Excess mortality due to high values of glycated haemoglobin among non-diabetic subjects

M.Fahlén (1), M. Österbrand (2), B.Eliasson (3), J.Ramebäck (4), A.Odén (5)

1.Kungälv Hospital, Sweden (e-mail martin.fahlen@mailbox.hogia.net). 2. Uddevalla Hospital, Sweden. 3. Sahlgrenska University Hospital, Göteborg, Sweden. 4. Journalia AB, Kil, Sweden. 5. Chalmers University of Technology, Göteborg, Sweden.

Background

In a study by Khaw et al (BMJ 2001;322:1-6) baseline of HbA1c was found to be a predictor of death of the same importance whether a diabetes diagnosis was present or not.

Aim

To use a stronger predictor (A) than the use of baseline of HbA1c (B) in order to quantify the size of the population of non-diabetic individuals characterized by high HbA1c levels and having the same risk of death as those with diabetes (ND-HH).

Material and methods

The frequency function of HbA1c was estimated as a mixture of two normal frequency functions among individuals without diabetes from Khaw et al. This study provided us with data showing that the increase in risk of death per each percentage-unit increase of a single measured HbA1c. In the age interval 45–79 years, 3.4 % had diabetes with a 2.30 times higher age- adjusted risk of death than individuals without diabetes. By using their estimations and our own data from the diabetes-management system Diab-Base (Österbrand et al IDF 2006 nr851-oral presentation) we were able to determine the proportion of ND-HH.

Results

The baseline HbA1c, that was used by Khaw et al., is probably not the best predictor of death among all functionals of the continuous HbA1c-curve. There is much evidence that a time-weighted function of the continuous HbA1c-curve is superior to the baseline value (Fig1).

If a predictor A comprises all predictive information that another predictor B comprises then the following relationship between their gradients is true: log(gradient of B) / log(gradient of A) = |r| , where r is the correlation coefficient between A and B. In our case the predictor B is the baseline HbA1c and A is a time-weighted function of the continuous HbA1c-curve. By simulation from our own data we have determined r to be around 0.50. In order to simplify the consideration we assume that the variable A could be transformed by an almost linear transformation so that the distribution coincides with that of B, the baseline HbA1c. The beta coefficient of baseline HbA1c was log(1.27) in the Cox model for death. Then the transformed variable will have a corresponding beta coefficient of log(1.27)/ 0.50 in accordance with the relationship above.

The distribution function of HbA1c among non-diabetic individuals was $0.95\cdot\Phi((x-5.30)/0.45) + 0.05\cdot\Phi((x-5.50)/2.55)$, where Φ denotes the standardised normal distribution function. The right tail of the corresponding frequency function is mapped in figure 2.

The hazard ratio for one percentage- unit increase of HbA1c was 1.27. We calculated that the group of non-diabetic individuals with HbA1c >7.13 had a relative risk versus all non-diabetic individuals of 2.30, i.e. the same as the diabetic individuals. The proportion of the non-diabetic individuals with HbA1c >7.13 was 1.30% of all non-diabetic individuals and 1.26% of the total population.

With the beta coefficient of predictor A we calculated that the group of non-diabetic individuals with a value of the trans-formed variable >6.05 had a relative risk versus all non-diabetic individuals of 2.30, i.e. the same as the diabetic individuals. The proportion of such individuals (ND-HH) among non-diabetic individuals was 6.72% (Fig2) and among all individuals 6.4% (Fig 3). The calculated attributable risk for diabetes and ND-HH was 12.3%.

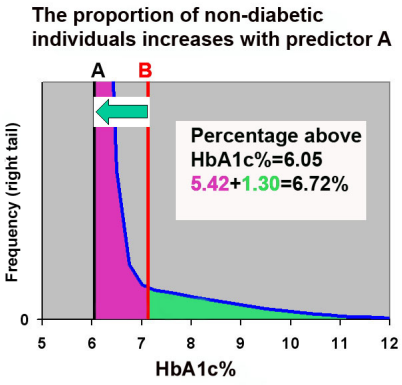


Fig 2

Conclusion

This study shows that the ND-HH group is almost twice the size of that of the individuals with diabetes. If the risk of death in both groups could be brought to the same level as the rest of the population, 12.3% of all deaths could be prevented in the age interval 45-79 years.

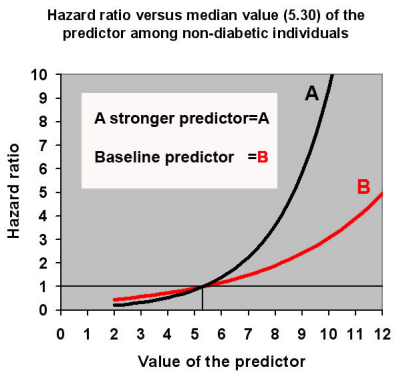
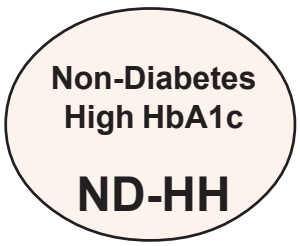
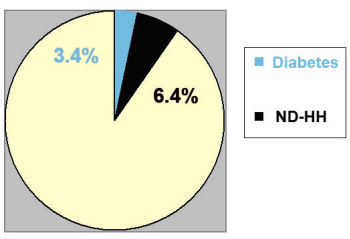


Fig 1





Two proportions with equal risk in the age group 45-79 years

Fig 3