose levels. We conducted separate analyses for participants with a previous diagnosis of diabetes on the basis of hospitalizations or general practice prescriptions for insulin, an oral hypoglycemic, or a home glucose-monitoring kit, but there still may have been some participants with diagnosed diabetes that were being treated with lifestyle interventions rather than medication, and there may also have been some participants with undiagnosed diabetes (particularly those with A1C levels ≥7.0%). As with all studies of this type, there may have been misclassification of specific causes of death because of the well-recognized tendency for diabetes to be underreported as a cause of death (19,20).

The current study was based on participants in an intensive population-based hepatitis B screening program, and these "volunteers" may not be representative of the general population. However, we have made internal comparisons (based on A1C levels) within the group that participated in the screening program, and it is highly unlikely that these internal comparisons would be biased due to any "volunteer effect."

On the other hand, the use of A1C levels to assess blood glucose concentrations over time is one of the major strengths of this study. These levels are not subject to day-to-day variations, as fasting and 2-h oral glucose tolerance tests can be (1,2). A second strength of this study is the large numbers involved, with 815 deaths compared with 521 in the study of Khaw et al. (10). This has provided relatively good power to examine cause-specific mortality, and also to examine the mortality risks by sex, ethnicity, and smoking status. A further strength is that the study is community based rather than being based on a selected patient group. Finally, an additional strength of the study is the likely near-complete ascertainment of mortality in the cohort using national New Zealand mortality data.

Bearing these limitations and strengths in mind, the findings are of considerable interest. As expected, excess mortality was evident at high A1C concentrations (≥7.0%), and there was a dose response with increasing level of A1C in those without diabetes. The HRs steadily increased from the A1C reference category to the highest category (≥7.0%; HR 2.36 [95% CI 1.72–3.25]). This is consistent with the previous findings of Khaw and colleagues (9,10), who also found increasing risks for total mortality throughout the whole range of concentrations, including those below the threshold commonly accepted for diabetes. In our study, a 1% increase in A1C level was associated with a 16% increase in mortality in those without diabetes, compared with the figure of 26% estimated by Khaw et al. (10).

A1C was strongly associated with mortality from "endocrine, nutritional and metabolic and immunity disorders." (The 47 deaths in this category included 38 categorized as being from diabetes.) and diseases of the circulatory system, particularly ischemic heart disease. There were weaker associations with deaths from cancer and other and unknown causes. The weak association with cancer mortality observed in the current analyses is consistent with our previously published findings (16) for cancer incidence in the same cohort.

A1C levels have also been associated

with mortality in patients with type 1 diabetes (13), with mortality in patients with nondiabetic chronic kidney disease (14), with incident cardiovascular disease (15), and with cardiovascular disease events (deaths and hospital admissions) (10). Other studies (8,12) have also found that A1C is associated with cardiovascular disease, but as Khaw et al. (9) note, they have generally focused on the high end of the A1C distribution. However, few of these studies have adjusted for other cardiovascular risk factors, and the current study also did not have information on such risk factors. In fact, a prospective cohort study of 26,563 U.S. female health professionals aged ≥45 years without diagnosed diabetes or vascular disease found that A1C levels predicted diabetes but not cardiovascular disease (21). In a case-control study nested in the Women's Health Study cohort, A1C was associated with future cardiovascular risk in women without diabetes, but the association disappeared when other cardiovascular risk factors (smoking, BMI, serum cholesterol, C-reactive protein level, systolic blood pressure, family history of premature myocardial infarction, and current use of hormone therapy) were adjusted for, whereas diabetes was a strong independent determinant of cardiovascular risk even after adjustment for A1C levels (22).

Our study is only the second major study (after Khaw et al. [10]) to include large numbers of women. We found very similar HRs in men and women for A1C and overall and cause-specific mortality, as did Khaw et al. (10).

Our study is apparently the first to have sufficient numbers of subjects to examine the effects of very low levels of A1C. Whereas the studies of Khaw and colleagues (9,10) used <5% as its lowest exposure category, in our study we had a small group of participants ($n = 142$) with A1C concentrations of <4.0%, and this group had the highest mortality rates among those without a previous diagnosis of diabetes (HR 2.90 [95% CI 0.92–9.19]). This figure was based on only three deaths and was of marginal statistical significance. To our knowledge, this finding has not been reported previously and warrants further investigation. However, it should be regarded as very preliminary, since it may be due to chance and because it is difficult to determine in a study of this type whether any increased risk of mortality in those with very low A1C levels is causal or merely a result of

reverse causation due to preexisting disease (23).

There was no overall association of A1C level (analyzed as a continuous variable) with subsequent mortality in those with a prior diabetes diagnosis at the time of A1C testing. However, this group is unlikely to be typical of people with diabetes, particularly since they did not report having diabetes at the time of the screening test. Those with a previous diabetes diagnosis and an A1C level in the range of 6.0 to <7.0% had a higher risk of dying during follow-up (25.4%) than those with a previous diabetes diagnosis and an A1C level of ≥7% (14.3%). The reasons for this are unclear, but the previous diabetes diagnosis group was defined based on hospitalizations or general practice prescriptions for insulin, an oral hypoglycemic, or a home glucose-monitoring kit. Thus, all of the prior diabetes diagnosis group had received treatment for their diabetes, which would have affected both their A1C levels and their risk of mortality. Furthermore, the number of deaths involved was not large, and the 95% CIs for the HR estimates in those with diabetes are, in general, not incompatible with those in participants without diabetes. A prior diabetes diagnosis was strongly associated with risk of death (HR 3.35 [95% CI 2.58–4.34]), but this risk was somewhat reduced (2.46 [1.86–3.26]) when adjusted for A1C. However, the reduction in risk was much less than that previously reported by Khaw et al. (9), who observed a much larger reduction from a relative risk of 2.56 to a relative risk of 1.33 after adjusting for A1C level.

In summary, this is the largest study conducted to date of A1C levels and subsequent risk of mortality. It confirms previous findings that A1C levels are strongly associated with subsequent mortality in both men and women who have not been diagnosed with diabetes. The excess mortality risk was from a range of causes but was particularly strong for endocrine, nutritional, and metabolic and immunity disorders and for cardiovascular disease. However, A1C levels only partially accounted for the excess mortality risk in participants with a previous diagnosis of diabetes.

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