Journal of Thrombosis and Haemostasis, **14**: 1572–1578 DOI: 10.1111/jth.13371

BRIEF REPORT

Risk of venous thrombosis in persons with increased body mass index and interactions with other genetic and acquired risk factors

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To cite this article: Ribeiro DD, Lijfering WM, Rosendaal FR, Cannegieter SC. Risk of venous thrombosis in persons with increased body mass index and interactions with other genetic and acquired risk factors. *J Thromb Haemost* 2016; **14**:1572–8.

Essentials

- Obesity, factor V Leiden (FVL) and blood group non-O are common.
- We studied the combined effect of these factors on the risk of venous thrombosis (VT).
- The combination of obesity, non-O blood group and FVL increased VT risk up to ten-fold.
- Identifying high VT may be beneficial in thrombosis prevention.

Summary. *Background:* Overweight/obesity has a substantial effect on the occurrence of venous thrombosis (VT). Blood group non-O has a high prevalence in Western populations, and the factor V Leiden mutation could be present in 5% of Caucasians. These frequent prothrombotic risk factors will have a considerable impact on the incidence of VT, especially when combined. *Objectives:* We investigated whether FV Leiden with blood group non-O modifies VT risk in individuals with different body mass index (BMI) strata in a case–control study (n = 11253). *Results:* We observed a progressively increasing risk of VT with higher BMI, with an odds ratio of 1.9 (95% confidence interval [CI] 1.6–2.3) for those in the upper BMI tertile (BMI > 26.7 kg m^{-2}), as compared with the first BMI tertile (BMI < 23.5 kg m^{-2}, blood group O, and no FV Leiden) (reference group). The addition of FV Leiden and blood group non-O to the model increased the risk in all BMI tertiles; the odds ratios were 3.8 (95% CI 3.2–4.6) in the third BMI tertile of individuals with blood group non-O, and 5.4 (95% CI 3.5–8.5) in the third BMI tertile of individuals with FV Leiden. When both FV Leiden and blood group non-O were present, the odds ratios were 9.1 (95% CI 5.9–14.0) in the first BMI tertile, 9.4 (95% CI 6.6–13.5) in the second BMI tertile, and 12.5 (95% CI 8.9–17.6) in the third BMI tertile. *Conclusion:* Individuals with a high BMI, blood group non-O and/or FV Leiden have a high VT risk. The high VT risks in some subgroups may justify targeted screening and thromboprophylaxis decisions in these patients.

Keywords: body mass index; epidemiology; interaction; risk factors; thrombophilia; venous thrombosis.

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Received 16 December 2015
Manuscript handled by: I. Pabinger
Final decision: I. Pabinger, 4 May 2016

Introduction

Obesity and overweight have considerable effects on the occurrence of a variety of disorders, such as coronary artery disease, hypertension, type II diabetes, and venous thrombosis (VT) [1,2]. A high and still increasing prevalence of obesity in developed countries (prevalence of 20–25% in Western populations) leads to a substantial impact on disease occurrence. Several studies have shown an association between blood group non-O and factor V Leiden, with a 23-fold increase in VT risk [3]. The prevalence of blood group non-O is ~ 50% in Western populations, and FV Leiden is present in 5% of Caucasians [4,5]. These frequent prothrombotic risk factors will have a considerable impact on the overall incidence of VT, especially as the frequent combined presence of these mutations has a positive joint effect on VT risk [4]. We previously reported that the increased VT risk in individuals with a high body mass index (BMI) is mediated by FVIII-induced activated protein C (APC) resistance, and that having blood group non-

O or FV Leiden plus a high BMI leads to higher VT risks than expected from separate analysis of these prothrombotic factors [6]. However, owing to small numbers, we were not able to study the VT risk for the combination of a high BMI with FV Leiden and blood group non-O, or to study whether these effects differ, for example, for provoked or unprovoked VT.

For this reason, we set out to determine whether the presence of FV Leiden alone or with blood group non-O modifies the VT risk in various BMI strata. This study was performed in a different and larger population (i.e. the Multiple Environmental and Genetic Assessment of risk factors for VT [MEGA] study) [5,7] than previously reported [6]. In addition, we evaluated the presence of gene–environment effect modification in specific subgroups.

Methods

The MEGA study is a population-based case–control study that has been described in detail elsewhere [5,7]. Participants were aged 18–70 years. Four thousand nine hundred and fifty-six consecutive patients with deep vein thrombosis or pulmonary embolism (PE) were enrolled, together with 6297 age-matched and sex-matched controls. A questionnaire was filled in for assessment of VT risk factors. The questionnaires included items on surgery, injury, plaster casts, immobilization, malignancies, pregnancy, the use of oral contraceptives, and hormone replacement therapy. BMI was calculated by dividing body weight (kg) by height squared (m^2). Overweight was defined as a BMI of 25–30 kg m^{-2}, and obesity was defined as a BMI of $\geq$ 30 kg m^{-2}. In addition, participants provided a blood or buccal swab sample for DNA analysis. FV Leiden and ABO blood group were determined by the use of PCRs with the TaqMan assay. Technicians were blinded regarding whether the samples came from patients or from controls. For the present analysis, data on BMI, blood group and FV Leiden were available for 4062 patients and 4659 controls.

Odds ratios (ORs) with 95% confidence intervals (CIs) for the VT risk of BMI tertiles (obtained from the control group) were calculated with logistic regression models, and were adjusted for age and sex. The combined effect of BMI, FV Leiden, blood group non-O and immobility (defined as being bedridden for >4 days, or surgery or hospitalization within 3 months prior to the index date) was evaluated by means of stratification. Subgroup analyses involved stratification by VT type (provoked or unprovoked event), VT location (deep vein thrombosis or PE), and sex. For transparent presentation of effect modification, we report both the separate effect of each exposure and the joint effect as compared with the unexposed group as a joint reference category, to permit evaluation of interactions on both an additive scale and a multiplicative scale [8].

Table 1 Risk of venous thrombosis according to the combinations of body mass index (BMI) tertiles, factor V Leiden, and blood group*

BMI	Factor V Leiden	Blood group	Cases, *n* (%)	Controls, *n* (%)	Overall OR† (95% CI)	Unprovoked OR† (95% CI)	Provoked OR† (95% CI)	DVT ± PE OR† (95% CI)	PE only OR† (95% CI)	Men OR† (95% CI)	Women OR† (95% CI)
Lowest tertile	−	O	241 (6)	674 (15)	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Median tertile	−	O	275 (7)	678 (15)	1.1 (0.9–1.3)	1.2 (0.8–1.7)	1.1 (0.8–1.3)	1.2 (0.9–1.5)	1.0 (0.7–1.3)	1.1 (0.8–1.5)	1.1 (0.8–1.5)
Upper tertile	−	O	482 (12)	682 (15)	1.9 (1.6–2.3)	1.7 (1.3–2.5)	1.9 (1.6–2.4)	2.1 (1.7–2.7)	1.7 (1.3–2.2)	1.5 (1.1–2.1)	2.3 (1.8–2.9)
Lowest tertile	−	Non-O	567 (14)	754 (16)	2.1 (1.8–2.5)	2.1 (1.5–2.9)	2.1 (1.7–2.6)	2.4 (1.9–3.0)	1.8 (1.4–2.3)	2.2 (1.6–3.0)	2.1 (1.7–2.7)
Median tertile	−	Non-O	748 (18)	806 (17)	2.5 (2.1–3.0)	2.0 (1.5–2.8)	2.7 (2.2–3.3)	3.2 (2.6–4.0)	1.7 (1.3–2.2)	2.7 (2.0–3.6)	2.5 (2.0–3.2)
Upper tertile	−	Non-O	1098 (27)	822 (18)	3.8 (3.2–4.6)	3.4 (2.5–4.6)	3.9 (3.2–4.8)	4.9 (3.9–6.1)	2.7 (2.1–3.4)	3.4 (2.5–4.5)	4.2 (3.4–5.3)
Lowest tertile	+	O	41 (10)	31 (1)	3.7 (2.3–6.1)	3.5 (1.6–7.7)	3.5 (2.1–6.0)	5.1 (3.0–8.8)	1.9 (0.9–3.9)	7.1 (2.9–17.5)	2.7 (1.5–4.9)
Median tertile	+	O	52 (1)	47 (1)	3.1 (2.0–4.7)	4.4 (2.4–8.1)	2.6 (1.6–4.2)	4.4 (2.7–6.9)	1.4 (0.7–2.9)	3.5 (1.9–6.3)	2.8 (1.5–5.2)
Upper tertile	+	O	67 (2)	34 (1)	5.4 (3.5–8.5)	7.2 (3.9–13.3)	4.5 (2.7–7.3)	7.9 (4.9–12.6)	2.3 (1.2–4.7)	5.6 (3.0–10.4)	5.5 (2.8–10.7)
Lowest tertile	+	Non-O	99 (2)	32 (1)	9.1 (5.9–14.0)	5.3 (2.6–10.7)	9.8 (6.3–15.3)	13.4 (8.5–22.1)	4.0 (2.1–7.3)	8.6 (4.3–17.3)	10.1 (5.7–17.7)
Median tertile	+	Non-O	164 (4)	48 (1)	9.4 (6.6–13.5)	9.1 (5.5–15.0)	8.9 (6.1–13.1)	14.2 (9.7–20.9)	3.3 (2.0–5.7)	9.0 (5.4–15.0)	9.7 (5.8–16.3)
Upper tertile	+	Non-O	228 (6)	51 (1)	12.5 (8.9–17.6)	12.4 (7.8–19.7)	11.1 (7.7–15.9)	18.8 (13.1–27.1)	4.7 (2.9–7.5)	14.7 (8.6–25.3)	10.5 (6.8–16.3)

CI, confidence interval; DVT, deep vein thrombosis; OR, odds ratio; PE, pulmonary embolism. Upper tertile: BMI of $\geq$ 26.7 kg m^{-2}. Median tertile: BMI of 23.5–26.7 kg m^{-2}. Lowest tertile: BMI of < 23.5 kg m^{-2}. *Tertiles derived from the MEGA control population. †ORs adjusted for age and sex, when appropriate.

Table 2 Risk of venous thrombosis according to the combinations of body mass index (BMI) tertiles, factor V Leiden, and blood group: subgroup analysis

BMI	Factor V Leiden	Blood group	Acquired risk factor	Cases, *n* (%)	Controls, *n* (%)	Overall OR* (95% CI)
Lowest tertile	–	O	Hormone use	78 (7)	149 (23)	Reference
Median tertile	–	O	Hormone use	50 (4)	83 (13)	1.2 (0.7–1.8)
Upper tertile	–	O	Hormone use	129 (11)	68 (10)	3.7 (2.4–5.5)
Lowest tertile	–	Non-O	Hormone use	229 (19)	160 (24)	2.7 (1.9–3.8)
Median tertile	–	Non-O	Hormone use	191 (16)	108 (16)	3.3 (2.3–4.8)
Upper tertile	–	Non-O	Hormone use	312 (26)	61 (9)	10.1 (6.8–15.0)
Lowest tertile	+	O	Hormone use	16 (1.3)	3 (0.5)	10.1 (2.9–35.7)
Median tertile	+	O	Hormone use	15 (1.2)	7 (1.1)	4.1 (1.6–10.5)
Upper tertile	+	O	Hormone use	18 (1.5)	5 (0.8)	6.9 (2.5–19.7)
Lowest tertile	+	Non-O	Hormone use	46 (4)	6 (0.9)	14.6 (6.0–35.8)
Median tertile	+	Non-O	Hormone use	47 (4)	3 (0.5)	30.0 (9.1–99.6)
Upper tertile	+	Non-O	Hormone use	78 (7)	7 (1.1)	21.4 (9.4–48.5)
Lowest tertile	–	O	Travel	22 (3)	134 (17)	Reference
Median tertile	–	O	Travel	31 (5)	119 (15)	1.8 (1.0–3.4)
Upper tertile	–	O	Travel	73 (11)	116 (15)	4.6 (2.6–8.1)
Lowest tertile	–	Non-O	Travel	97 (14)	138 (18)	4.7 (2.7–7.9)
Median tertile	–	Non-O	Travel	133 (20)	136 (18)	5.9 (3.5–10.0)
Upper tertile	–	Non-O	Travel	197 (29)	125 (16)	11.3 (6.6–19.3)
Lowest tertile	+	O	Travel	9 (1.3)	4 (0.5)	13.9 (3.9–49.6)
Median tertile	+	O	Travel	6 (0.9)	11 (1.4)	3.8 (1.2–11.9)
Upper tertile	+	O	Travel	10 (1.5)	4 (0.5)	18.5 (4.8–71.4)
Lowest tertile	+	Non-O	Travel	22 (3)	9 (1.2)	19.7 (7.4–52.8)
Median tertile	+	Non-O	Travel	33 (5)	13 (1.7)	20.7 (8.5–50.3)
Upper tertile	+	Non-O	Travel	44 (7)	7 (0.9)	44.7 (17.0–117.0)
Lowest tertile	–	O	Immobile†	98 (8)	54 (17)	Reference
Median tertile	–	O	Immobile	104 (8)	44 (14)	1.2 (0.7–2.0)
Upper tertile	–	O	Immobile	162 (12)	37 (12)	2.3 (1.4–3.8)
Lowest tertile	–	Non-O	Immobile	172 (13)	51 (16)	1.9 (1.2–3.0)
Median tertile	–	Non-O	Immobile	247 (19)	66 (21)	1.9 (1.2–2.9)
Upper tertile	–	Non-O	Immobile	334 (26)	48 (15)	3.8 (2.4–6.0)
Lowest tertile	+	O	Immobile	12 (0.9)	2 (0.6)	3.5 (0.7–16.1)
Median tertile	+	O	Immobile	13 (0.9)	1 (0.3)	7.0 (0.9–55.2)
Upper tertile	+	O	Immobile	21 (1.6)	3 (0.9)	3.6 (1.0–12.6)
Lowest tertile	+	Non-O	Immobile	27 (2)	2 (0.6)	8.6 (1.9–38.1)
Median tertile	+	Non-O	Immobile	47 (4)	2 (0.6)	12.5 (2.9–53.8)
Upper tertile	+	Non-O	Immobile	60 (5)	6 (2)	5.5 (2.2–13.5)

CI, confidence interval; OR odds ratio. *Odds ratio adjusted for age and sex when appropriate. †Defined as bedridden for > 4 days, or surgery or hospitalization within 3 months prior to the index date.

Results and discussion

Our study included 2363 patients with deep vein thrombosis only, and 1699 patients with PE with or without a diagnosed deep vein thrombosis. The median age was 50 years (interquartile range [IQR] 39–59) for patients, and 49 years (IQR 39–58) for controls. The prevalence rates of FV Leiden and blood group non-O in patients were 16% (n = 651) and 72% (n = 2907), respectively. In controls, these prevalence rates were 5% (n = 243) and 54% (n = 2513), respectively. Patients were more often overweight (43% versus 37% in controls) or obese (21% versus 14% in controls).

Table 1 shows the combined effects of ABO blood group and FV Leiden within increasing BMI categories on VT risk. A progressive increase in BMI was associated with an increased VT risk (OR 1.1 [95% CI 0.9–1.3] for those in the median BMI tertile, and OR 1.9 [95% CI 1.6–2.3] for those in the upper BMI tertile, as compared with participants in the first BMI tertile, with blood group O, and with no FV Leiden, i.e. the reference group). The addition of FV Leiden and blood group non-O increased the risk in all BMI tertiles; ORs for VT were 3.8 (95% CI 3.2–4.6) in the third BMI tertile of participants with blood group non-O, and 5.4 (95% CI 3.5–8.5) in the third BMI tertile of participants with FV Leiden. When both FV Leiden and blood group non-O were present, ORs for VT were 9.1 (95% CI 5.9–14.0) in the first BMI tertile, 9.4 (95% CI 6.6–13.5) in the second BMI tertile, and 12.5 (95% CI 8.9–17.6) in the third BMI tertile, as compared with the reference group. In subgroup analyses, which involved stratification by VT location (i.e. deep vein thrombosis or PE), sex, and the presence or absence of acquired VT risk factors, the positive joint

effects of BMI with blood group non-O and FV Leiden on VT risk were maintained, with the exception of PE. Effect modification on at least the additive scale between the risk factors involved was observed for most groups. For instance, if blood group non-O and FV Leiden were combined in those with a BMI in the lowest tertile, there was effect modification on the multiplicative scale ($1 \times 2.1 \times 3.1 < 9.1$). There was also effect modification on the additive scale of blood group non-O with FV Leiden and BMI in the upper tertile ($1.9 + 3.8 + 5.4 - 1 < 12.5$). The only participants in whom effect modification was not observed were those with PE. For these, the addition of several risk factors increased the risk of PE without synergy between these factors.

We next focused on participants who were exposed to hormone use ($n = 1869$), recent travel ($n = 1452$), or immobility ($n = 1613$) (Table 2). Again, a dose–response relationship was observed when BMI level increased, with an effect for blood group non-O. Participants who were FV Leiden and blood group non-O carriers appeared to have the highest VT risk, independently of BMI, although there was no longer a dose–response relationship. Similar results as shown in Tables 1 and 2 were obtained when exposure categories were based on the World Health Organization classification of overweight/obesity (Tables 3 and 4).

This study shows that individuals with high BMI, blood group non-O and/or FV Leiden have a high VT risk. This confirms the results from our previous study [6]. In addition, we showed that the risk increased with the degree of obesity, and was also increased for unprovoked or provoked VT, for deep vein thrombosis, and in both men and women. We observed little effect of FV Leiden on PE risk (also known as the FV Leiden paradox) when combined with increasing BMI and/or blood group non-O [9,10]. This results adds credence to the hypothesis that APC resistance (present in FV Leiden carriers and in individuals with high BMI) [6,11] preferentially affects the risk of deep vein thrombosis and not of PE. Furthermore, we found that the combination of high BMI and blood group non-O in non-FV Leiden carriers increased the VT risk in a dose-dependent fashion in individuals who were exposed to oral contraceptives/hormone replacement therapy (ORs increased up to 10-fold), recent travel (ORs increased up to 11-fold), or immobility (ORs increased > 3.5-fold).

Apart from FVIII-induced APC resistance, another factor that could explain our observed increased risk estimates is the presence of microparticles. Recent evidence points towards microparticles as potential promoters of a hypercoagulable state in both obese individuals and FV Leiden carriers [12,13]. Interestingly, microparticle activity is reduced in obese individuals after weight loss [14]. Therefore, our study, combined with other studies that have investigated the etiologic aspects of hypercoagulability in obesity [1,4,6,12–14], suggests that weight loss,

Table 3 Risk of venous thrombosis according to the combinations of overweight/obesity, factor V Leiden, and blood group*

BMI	Factor V Leiden	Blood group	Cases, *n* (%)	Controls, *n* (%)	Overall OR† (95% CI)	Unprovoked OR† (95% CI)	Provoked OR† (95% CI)	DVT ± PE OR† (95% CI)	PE only OR† (95% CI)	Men OR† (95% CI)	Women OR† (95% CI)
Normal weight	–	O	344 (9)	982 (21)	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Overweight	–	O	425 (11)	749 (16)	1.6 (1.3–1.9)	1.9 (1.4–2.6)	1.4 (1.2–1.7)	1.5 (1.2–1.9)	1.6 (1.2–2.0)	1.5 (1.2–2.0)	1.7 (1.3–2.1)
Obesity	–	O	212 (5)	279 (6)	2.1 (1.7–2.6)	2.1 (1.4–3.1)	2.0 (1.6–2.6)	2.4 (1.8–3.0)	1.7 (1.3–2.4)	1.6 (1.1–2.3)	2.5 (1.9–3.3)
Normal weight	–	Non-O	889 (23)	1129 (25)	2.3 (1.9–2.6)	2.3 (1.8–3.1)	2.2 (1.9–2.6)	2.5 (2.0–2.9)	2.0 (1.6–2.5)	2.4 (1.9–3.1)	2.2 (1.8–2.7)
Overweight	–	Non-O	1010 (26)	894 (20)	3.1 (2.7–3.7)	3.2 (2.5–4.2)	3.1 (2.6–3.6)	3.7 (3.1–4.4)	2.4 (1.9–3.0)	3.4 (2.7–4.3)	3.1 (2.5–3.8)
Obesity	–	Non-O	484 (13)	329 (7)	4.2 (3.5–5.1)	4.2 (3.1–5.8)	4.1 (3.3–5.0)	5.2 (4.2–6.5)	2.9 (2.2–3.8)	3.3 (2.4–4.4)	5.0 (3.9–6.4)
Normal weight	+	O	63 (2)	52 (1)	3.5 (2.4–5.2)	4.3 (2.3–7.9)	3.1 (2.0–4.8)	4.6 (3.0–7.0)	2.0 (1.1–3.6)	5.3 (2.8–9.9)	2.6 (1.6–4.4)
Overweight	+	O	64 (2)	42 (1)	4.4 (2.9–6.6)	6.8 (3.9–11.9)	3.4 (2.1–5.5)	5.6 (3.6–8.7)	2.5 (1.3–4.7)	4.5 (2.7–7.7)	4.5 (2.3–8.9)
Obesity	+	O	32 (1)	16 (0.3)	5.6 (3.0–10.4)	8.2 (3.6–18.9)	4.3 (2.2–8.7)	8.7 (4.6–16.3)	1.3 (0.4–4.6)	6.4 (2.5–16.4)	5.1 (2.3–11.7)
Normal weight	+	Non-O	99 (3)	32 (1)	9.1 (5.9–14.0)	7.9 (4.8–13.0)	9.1 (6.5–12.9)	13.0 (9.2–18.4)	4.0 (2.5–6.5)	8.7 (5.2–14.4)	9.9 (6.4–15.4)
Overweight	+	Non-O	210 (5)	56 (1)	10.7 (7.7–14.8)	12.3 (8.0–18.8)	9.3 (6.6–13.1)	15.3 (10.9–21.5)	3.8 (2.3–6.1)	11.1 (7.1–17.3)	9.9 (6.2–15.8)
Obesity	+	Non-O	100 (3)	19 (0.4)	15.7 (9.4–25.9)	18.3 (9.5–35.5)	13.4 (7.9–22.8)	21.7 (12.8–36.7)	7.3 (3.8–14.0)	26.5 (10.1–69.7)	11.6 (6.3–21.1)

BMI, body mass index; CI, confidence interval; DVT, deep vein thrombosis; OR odds ratio; PE, pulmonary embolism. *Obesity: BMI of ≥ 30 kg m−2. Overweight: BMI of 25–30 kg m−2. Normal weight: BMI of 18.5–25 kg m−2. †OR adjusted for age and sex, when appropriate.

Table 4 Risk of venous thrombosis according to the combinations of overweight/obesity, factor V Leiden, and blood group: subgroup analysis

BMI	Factor V Leiden	Blood group	Acquired risk factor	Cases, *n* (%)	Controls, *n* (%)	Overall OR* (95% CI)
Normal weight	−	O	Hormone use	102 (10)	184 (29)	Reference
Overweight	−	O	Hormone use	76 (7)	75 (12)	1.8 (1.2–2.7)
Obesity	−	O	Hormone use	76 (7)	31 (5)	4.4 (2.7–7.1)
Normal weight	−	Non-O	Hormone use	313 (31)	209 (33)	2.7 (2.0–3.6)
Overweight	−	Non-O	Hormone use	243 (24)	89 (14)	5.1 (3.6–7.2)
Obesity	−	Non-O	Hormone use	163 (16)	23 (4)	12.6 (7.7–20.8)
Normal weight	+	O	Hormone use	23 (2)	8 (1)	5.1 (2.2–11.9)
Overweight	+	O	Hormone use	16 (2)	5 (0.8)	5.7 (2.0–16.1)
Obesity	+	O	Hormone use	9 (1)	2 (0.3)	7.7 (1.6–36.4)
Normal weight	+	Non-O	Hormone use	75 (7)	7 (1)	19.5 (8.6–43.8)
Overweight	+	Non-O	Hormone use	58 (6)	5 (0.8)	21.0 (8.2–54.0)
Obesity	+	Non-O	Hormone use	37 (4)	4 (0.6)	16.8 (5.8–48.5)
Normal weight	−	O	Travel	36 (5)	186 (23)	Reference
Overweight	−	O	Travel	61 (9)	139 (17)	2.6 (1.6–4.3)
Obesity	−	O	Travel	27 (4)	39 (5)	3.6 (1.9–6.8)
Normal weight	−	Non-O	Travel	162 (24)	202 (25)	4.3 (2.8–6.5)
Overweight	−	Non-O	Travel	174 (26)	155 (19)	5.9 (3.9–9.1)
Obesity	−	Non-O	Travel	84 (13)	39 (5)	11.8 (6.9–20.4)
Normal weight	+	O	Travel	14 (2)	13 (2)	5.6 (2.4–12.9)
Overweight	+	O	Travel	6 (0.8)	3 (0.4)	13.6 (3.1–60.9)
Obesity	+	O	Travel	5 (0.7)	3 (0.4)	9.2 (2.0–42.2)
Normal weight	+	Non-O	Travel	35 (5)	14 (2)	16.3 (7.5–35.4)
Overweight	+	Non-O	Travel	43 (6)	12 (1)	21.7 (10.0–47.1)
Obesity	+	Non-O	Travel	21 (3)	3 (0.4)	37.5 (10.5–133)
Normal weight	−	O	Immobile†	144 (11)	75 (24)	Reference
Overweight	−	O	Immobile	143 (11)	44 (14)	1.6 (1.0–2.5)
Obesity	−	O	Immobile	69 (5)	14 (4)	2.5 (1.3–4.7)
Normal weight	−	Non-O	Immobile	287 (22)	87 (28)	1.7 (1.2–2.5)
Overweight	−	Non-O	Immobile	312 (24)	51 (16)	3.1 (2.0–4.6)
Obesity	−	Non-O	Immobile	147 (11)	25 (8)	3.0 (1.8–5.0)
Normal weight	+	O	Immobile	19 (1)	2 (0.6)	5.5 (1.2–24.5)
Overweight	+	O	Immobile	14 (1)	3 (0.9)	2.0 (0.5–7.3)
Obesity	+	O	Immobile	13 (1)	1 (0.3)	7.1 (0.9–55.4)
Normal weight	+	Non-O	Immobile	48 (4)	2 (0.6)	14.4 (3.4–61.6)
Overweight	+	Non-O	Immobile	58 (5)	6 (2)	4.9 (2.0–11.9)
Obesity	+	Non-O	Immobile	26 (2)	2 (0.6)	7.2 (1.7–31.2)

BMI, body mass index; CI, confidence interval; OR, odds ratio. *OR adjusted for age and sex, when appropriate. †Defined as bedridden for > 4 days, or surgery or hospitalization within 3 months prior to the index date.

especially in obese individuals with FV Leiden, could contribute to a decrease in VT risk.

A limitation of our study is that we cannot directly obtain absolute risk estimates from case–control data, which hampers clinical decision-making with respect to thromboprophylaxis. As in persons with immobility the absolute VT risk is estimated to be as high as 3.5% within 3 months after immobilization [15], whereas thromboprophylaxis with anticoagulant drugs reduces this risk by ~ 60% [16], the number needed to treat would be 13–20 in this group of individuals (i.e. immobilized individuals with a high BMI, blood group non-O, and/or FV Leiden). Because the absolute VT risk in oral contraceptive users (estimated to be six per 10 000 per year) [17] or those with recent travel (estimated to be one per 4500 passengers) [18] is much lower, a 10-fold or 11-fold increased risk probably does not justify screening for blood group non-O in overweight/obese persons who are willing to travel or take oral contraceptives. It is difficult at this stage to propose a balance of benefits and risks for the combination of FV Leiden with blood group non-O in overweight/obese women who use hormones or individuals who travel (which revealed 15-fold to 45-fold increased VT risks). Although it might be tempting to screen, such an undertaking would probably not be cost-effective, as the population frequency of these combined genetic variations is 2%, whereas nearly half of the Western population is overweight/obese. Therefore, we would not consider thromboprophylaxis decisions in overweight/obese women, such as advice to use non-oral contraceptives, and the same applies for air travel.

The strengths of this study include the large patient sample, the detailed information about VT risk factors in both patients and controls, and the combination with

data on prothrombotic genes. A limitation of this study is that we did not have full information available for all patients and controls, as some of them had not reported their BMI (9%) or did not supply DNA (19%). Although this may have led to reduced statistical power, it did not introduce bias, as the frequencies of both FV Leiden and blood group non-O (in patients and controls) were similar to those that have been reported previously in unselected populations [19]. Also, the prevalence of overweight and obesity in control subjects was similar to that observed in the Dutch population (35% for overweight and 11% for obesity) [20]. Second, height and weight were self-reported. Because, in general, underweight persons tend to over-report their body weight, whereas overweight persons tend to under-report their body weight [21], the actual risks would be somewhat higher if this phenomenon had occurred. Third, we analyzed the combination of oral contraceptives and hormone replacement therapy, whereas it would have been preferable to analyze these two risk factors separately. Unfortunately, small numbers of the control subjects with FV Leiden and/or blood group non-O prevented us from investigating these two risk factors separately.

We conclude that individuals with a high BMI, blood group non-O and/or FV Leiden have a high VT risk. The high VT risk in immobilized individuals with a high BMI, blood group non-O and/or FV Leiden suggests that these individuals are candidates for receiving (extended) thromboprophylaxis with anticoagulant drugs.

Addendum

D. D. Ribeiro had full access to the database, performed statistical analysis, interpreted the data, and drafted the manuscript. W. M. Lijfering had full access to the database, supervised statistical analysis, and revised the manuscript. F. R. Rosendaal designed the MEGA study and revised the manuscript. S. C. Cannegieter interpreted the data, supervised statistical analysis, and revised the manuscript.

Acknowledgements

The MEGA study was supported by the Netherlands Heart Foundation (NHS 98.113), the Dutch Cancer Foundation (RUL 99/1992), and the Netherlands Organization for Scientific Research (912-09-033/2003). D. D. Ribeiro was financially supported by CAPES (Edital DRI/CGCI no. 006/2009). W. M. Lijfering is a postdoctoral fellow of the Netherlands Heart Foundation (2011T12).

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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