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SHORT COMMUNICATION

ABO and Rhesus blood groups and risk of type 2 diabetes: evidence from the large E3N cohort study

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Abstract
Aims/hypothesis The objective of this study was to evaluate the relationship of ABO blood type (A, B, AB and O), Rhesus factor (positive or negative) and a combination of the two (ABO×Rhesus) with type 2 diabetes mellitus risk.
Methods In total, 82,104 women from the large prospective E3N cohort were followed between 1990 and 2008. Multivariate Cox regression models were used to estimate HRs and 95% CIs.
Results Those with either the A (HR 1.10 [95% CI 1.02, 1.18]) or B (HR 1.21 [95% CI 1.07, 1.36]) group were at increased risk of type 2 diabetes mellitus compared with those with the O group. The association with the AB group did not reach statistical significance (HR 1.17 [95% CI 0.99, 1.39]). There was no difference in type 2 diabetes mellitus risk between Rhesus positive and negative groups (HR 0.96 [95% CI 0.88, 1.05]). When the universal donors (O^-) were taken as the reference category, we observed an increased risk for both A^+ (HR 1.17 [95% CI 1.02, 1.35]) and A^- (HR 1.22 [95% CI 1.03, 1.45]) individuals. The greatest increase in risk was seen for those with the B^+ blood group (HR 1.35 [95% CI 1.13, 1.60]). We also observed a greater type 2 diabetes mellitus risk for those with the AB^+ group (HR 1.26 [95% CI 1.02, 1.57]). Adjustment for fasting plasma glucose and lipid concentrations in a case–control subsample did not alter the associations.
Conclusions/interpretation This study suggests that people with the O blood type have a lower risk of developing type 2 diabetes mellitus. Therefore, blood group should be investigated in future clinical and epidemiological studies on diabetes, and further pathophysiological research is needed to determine why individuals with blood type O have a lower risk of type 2 diabetes mellitus.

Keywords ABO · Blood group · Cohort · Diabetes · Risk factor

Abbreviations

E3N	Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale
ICAM-1	Intercellular adhesion molecule 1
TNF-R2	TNF receptor 2

Introduction

ABO blood type and Rhesus factors are inherited traits that have been associated with cardiovascular [1] and cancer outcomes. In particular, the AB blood type is suggested to be

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associated with a high risk of stroke compared with the O blood type [2]. In the same study, an over-representation of diabetes cases was reported among individuals with the AB blood group compared with other groups.

A few studies have investigated the relationship between blood group and type 2 diabetes. Most were small cross-sectional studies of specific hospital-based populations [3, 4]. Only one study of white women of European ancestry found that blood group B was associated with a decreased risk of diabetes compared with blood group O, but this study did not evaluate type 2 diabetes risk in cross categories of ABO and Rhesus groups [5].

Therefore, we investigated the association of ABO blood group, Rhesus factor and a combination of the two (ABO×Rhesus) with type 2 diabetes risk in the large prospective E3N (Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale) cohort. In a nested case–control study, we also evaluated the influence of fasting plasma glucose and lipid concentration on the relationship between blood group and type 2 diabetes risk.

Research design and methods

Study population The E3N study is a French prospective cohort study of 98,995 female teachers initiated in 1990. It was approved by the French institutional review board (Comité de protection des personnes d'Ile-de France Paris VII; 3 December 2008). Potential diabetes cases were identified via nine follow-up questionnaires through self-reporting of diabetes, diabetes diet, diabetes drugs and hospitalisation for diabetes, and then through the file listing drugs reimbursed by their medical insurance between January 2004 and February 2012. Type 2 diabetes cases were validated if confirmed by at least two of the following sources: self-reported diabetes in the follow-up questionnaires; ascertained diabetes in a specific diabetes questionnaire; and drugs reimbursed by health insurance.

Of the 98,995 women in the cohort, we excluded those who did not complete any questionnaires after inclusion (n=3,506), those with prevalent diabetes (n=938), those with prevalent cancer or cardiovascular diseases (n=4,509) and those lacking information on ABO or Rhesus blood group (n=7,938). Thus, a total of 82,104 women were included in the analysis, of whom 3,553 had a validated diagnosis of type 2 diabetes during follow-up (1990–2008).

Nested case–control study Blood samples were collected from a subcohort of the E3N study between 1995 and 1997. Concentrations of biomarkers potentially involved in mechanisms leading to diabetes were measured in 271 type 2 diabetes cases and 526 control participants matched for age, fasting status and blood collection centre.

Statistical analysis Cox regression models with age as the timescale were used to estimate HRs and 95% CIs in the entire cohort. Time at entry was defined as age at the beginning of follow-up and exit time was defined as the age at which participants were diagnosed with diabetes, lost to follow-up or censored at the end of the follow-up period, or died, whichever came first.

Conditional logistic regression models were used in the nested case–control study. The main exposure variables were ABO blood group (O, A, B or AB; O was used as the reference), Rhesus factor (positive or negative; positive was used as the reference) and a combination of ABO×Rhesus (O^+, O^-, A^+, A^-, B^+, B^-, AB^+ or AB^-; O^- was used as the reference). Both crude (M_0) and multivariate models (M_1) adjusted for established type 2 diabetes risk factors (see Table 1 footnote) were calculated. Crude and multivariate models gave similar results; therefore, only M_1 models will be discussed.

Results

Baseline characteristics of the study population There was little difference between baseline characteristics across the blood group categories (electronic supplementary material

Table 1 HRs and 95% CIs for type 2 diabetes by ABO, Rhesus and ABO×Rhesus groups

Blood group	Cases (n)	Model M_0	Model M_1
ABO			
O	1,440	1 (reference)	1 (reference)
A	1,622	1.10 (1.03, 1.18)	1.10 (1.02, 1.18)
B	344	1.23 (1.09, 1.38)	1.21 (1.07, 1.36)
AB	147	1.19 (1.00, 1.41)	1.17 (0.99, 1.39)
Rhesus			
Positive	2,958	1 (reference)	1 (reference)
Negative	595	0.96 (0.88, 1.05)	0.96 (0.88, 1.05)
ABO×Rhesus			
O^-	233	1 (reference)	1 (reference)
O^+	1,207	1.07 (0.93, 1.23)	1.09 (0.95, 1.25)
A^+	1,332	1.16 (1.01, 1.33)	1.17 (1.02, 1.35)
A^-	290	1.19 (1.00, 1.41)	1.22 (1.03, 1.45)
B^+	297	1.37 (1.16, 1.63)	1.35 (1.13, 1.60)
B^-	47	0.97 (0.71, 1.32)	1.04 (0.76, 1.42)
AB^+	122	1.26 (1.01, 1.57)	1.26 (1.02, 1.57)
AB^-	25	1.24 (0.82, 1.87)	1.23 (0.82, 1.86)

E3N cohort data; n=82,104

Data are HR (95% CI)

M_0, crude model; M_1, M_0 adjusted for family history of diabetes, education level, physical activity, hypertension, smoking and BMI

[ESM] Table 1), even in the two cases that showed some significant differences.

ABO, Rhesus and type 2 diabetes risk Mean follow-up was 13.20 years for type 2 diabetes cases and 16.48 years for non-diabetes cases. Compared with individuals with the O blood group, those with either A or B groups were at an increased risk of type 2 diabetes (HR 1.10 [95% CI 1.02, 1.18] and HR 1.21 [95% CI 1.07, 1.36], respectively; see Table 1). The increased type 2 diabetes risk associated with the AB group did not reach statistical significance (HR 1.17 [95% CI 0.99, 1.39]). There was no association between Rhesus group and type 2 diabetes risk. When ABO and Rhesus groups were combined in the same multivariate model (data not shown), associations with diabetes risk were unchanged.

We observed an increased diabetes risk for individuals in both A^+ and A^- groups (HR 1.17 [95% CI 1.02, 1.35] and 1.22 [95% CI 1.03, 1.45], respectively) compared with universal donors (O^-). The highest risk was seen for those with the B^+ blood group (HR 1.35, [95% CI 1.13, 1.60]). We also observed an increased risk for those with the AB^+ group (HR 1.26 [95% CI 1.02, 1.57]). No difference was seen for the other categories. Trends in risk were identical when prevalent cases were included and logistical regression analyses performed.

Influence of fasting plasma glucose and lipid concentrations There was no association of either fasting plasma glucose or lipid concentration with ABO blood group or Rhesus factor (ESM Table 2) among the 526 control participants of the nested case–control study. Moreover, as observed in the entire cohort, we found higher risks of type 2 diabetes for individuals in the non-O blood type group, with ORs between 1.21 and 1.95, even after adjusting for metabolic covariates such as fasting plasma glucose and lipid concentrations (Table 2, models M_1 and M_2).

Discussion

The present study shows for the first time in a large prospective cohort that specific ABO blood groups are associated with an increased type 2 diabetes risk. Individuals with the O blood group were found to have the lowest risk of developing type 2 diabetes. When the Rhesus factor was taken into account, those with A^+, A^-, B^+ and AB^+ blood groups were found to be at a higher risk of developing type 2 diabetes compared with universal donors (O^- group). Although the associations did not reach statistical significance, adjusting for fasting plasma glucose and lipid concentrations did not substantially alter the observed associations in the nested case–control study.

A few studies have examined the relationship between ABO blood groups and the risk of diabetes, but the results have been contradictory. Higher total cholesterol levels, glucose levels and BP have been reported in individuals with the O blood group in an Iraqi population, with a decreasing trend from those with blood group A to B, and then to AB [3]. Some of the differences with our results may be explained by the different study designs, our larger set of covariates and the different genetic backgrounds. Another cross-sectional study reported results consistent with ours [4]. A higher frequency of the B blood group was found in individuals in the type 2 diabetes group than in the general population, whereas a lower frequency of the O blood group was reported. A study of white women of European ancestry found the B blood group to be associated with a decreased risk of diabetes compared with the O blood group [5]. The difference from our results could be caused by the smaller sample size: only 1,005 women and 501 cases of diabetes were included, compared with 3,553 cases in our study [5].

In contrast to previous studies, we analysed the combined effect of ABO and Rhesus blood groups on diabetes risk. These differences highlight the importance of using a large

Table 2 Association between ABO blood group and type 2 diabetes risk in the nested case–control study, with adjustment for several biomarkers

Blood group	Cases (*n*)	Model M_0	Model M_1	Model M_2	Model M_3
ABO					
O	123	1 (reference)	1 (reference)	1 (reference)	1 (reference)
A	13	1.21 (0.89, 1.66)	1.23 (0.87, 1.74)	1.21 (0.82, 1.78)	1.22 (0.78, 1.89)
B	25	1.33 (0.76, 2.31)	1.37 (0.75, 2.52)	1.26 (0.64, 2.48)	1.13 (0.53, 2.43)
AB	110	1.37 (0.64, 2.94)	1.49 (0.64, 3.49)	1.95 (0.75, 5.11)	2.02 (0.70, 5.87)
Rhesus					
Positive	233	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Negative	38	0.72 (0.47, 1.10)	0.74 (0.46, 1.18)	0.78 (0.47, 1.28)	0.72 (0.41, 1.28)

n=271 cases; *n*=526 control participants

Data are OR (95% CI)

M_0, crude model; M_1, M_0 adjusted for fasting plasma glucose; M_2, M_1 adjusted for total cholesterol, LDL- and HDL-cholesterol and triacylglycerol; M_3, M_2 adjusted for family history of diabetes, education level, physical activity, hypertension, smoking and BMI

sample size with appropriate adjustment for possible confounding factors to delineate the precise effect of each ABO blood group and the Rhesus factor on diabetes risk.

The mechanisms underlying the observed association are unknown. It has been suggested that the human ABO locus might influence endothelial or inflammation markers, such as the factor VIII–von Willebrand factor (vWF) complex, which is present in higher levels in non-O individuals [6]. In addition, the ABO blood groups have been associated with plasma soluble intercellular adhesion molecule 1 (ICAM-1) and TNF receptor 2 (TNF-R2) levels [5]. These markers have both been associated with an increased type 2 diabetes risk, thus providing a potential explanation for the observed relationships [7, 8]. Finally, a recent paper suggested that the ABO blood group is one of the genetically determined host factors that modulate the composition of the intestinal microbiota [9], which participates in metabolism by affecting the energy balance, glucose metabolism and low-grade inflammation [10].

Although residual confounding cannot be completely ruled out, most of the known type 2 diabetes risk factors were controlled for. Our study population included only women but, to our knowledge, no biological mechanisms are likely to explain a sex-dependent association. Information on the participants was self-reported but this is unlikely to substantially affect the results. This is the first study to investigate a relationship between blood type and type 2 diabetes risk using such a large cohort size and a prospective design. Type 2 diabetes cases were validated; some residual misclassifications with respect to diabetes status may exist but are likely to be non-differential.

Conclusion

Our findings support a strong relationship between blood group and diabetes risk, with participants with the O blood type having a lower risk of developing type 2 diabetes. Therefore, the effects of blood groups should be investigated in future clinical and epidemiological studies on diabetes. Further pathophysiological research is also needed to determine why the individuals with blood type O have a lower risk of type 2 diabetes.

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Contribution statement Author contributions were as follows: GF designed the research, conducted the research and analysed data; GF, GG, FB and BB interpreted the data; GF drafted the article, and BB, GG, FB and FC-C revised it critically; FC-C contributed substantially to data acquisition and had primary responsibility for the final content of the manuscript; all authors read and approved the final manuscript.

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