# Non-O Blood Group is Associated With a Higher Risk of Dyslipidaemia Amongst French Women

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**Research**

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# Abstract

### Introduction

The non-O blood groups have previously been associated with higher risk of cardiovascular disease in prospective cohort studies. While cross-sectional studies have identified higher serum cholesterol amongst A-group individuals, there is no evidence from prospective studies whether this translates into a higher risk of dyslipidaemia that requires treatment. This study aimed to prospectively determine potential associations between ABO blood groups and risk of incident dyslipidaemia requiring treatment.

### Methods

We assessed associations between blood ABO group and dyslipidaemia in women participating in the E3N cohort. We included women who did not have cardiovascular disease at baseline. We used logistic regression to determine associations between ABO group and prevalent dyslipidaemia at baseline. Cox proportional hazard models were used to determine if blood ABO group was associated with an increased risk of incident dyslipidaemia, controlling for potential confounding.

### Results

At baseline, 55,512 women were included, and 10,058 incident cases of dyslipidaemia were identified at a rate of 17.6/1,000 PY. Of these participants, 24,510 reported being of the *O*-group, and 31,002 of *non-O*. Non-O blood groups were associated with prevalent dyslipidaemia (OR = 1.17 [1.13: 1.21]). The non-O blood groups were associated with an increased risk of dyslipidaemia ($HR_{non\text{-}O}$ = 1.14 [1.10: 1.19]), specifically the A group ($HR_A$ = 1.18 [1.13: 1.23]). Interactions with smoking were considered possible (*p-interaction* = 0.06), with AB smokers showing the highest risk of dyslipidaemia ($HR_{AB\ smokers}$ = 1.54 [1.12: 2.11]).

### Conclusion

Non-O blood group, specifically the A group were associated with a moderately increased risk of dyslipidaemia.


# Introduction

The non-O blood groups, most commonly the A-group, has been identified as a genetic risk factor for cardiovascular disease in multiple studies [1] and have long been associated with higher rates of ischemic heart disease. Recently, the A blood group has been identified with the severity of coronary artery disease [2] [3], [4], including in patients with diabetes [5], and those with poor blood pressure control [6]. Large prospective studies have confirmed these findings [7].

Coronary artery disease commonly follows dyslipidaemia [8], which may be a pre-requisite for the disease, and is considered causal. In the 90s, the A blood group was found to be associated with higher

serum cholesterol levels [9], and it has been suggested that associations between non-O groups and cardiovascular disease are mediated by serum cholesterol levels [10]. Despite this knowledge, prospective studies into the associations between ABO blood group and incident dyslipidaemia requiring treatment are lacking. Similarly, smoking is a major risk-factor for dyslipidaemia [11], and it has been shown to interact with ABO blood group in other vascular diseases such as thromboembolism [12], studies have not assessed if interactions are present when considering dyslipidaemia. We aimed to determine if non-O blood group was associated with an increased risk of dyslipidaemia, in a large prospective cohort of French women, and to determine if there was evidence for an interaction with smoking.

# Methods

### The E3N cohort

The E3N is a French prospective cohort started in 1990 comprising 98,995 women aged 40-65 years at baseline and insured by the MGEN, a health insurance plan for employees of the French education system and their families [13]. The cohort received ethical approval from the French National Commission for Computerized Data and Individual Freedom (Commission Nationale Informatique et Libertés), and all participants in the study signed an informed consent form. Participants returned mailed questionnaires on lifestyle information and disease occurrence every 2 to 3 years (1990, 1992, 1993, 1995, 1997, 2000, 2002, 2005, 2008, 2011, and 2014), resulting in 11 questionnaires (Q1-11). The average response rate at each questionnaire cycle was 83 %, and the total loss to follow-up was 3%. Furthermore, for each participant, the MGEN health insurance plan provided data that included all drug reimbursements since January 1, 2004.

### Assessment of dyslipidaemia

In the first two questionnaires sent in 1990 and 1992, participants were asked if they were undergoing treatment for raised blood cholesterol. No questions were asked in the 3$^{rd}$, 4$^{th}$ or 5$^{th}$ questionnaire about dyslipidaemia, thus the 2000 questionnaire (Q6) was considered baseline, and those reporting abnormal or treated cholesterol at or before baseline were considered prevalent cases. In Q7 and Q8 questionnaires participants were asked if their previous cholesterol measurement was abnormal. In Q9, Q10 and Q11, participants were asked to report if they were undergoing treatment for high cholesterol. The drug reimbursement database allowed us to identify reimbursement for lipid lowering medications in 2004 (identified using Anatomical Therapeutic Chemical Classification System C10A and C10B). We considered incident cases of dyslipidaemia as those reporting high or treated blood cholesterol, confirmed by a reimbursement for lipid lowering medications at the same time as the questionnaire (+- 1 year, except for Q7 which considered reimbursements at 2004).

### Assessment of Blood ABO group

Participants were asked to report their blood ABO group in Q1questionnaire as *O*, *A*, *B*, or *AB*, as well as their Rhesus group as positive or negative.

## Assessment of covariates

Height and weight were self-reported at each questionnaire and used to calculate body mass index (BMI (kg / m²)). Smoking was self-reported at each questionnaire and participants were classified as current smokers, ex-smokers, or never smokers. Family history of cardiovascular disease was based on self-reports. Education level was self-reported and used as a proxy for social class. Total physical activity was self-reported in Q5, and detailed time spent undergoing various activities (such as walking, housework, sports). Total Metabolic equivalents (MET-hours) were estimated for each individual using the compendium of physical activity. Hypertension was self-reported and verified by cross-correlation with the drug reimbursement database, to confirm that the participants were undergoing treatment. Use of menopausal hormone therapy (MHT) was self-reported during follow-up. The complete history of HT use was established using data from all the questionnaires [14]. Among postmenopausal women, age at menopause was defined as either (in decreasing order of priority) age at last menstrual period, age at bilateral oophorectomy, self-reported age at menopause, age at start of MHT, or the age at the start of menopausal symptoms. If unavailable, the median age at menopause for the cohort (51 years for natural menopause, 47 years for artificial menopause) was imputed. Dietary data was collected in Q3. Using nutritional databases, daily intakes of energy, alcohol, and micro- and macro-nutrients were estimated. A 'western' dietary score was determined using principal factor analysis, as previously described [15].

## Study population

We excluded women for whom there was no information on potential dyslipidaemia at Q6 (n = 22,973), resulting in 76,022 women included. When considering time-to-event models, we excluded women with prevalent dyslipidaemia, (N = 17,612), and then women who were not affiliated to the drug reimbursement database associated with the study, or died prior to 2004 (N = 2,007), and women with prevalent cardiovascular disease (stroke or ischaemic heart disease, N = 891) at baseline, leaving 55,512 participants free from dyslipidaemia as baseline.

## Statistical analysis

Initially, we assessed associations between baseline variables at Q6 (age at inclusion, blood ABO group, blood Rhesus group, BMI, physical activity, education, treated hypertension, family history of CVD, and finally smoking status) and self-reported prevalent dyslipidaemia using a logistic regression model, with prevalent dyslipidaemia as a binary variable.

Following this, we considered a time-to-event model, and excluded all prevalent cases from this analysis. Participants contributed person years to the study from inclusion until the participant reported dyslipidaemia, death, loss to follow up, or the end of the study period (June 2014). ABO group was considered an exposure in Cox proportional hazard models, with the O-group as reference. ABO group was considered as *O/ non-O*, then as *O*, *A*, *B*, and *AB,* and also Rhesus + or -. Models were initially adjusted with age as the timeline (crude), followed by potential confounders BMI (continuous), physical activity (continuous), education (university degree or not), treated hypertension (yes/no), family history of CVD

(yes/no), ever use of menopausal hormone therapy (yes/no), age at menopause, and smoking status as current/ex/never (adjusted).

We assessed a-priori an interaction with smoking status by including the joint term in the main model. Participants were then stratified according to their blood group, and impact of smoking across these groups was assessed. Models were adjusted as previously described. As a sensitivity analysis, we included dietary variables in the subset of the population who completed the dietary questionnaire (47,440 participants), further adjusting models for calorie and alcohol intake, and a western dietary score, as continuous variables.

Data is presented as mean (standard deviation) for continuous variables, and % for categorical variables. All analysis was conducted using the statistical software R, version 3.5, with the survival package.

# Results

At baseline 17,612 women reported prevalent dyslipidaemia. Using a multivariate logistic regression model, it was observed that those with prevalent dyslipidaemia were more likely to be of a non-O blood group (OR = 1.17 [1.13: 1.21], table 1). They were also more likely to be older, have a higher BMI, more likely to have familial history of cardiovascular disease, have diabetes or hypertension, and less likely to smoke (table 1).

During 572,979 person years (PY) of follow up of 55,512 women, 10,058 incident cases of dyslipidaemia were identified at a rate of 17.6/1,000 PY. Of these participants, 24,510 reported being of the O-group, and 31,002 of non-O. No major differences in women's characteristics were observed according to blood-group (table 2).

Compared to the O group, the non-O groups were associated with an increased risk of incident dyslipidaemia ($HR_{non\text{-}O}$ = 1.14 [1.10: 1.19], table 3). Specifically, the *A* blood group was associated with an increased risk of dyslipidaemia ($HR_A$ = 1.18 [1.13: 1.23], table 3), independent of other risk factors. Other blood groups were not associated with the risk of dyslipidaemia ($HR_B$ = 1.03 [0.98: 1.09], $HR_{AB}$ = 1.04 [0.97: 1.12], table 3). Rhesus group was not associated with the risk of dyslipidaemia (data not shown).

Interaction was observed between blood group and smoking, although the p-value was borderline (*p-interaction* = 0.06, table 3). When models were stratified over ABO blood groups, current smokers of the *AB*-group were at the highest risk of incident dyslipidaemia, compared to non-smokers ($HR_{AB\ smokers}$ = 1.54 [1.12: 2,11]).

In sensitivity analyses, models were additionally controlled for dietary factors, by including the total daily energy consumption, and a western dietary score. Associations were similar for *A*-group ($HR_A$ = 1.18 [1.13: 1.24], not tabulated).

# Discussion

In this large prospective study, women of the A blood group were at a higher risk of developing dyslipidaemia, regardless of other risk factors including diet, smoking, physical activity, and BMI. We observed a possible interaction between the AB-group and smoking with regards to dyslipidaemia.

The A-blood group has previously been associated with a higher risk of coronary artery disease [1], likely due to associations with serum cholesterol. Previous studies have shown that high concentrations of cholesterol are more common in *non-O* blood group persons [16], [17], and serum cholesterol has been known to be higher in A-group people since the 1970s [18]. Similarly, studies have shown that risk alleles in ABO group are associated with higher absorption of cholesterol in the intestines [19], which may be the mechanism in which cholesterol is chronically higher in the serum, resulting in a higher lifetime cholesterol burden. However, until now, it has not been observed in prospective studies if this translates into a higher risk of dyslipidaemia requiring treatment. Mechanisms between blood-group and cardiovascular diseases are commonly explained via increases in the von Willebrand factor, and increased likelihood of dyslipidaemia, and higher cholesterol burden.

We observed that the risk of dyslipidaemia was highest amongst AB women who were current smokers. Smoking has long been known as a major risk-factor for dyslipidaemia [20] and is associated with increased triglycerides, and decreased HDL-cholesterol [21], [22]. Multiple previous studies have shown that cigarette smoking is associated with alterations in lipid metabolism [23]–[27], and increases LDL-cholesterol oxidation [28]. It is possible that this effect is augmented amongst *AB* people*,* resulting in an even higher risk of dyslipidaemia. Smoking may raise serum lipid levels by increasing catecholamine levels, which then act to alter lipid metabolism [23]. However, this observation could also be due to confounding in this specific group, and would need replicated in other cohort studies.

The strengths of this study include its prospective design, control for several potential confounders (although as the exposure was genetic this changed little), and dyslipidaemia cases validated against the use of lipid-lowering medications,. Associations were consistent when considering dietary factors, such as the Western diet score which is strongly associated with cholesterol intake [29], which is in turn associated with serum cholesterol [30]. The limitations include those common to all observational research; we cannot claim causality, there may be unmeasured confounding, and participants may have misreported information, although we expect that this would attenuate any associations, and assessment of dyslipidaemia was also based on drug prescriptions. Sample sizes in certain subgroups, for example AB women who smoked, were small.

# Conclusions

Non-O blood groups were associated with an increased risk of dyslipidaemia. In the whole cohort, the association was specifically attributed to the A-group. Interaction was observed with smoking. Amongst participants with the AB-blood group the highest risk was observed amongst current smokers.

# List Of Abbreviations

BMI =body mass index

MHT = menopausal hormone therapy

# Declarations

### Ethical Approval and Consent to participate

The cohort received ethical approval from the French National Commission for Computerized Data and Individual Freedom (Commission Nationale Informatique et Libertés), and all participants in the study signed an informed consent.

### Consent for publication

Not applicable.

### Authors' contributions

CJM - designed research, conducted research, analysed data, wrote paper

ALM – conducted research, analysed data

AF – conducted research, analysed data

GS – designed research, conducted research

MCBR - primary responsibility for final content

All authors read and approved the final manuscript.

### Availability of data

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

### Competing interests

The authors have no conflicts of interest to declare.

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# Tables

Table 1: Associations between baseline characteristics and prevalent dyslipidaemia

| | No dyslipidaemia<br><br>N = 58,480 | Prevalent dyslipidaemia<br><br>N= 17,612 | Odds ratio* |
|---|---|---|---|
| Non-O blood group (%) | 55.9 | 59.4 | 1.17 [1.13: 1.21] |
| Rhesus group + (%) | 83.0 | 82.5 | 0.98 [0.93: 1.02] |
| Age at baseline (years) | 58.4 (6.2) | 61.3 (6.6) | 1.07 [1.06: 1.07] |
| BMI (kg / $m^2$) | 23.7 (3.7) | 24.2 (3.8) | 1.02 [1.02: 1.03] |
| Total physical activity (Mets-h / week) | 65.0 (38.7) | 66.9 (39.6) | 1.00 [1.00: 1.01] |
| Family history of cardiovascular disease (%) | 34.1 | 38.3 | 1.21 [1.17: 1.26] |
| Current smoking (%) | 10.1 | 7.6 | 0.88 [0.82: 0.94] |
| Ex smoking (%) | 37.2 | 35.7 | 0.98 [0.95: 1.02] |
| Never smoking | 52.5 | 55.8 | 1 (Ref) |
| Prevalent hypertension (%) | 40.9 | 49.6 | 1.16 [1.12: 1.20] |
| Prevalent diabetes (%) | 2.8 | 4.7 | 1.31 [1.19: 1.44] |
| Education (university or higher) | 89.5 | 87.6 | 0.93 [0.88: 0.98] |
| Ever use of MHT (yes or no) | 60.3 | 60.4 | 1.00 [0.97: 1.05] |
| Age at menopause (years) | 50.5 (3.7) | 50.2 (4.2) | 0.98 [0.98: 0.99] |

* adjusted simultaneously for all variables

BMI = body mass index; MHT= menopausal hormone therapy

Table 2: Participant characteristics at the start of follow up depending on blood ABO group.

| | O group (n = *24,510*) | Non-O group (n = *31,002*) |
|---|---|---|
| Group *A* / *B* / *AB* (%) | - | 77.9 / 15.4 / 6.7 |
| Age at baseline (years), mean (SD) | 58.5 (6.2) | 58.3 (6.2) |
| BMI (kg / $m^2$), mean (SD) | 23.7 (3.7) | 23.7 (3.7) |
| Total physical activity (Mets-h / week), mean (SD) | 65.0 (38.7) | 65.1 (38.6) |
| Family history of cardiovascular disease (%) | 33.8 | 34.3 |
| Smoking (N / X / C) (%) | 52.6 / 37.2 / 10.2 | 52.4 / 37.5 / 10.1 |
| Prevalent hypertension (%) | 41.1 | 40.4 |
| Prevalent diabetes (%) | 2.6 | 2.9 |
| Education (university or higher) | 89.3 | 89.7 |
| Age at menopause, mean (SD) | 50.5 (3.8) | 50.4 (3.8) |
| Ever use of MHT (%) | 60.6 | 60.2 |

Abbreviations: BMI = body mass index, METs-h = Metabolic equivalent task-hours, N = never smoker, X = ex-smoker, C = current smoker, MHT = menopausal hormone therapy

Table 3: Risk of incident dyslipidaemia depending on blood ABO group, hazard ratios (HR) estimated from Cox proportional hazards models.

| Blood group | Crude HR | Adjusted* HR |
|---|---|---|
| *O (n= 24,510, cases = 4151)* | Ref | Ref |
| *Non-O (n = 31,002, cases = 5907)* | 1.15 [1.10: 1.19] | 1.14 [1.09: 1.19] |
| *A (n = 24,138, cases = 4721)* | 1.18 [1.13: 1.23] | 1.17 [1.13: 1.22] |
| *B (n = 4792, cases = 822)* | 1.02 [0.94: 1.10] | 1.01 [0.94: 1.09] |
| *AB (n = 2072, cases = 364)* | 1.04 [0.93: 1.15] | 1.04 [0.93: 1.16] |
| *Rhesus + (n = 46,071, cases = 8342)* | Ref | Ref |
| *Rhesus – (n =9441, cases =1716 )* | 0.98 [0.93: 1.03] | 0.98 [0.93: 1.04] |

* adjusted for body mass index, physical activity, education level, diabetes, hypertension, family history of cardiovascular disease, use of menopausal hormone therapy, age at menopause, and smoking status

Age as the timescale.

Table 4: Risk of incident dyslipidaemia depending on smoking status, stratified by blood ABO group, hazard ratios estimated from Cox proportional hazard models.

| | Blood group | | | |
|---|---|---|---|---|
| Smoking | O (n = 24,510) | A (n = 24,135) | B (n = 4792) | AB (n = 2030) |
| Never smokers (n = 29,151) | ref | Ref, | ref | Ref |
| Ex smokers (n = 20,739) | 0,92 [0,86: 0,99] | 0,99 [0,89: 1,09] | 0,98 [0,77: 1,25] | 0,86 [0,96: 1,09] |
| Smokers (n = 5622) | 1,04 [0,93: 1,15] | 0,99 [0,94: 1,06] | 0,96 [0,83: 1,11] | 1,54 [1,12: 2,11] |

adjusted for  body mass index, physical activity, education level, treated hypertension, family history of cardiovascular disease, use of menopausal hormone therapy, and age at menopause Age as the timescale.