**Joint effect of multiple prothrombotic genotypes and obesity on the risk of incident venous thromboembolism**

**Running head:** Genotypes, obesity and venous thromboembolism

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**Abstract**

**Background:** The impact of the combination of obesity and multiple prothrombotic genotypes on venous thromboembolism (VTE) risk remains unclear.

**Objective:** To investigate the joint effect of obesity and a genetic risk score (GRS) comprised of established prothrombotic single nucleotide polymorphisms (SNPs) on VTE risk using a population-based case-cohort.

**Methods:** Cases with incident VTE (n=1,470) and a subcohort (n=12,826) were derived from the Tromsø Study (1994-2012) and the Trøndelag Health Study (HUNT) (1995-2008). Participants were genotyped for *ABO* (rs8176719), *F5* (rs6025), *F2* (rs1799963), *FGG* (rs2066865) and *F11* (rs2036914) SNPs. Age- and sex-adjusted hazard ratios (HRs) were estimated according to body mass index (BMI) categories and number of risk alleles for individual SNPs and the GRS (0-1, 2, 3, ≥4 alleles).

**Results:** The combination of obesity (BMI≥30kg/m$^2$) and risk alleles, either as individual SNPs or as a GRS, had an additive effect on VTE risk (i.e. no biological interaction). Obese subjects who were carriers of ≥4 risk alleles had a 2.85-fold (95% confidence intervals [CI] 2.05-3.96) increased risk of overall VTE compared to those with BMI<25kg/m$^2$ and 0-1 risk allele. However, in subgroups, the combination of obesity and ≥4 risk alleles was more pronounced for deep vein thrombosis (DVT) (HR 3.20, 95% CI 2.09-4.90) and unprovoked VTE (HR 3.82, 95% CI 2.25-6.47), suggesting a supra-additive effect.

**Conclusion:** Our findings indicate that the combination of obesity and GRS has an additive effect on the risk of overall VTE. However, it may have a supra-additive effect on the risk of DVT and unprovoked VTE.

**Keywords:** deep vein thrombosis; interaction; obesity; single nucleotide polymorphism; venous thromboembolism.

## Introduction

Venous thromboembolism (VTE), a collective term for deep vein thrombosis (DVT) and pulmonary embolism (PE), is a multicausal disease, affecting 1 to 2 per 1,000 individuals each year.[1,2] Obesity, defined as a body mass index (BMI) ≥30 kg/m$^2$,[3] has emerged over the past decades as one of the most relevant modifiable risk factors for VTE. Obesity is associated with a two- to three-fold increased risk of VTE, the risk increases linearly with an increasing BMI,[4,5] and weight gain over time is associated with additional VTE risk, particularly in obese.[6] Approximately one-third of the unprovoked VTE cases in the population can be attributed to obesity,[7] and Mendelian randomization studies have revealed that genetically elevated BMI is associated with a higher risk of VTE,[8-11] supporting a causal relationship.

During the last decades, several single nucleotide polymorphisms (SNPs) associated with VTE have been identified. To improve the risk prediction of incident VTE, de Haan *et al.*[12] developed a genetic risk score (GRS) comprising the five SNPs (out of 31) that individually showed the strongest association with VTE. This 5-SNP score included rs8176719 (non-O blood group) in *ABO*, rs6025 (factor V Leiden [FVL]) in *F5*, rs1799963 (prothrombin G20210A) in *F2*, rs2066865 in the fibrinogen gamma gene (*FGG)* and rs2036914 in *F11,* and identified subjects at increased risk of VTE similarly to the score with all 31 SNPs.[12]

The multicausal nature of VTE implies that more than one risk factor is required for an event to occur.[13] In obese subjects, the presence of genetic variants associated with a prothrombotic state, such as FVL, prothrombin G20210A and non-O blood group, has been suggested to synergistically increase the risk of VTE because of biological interaction.[14-17] A recent nested case-control study derived from the Nurses' Health Study and the Health Professionals Follow-up Study reported a synergistic effect between obesity and a GRS based

on 16 VTE-associated SNPs on the risk of VTE.[18] However, whether and to what extent the combination of obesity and multiple established prothrombotic SNPs affects VTE risk in the general population remains uncertain. Moreover, FVL has been consistently associated with a higher risk of DVT than of PE (the so-called FVL paradox),[19] and thrombophilia has been shown to have a higher prevalence among patients with unprovoked VTE.[20] Hence, the combination of obesity and some prothrombotic genotypes may have a differential impact on the risk of VTE subgroups (i.e. DVT, PE, provoked and unprovoked VTE). Clarification of these questions may provide novel insights into the mechanism of VTE in obesity and improve the identification of obese subjects at a substantially high risk of VTE, guiding clinical decisions for VTE prevention. We therefore aimed to investigate the joint effect of obesity and established prothrombotic genotypes, either individually or in a GRS, on the risk of overall VTE and subgroups in a case-cohort study derived from the general population. We hypothesized that the joint presence of obesity and prothrombotic genotypes would have a synergistic effect on the risk of VTE due to biological interaction.

## Methods

*Study population*

Two Norwegian population-based cohorts, the Tromsø Study[21] and the Trøndelag Health Study (HUNT),[22] served as the source population for our case-cohort study. The entire population in the municipality of Tromsø aged ≥25 years was invited to the Tromsø 4 cohort (baseline 1994/95) and 77% (27,158) participated. Similarly, all inhabitants in Nord-Trøndelag county aged ≥20 years were invited to the HUNT 2 cohort (baseline 1995/97) and 71% (66,140) participated. The participants were followed from the date of enrolment until the date of incident VTE, migration, death or end of follow-up, whichever occurred first (the follow-up ended on December 31, 2012 in Tromsø 4 and on December 31, 2008 in HUNT 2).

The VTE identification and adjudication process have previously been described in detail for the Tromsø Study[23] and the HUNT Study.[1] In brief, VTE events were identified by searching the relevant discharge registries (diagnosis, autopsy, radiology) of the hospitals serving the cohort regions (Tromsø: University Hospital of North Norway; HUNT: local hospitals at Levanger and Namsos, and St. Olav's Hospital in Trondheim). Each potential VTE case was reviewed by trained personnel and the adjudication criteria included clinical signs and symptoms of DVT or PE, combined with objective confirmation by radiological procedures, and treatment initiation unless contraindications were specified.

The composition of the case-cohort from the merged Tromsø and HUNT cohorts (n=93,298) is summarized in Figure 1. During follow-up, a total of 1,493 participants developed an incident VTE and were included as cases in the present study, as previously described.[24] From both cohorts, a total of 13,072 individuals were randomly selected for the subcohort. In the case-cohort design, every participant in the cohort has the same probability of being selected to the subcohort, including the cases. In total, 217 of the subjects randomly selected to the subcohort were also VTE cases. Study participants who were not officially registered as inhabitants of Tromsø or Nord-Trøndelag at baseline (n=3) were excluded. Additionally, participants with missing information on BMI (n=91) or one of the SNPs of interest (n=175) were excluded. Consequently, 1,470 incident VTEs and 12,826 subcohort participants were included into the present study, as illustrated in Figure 1. The regional committees for medical and health research ethics approved both studies, and all participants provided written consent.

*Classification of VTE events*

All events were classified as either PE (with or without DVT) or isolated DVT and as provoked or unprovoked based on the presence of provoking factors at the time of diagnosis.

In the Tromsø Study, the VTE events were classified as provoked if one or more of the following provoking factors were present: surgery, trauma or acute medical conditions (acute myocardial infarction, acute ischemic stroke, or acute infection) within 8 weeks prior to the event, immobilization (bed rest >3 days or confinement to wheelchair within the last 8 weeks, or long-distance travel ≥4 h within the last 14 days), active cancer at the time of VTE diagnosis, or other factors specifically described as provoking by a physician in the medical record (e.g., intravascular catheter). In the HUNT Study, provoking factors included trauma or surgery, cancer (active malignancy at the time of the event or within 6 months after the event), marked immobilization (paresis, paralysis, prolonged bedrest due to acute medical illness, or travel >8 hours) within the previous 3 months, pregnancy or puerperium at the time of the event, or use of oral contraceptives at the time of the event or up to one month prior to the event.

*Baseline measurements*

Baseline information in the Tromsø and HUNT studies was obtained from physical examinations, blood samples and self-administered questionnaires. Body height (to the nearest centimeter) and weight (to the nearest 0.5 kilograms) were measured with subjects wearing light clothes and no shoes. BMI was calculated as weight in kilogram per square of height in meters ($kg/m^2$). A detailed self-reported questionnaire was used to obtain information on chronic diseases, including arterial cardiovascular disease (CVD), i.e. angina pectoris, stroke, and myocardial infarction.

*Prothrombotic genotypes*

Samples from the Tromsø Study were genotyped using the Sequenom and the TaqMan platforms, as previously described.[25] The HUNT samples were genotyped using the Illumina

HumanCore Exome array. The following SNPs were assessed: rs8176719 in *ABO* (non-O blood group), rs6025 in *F5* (FVL), rs1799963 in *F2* (prothrombin G20210A), rs2066865 in *FGG*, and rs2036914 in *F11*. Individuals were classified as carriers of a prothrombotic SNP if one or two risk alleles were present, and as non-carriers if no risk allele was present. For rs2036914 in *F11*, the minor allele is associated with a reduced risk of VTE, and we therefore considered the common allele as the risk allele.[26] The 5-SNP score conceived by de Haan *et al.*[12] was created by summing up the number of risk alleles of the five aforementioned SNPs, with a theoretical maximum number of ten risk alleles for an individual.

*Statistical analysis*

Statistical analysis was carried out with STATA (version 16; Stata Corporation, College Station, TX, USA). The study participants were divided into three BMI categories according to cutoff values defined by the World Health Organization (WHO): BMI <25 kg/m$^2$, BMI 25-30 kg/m$^2$ (overweight) and BMI ≥30 kg/m$^2$ (obesity).[3] Means (± standard deviation) and proportions of baseline characteristics across BMI categories were calculated using descriptive statistics. For each individual SNP, Cox proportional hazards regression models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for incident VTE across categories of BMI. Non-carriers (0 risk alleles) with a BMI <25 kg/m$^2$ served as the reference group. Age was used as a time scale, with the age at enrollment defined as the entry time, and the age at incident VTE or censoring defined as the exit time. Further, we utilized the non-weighted 5-SNP score described by de Haan *et al*.[12] to investigate the effect of multiple prothrombotic risk alleles across categories of BMI on the risk of incident VTE. For the GRS, four categories of risk alleles were conceived, i.e. 0-1, 2, 3 and ≥4 risk alleles, and subjects with 0-1 risk alleles and a BMI <25 kg/m$^2$ served as the reference group in the Cox regression models. All analyses were adjusted for age (as a time scale) and sex. Subgroup

analyses were performed for individual SNPs and the GRS according to anatomical location (DVT and PE) or the presence of provoking factors (provoked and unprovoked events). The proportional hazard assumption was tested by the use of Schoenfeld residuals.

The presence of biological interaction between overweight or obesity and the prothrombotic risk alleles was assessed on an additive scale by calculating the relative excess risk attributable to interaction (RERI), the attributable proportion (AP) due to interaction, and the synergy index (SI) with corresponding 95% CIs for overall VTE and subgroups.[27,28] Briefly, the RERI can be interpreted as part of the total effect on the outcome that is attributable to interaction, and the AP as the proportion of the combined effect that is due to interaction between the two exposures.[27] For interpretation, a RERI >0, an AP >0 and a SI >1.0 indicate a departure from additivity of effects, suggesting positive interaction, i.e. the effect of the joint exposure (having both risk factors) on the outcome is greater than the sum of the two separate effects.[27,28] Even though the focus of this study was on biological interaction, for a transparent presentation of interaction effects, we reported the separate effect of each exposure as well as the joint effect compared to the unexposed group as a joint reference category to allow assessment of interaction on both an additive and multiplicative scale.[29]

**Results**

The baseline characteristics of the study participants across BMI categories (i.e. <25 kg/m$^2$, 25-30 kg/m$^2$, and ≥30 kg/m$^2$) are presented in Table 1. The mean age of study participants and the proportion of arterial CVD increased across categories of BMI. The five prothrombotic SNPs were similarly distributed in BMI categories, with rs1799963 in *F2* (prothrombin G20210A) being the least prevalent. For the GRS, the median number of risk alleles in the

study population was 2, ranging from 0 to 7. The distribution of the number of risk alleles was similar across BMI categories, as visualized in Figure 2.

The risk of overall VTE according to the presence of prothrombotic risk alleles and BMI categories for the individual SNPs is shown in Table 2. In non-carriers of risk alleles, the risk of VTE increased with an increasing BMI for all the SNPs. Compared to the reference, risk estimates increased across categories of BMI in a dose-response manner in carriers of ≥1 risk alleles for the individual SNPs, with the exception of rs1799963 in *F2*. Further, we estimated interaction on an additive scale (see also Supplementary Table 1 describing measures of biological interaction, i.e. RERI, AP, and SI). Compared to subjects with a BMI <25 kg/m$^2$ and 0 risk allele, the joint exposure to obesity and ≥1 risk alleles for the SNPs in *ABO* (non-O blood group), *F5* (FVL), *FGG* and *F11* resulted in an additive effect on VTE risk, as the thrombosis risk approximated the sum of the separate effects of obesity and having ≥1 risk alleles. The analyses of rs1799963 in *F2* were limited due to a low prevalence of this SNP in the study population (Table 2).

Next, we assessed the risk of overall VTE according to the GRS (Table 3). In the analysis stratified by BMI, the risk of VTE increased with an increasing number of risk alleles within each BMI category. When subjects with 0-1 risk allele and a BMI <25 kg/m$^2$ were defined as the reference group, the highest risk estimates for VTE were observed in subjects in the high-risk category of the GRS (i.e. ≥4 risk alleles) in all BMI categories. The corresponding HRs were 2.19 (95% CI 1.62-2.95), 2.59 (95% CI 1.96-3.43) and 2.85 (95% CI 2.05-3.96) in subjects with BMI <25 kg/m$^2$, 25-30 kg/m$^2$ and ≥30 kg/m$^2$, respectively. Similar to the analysis of the individual SNPs, the joint exposure to obesity and the high-risk category of the GRS (i.e. ≥4 risk alleles) had an additive effect on VTE risk, with a RERI of 0.11 (95% CI -0.77 to 0.99), an AP of 0.04 (95% CI -0.27 to 0.34), and a SI of 1.06 (95% CI 0.65 to 1.74) (Supplementary Table 1). In summary, the combination of obesity and prothrombotic

genotypes (assessed either as individual SNPs or as a GRS) did not reveal interaction on an additive scale with regards to the risk of overall VTE, as suggested by the measures of biological interaction and their 95% CIs described in Supplementary Table 1.

The subgroup analyses were stratified according to VTE location and the presence of provoking factors. Compared to the reference category, when obesity was jointly present with ≥1 risk alleles in *ABO*, *F5, FGG* or *F11* SNPs (Supplementary Tables 2 and 3) or with the high-risk category of the GRS (Table 4), the association with thrombosis risk was more pronounced for DVT and unprovoked VTE than for PE and provoked VTE. The combination of obesity with the SNPs in *ABO* or *F5* or with the high-risk category of the GRS pointed towards a slight supra-additive effect on the risk of DVT, as suggested by measures of biological interaction (Supplementary Table 4). Of note, the point estimates of the RERI and AP in DVT and PE displayed opposite directions, as visualized in Figure 3. Further, the combination of obesity with the high-risk category of the GRS and particularly with rs2036914 in *F11* was suggestive of having a supra-additive effect on the risk of unprovoked VTE (Supplementary Table 4), with a RERI of 0.79 (95% 0 to 1.59) and an AP of 0.30 (-0.01 to 0.62) for rs2036914. No interactions on a multiplicative scale were detected between BMI categories and the individual SNPs or the GRS in overall VTE and subgroups (data not shown).

**Discussion**

In this population-based case-cohort study, we investigated the joint effect of obesity and established prothrombotic genotypes on the risk of VTE, evaluated either as individual SNPs or as categories of a GRS. We found that the VTE risk increased both with the number of risk alleles and an increasing BMI, and the highest risk estimates were obtained when obesity was jointly present with prothrombotic risk alleles, for the individual SNPs (i.e. ≥1 risk alleles)

and the high-risk category of the GRS (i.e. ≥4 risk alleles). The combination of obesity and prothrombotic risk alleles had additive effects on the risk of overall VTE, as the risk in the combined category approximated, but did not exceed, the sum of the separate effects of the two exposures (i.e. no biological interaction). Still, when obesity was combined with the SNPs in *F5* (FVL), *ABO* (non-O blood group) or *F11* or with the high-risk category of the GRS, the association with thrombosis risk was more pronounced for DVT and unprovoked VTE than for PE and provoked VTE, which may suggest a synergistic effect in these subgroups.

A few studies have previously investigated the combined effects of obesity and prothrombotic genotypes, including FVL, prothrombin G20210A, and non-O blood group, on VTE risk.[14-17] In the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA) case-control study and in the case-cohort derived from the Danish Diet, Cancer and Health study, the combination of obesity with FVL or prothrombin G20210A resulted in a VTE risk that was higher than the sum of the separate effects.[14,15] A synergistic effect on thrombosis risk was also found for the joint exposure to a high BMI and non-O blood group in case-control studies.[16,17] Only two studies, conducted by Crous-Bou *et al.*[30] and Kim *et al.,*[18] evaluated interaction between obesity and multiple SNPs with regards to VTE risk. However, the authors conceived their nested case-control designs using the same cohorts consisting of health care professionals. In these studies, the exposure (BMI) and the outcome (incident VTE) were self-reported in questionnaires, and a weighted GRS was built using 16 SNPs associated with VTE in genome-wide association studies.[18,30] Only FVL and prothrombin G20210A overlapped with the SNPs included in our genetic score, and not all the SNPs were related to hemostatic factor genes. In both studies, no interaction on a multiplicative scale was detected,[18,30] but Kim *et al*. reported interaction on an additive scale for the combination of a high GRS and a high BMI.[18] On the whole, the findings of the prior

studies[14-18] appear not to be in line with our results, since we found no clear deviation from additivity for the joint effect of obesity and prothrombotic genotypes on the risk of overall VTE, in the analysis of the individual SNPs and the GRS. However, several reasons may account for the distinct findings, including differences in the study designs, the clinical characteristics of the source population that originated the studies, and the SNPs used to create the genetic scores. Further, in the aforementioned reports,[14-18] the population was mostly comprised of subjects younger than 70 years at study inclusion, who would have a lower baseline risk and presumably less comorbidities associated with risk of VTE, which could result in higher relative effects of prothrombotic genotypes and obesity. In contrast, participants in our study had a wide age distribution at baseline that was representative of the general population. Finally, the low prevalence of prothrombin G20210A in our case-cohort (~1.5%) limited the interaction analysis related to this SNP and comparison with other studies.

We found that obesity in combination with the SNPs in *F5* (FVL), *ABO* (non-O blood group) or *F11* or with the high-risk category of the GRS had a stronger impact on the risk of DVT and unprovoked VTE than on the risk of PE and provoked VTE. Notably, measures of biological interaction suggested that the combination of obesity and some of the prothrombotic genotypes had a slight supra-additive effect on the risk of DVT (obesity plus FVL or non-O blood group) and unprovoked VTE (obesity plus rs2036914 in *F11*). It is important to address that a substantial proportion of our VTE cases had provoked events (56%) and PE (41%), which may help explain why the analyses of the overall population did not reveal any consistent finding of biological interaction between obesity and prothrombotic genotypes.

In this study, when obesity was combined with FVL or non-O blood group, the association was not only more pronounced for DVT as compared with PE, but measures of

biological interaction displayed even opposite directions. Similar results were obtained for the high-risk category of the GRS, which appeared to be essentially driven by FVL and non-O blood group. In accordance with our results, Ribeiro *et al*. showed in the MEGA case-control study that the combination of obesity and FVL or non-O blood group yielded a higher risk for DVT than for PE.[17] The other studies that investigated the joint effect of obesity and prothrombotic genotypes on VTE risk did not report separate analyses for DVT and PE, [15,16,18] thereby limiting comparison with our results. The differential effect on the risk of DVT and PE that we found might be interpreted in light of the FVL paradox, a well-recognized phenomenon in which FVL is associated with a higher risk of DVT than of PE.[19] Recently, an animal model study has provided insights into the rationale behind this paradox,[31] showing that venous thrombi in FVL mice were larger and embolized less compared with wild type mice, probably because of enhanced thrombus stability. FVL is associated with the phenotype of activated protein C (APC) resistance.[32] Interestingly, other factors that have been shown to also pose a higher risk for DVT than for PE, including oral contraceptive use and obesity,[19] may lead to APC resistance as well.[16,33] Furthermore, individuals with non-O blood group have higher levels of factor VIII than individuals with O blood group,[34] and factor VIII is known to increase APC resistance.[15] Accordingly, APC resistance would be a common mechanism associated with obesity, FVL and non-O blood group that could explain our findings of a potential synergistic effect between obesity and these prothrombotic genotypes on the risk of DVT.

The considerable impact that the combination of obesity and some prothrombotic SNPs had on the risk of unprovoked VTE in this study is consistent with data reporting a higher prevalence of thrombophilia in patients with unprovoked VTE.[20] It is of interest that the joint exposure to obesity and rs2036914 in *F11* appeared to have a synergistic effect on the risk of unprovoked VTE. Indeed, the AP revealed that 30% of the unprovoked events

occurring in obese subjects who were carriers of rs2036914 could be attributed to the interaction between these risk factors. This synergism is biologically plausible, since both obesity and rs2036914 were reported to be associated with factor XI levels.[26,35]

Taken together, our findings suggest that obese individuals who are carriers of some prothrombotic SNPs may be at a particularly high risk of developing DVT or unprovoked events. Given the likely causal role of obesity in the risk of VTE, as revealed by Mendelian randomization studies,[8-11] the synergism between obesity and common prothrombotic genotypes may account for a substantial burden of VTE in the general population, mainly because of DVT and unprovoked VTE. Since the genetic factors are not modifiable, public health interventions to control the rising prevalence of obesity have the potential to reduce the incidence of VTE.

The main strengths of our study include the recruitment of participants from the general population with a wide age distribution, the long-term follow-up and the high attendance rates in the parent cohorts, the large number of genotyped participants, the objective validation of the VTE events, and the inclusion of a homogenous Caucasian population, which limited confounding by ethnicity in the subcohort. We used a GRS comprised of five established prothrombotic SNPs, thus facilitating comparison of results across studies. Some limitations merit attention. BMI was measured at baseline and could be susceptible to change over time due to the long-term follow-up, likely leading to an underestimation of the association between obesity and VTE because of regression dilution.[36] However, as demonstrated in the Tromsø Study, risk estimates for VTE based on one baseline measurement of BMI did not substantially differ from risk estimates based on repeated measurements.[37] Different techniques were used for SNP assessment, i.e. the Sequenom and TaqMan platforms for the Tromsø 4 cohort, and Illumina HumanCore Exome array for the HUNT 2 cohort. Of note, the prevalence of carriers of ≥ 1 risk alleles for each of the five

SNPs studied was similar among the participants from the Tromsø 4 and HUNT 2 cohorts (data not shown), implying that the use of different techniques for SNP detection most likely did not influence our results. Even though our study was derived from large cohorts, the number of VTE events was low in some subgroups, especially for the rare genetic variants, which resulted in limited statistical power. Our results on measures of biological interaction should be interpreted with caution, as the 95% CIs around these measures were generally wide, indicating low precision.

In conclusion, the combination of obesity and established prothrombotic genotypes, assessed either as individual SNPs or as a GRS, had an additive effect on the risk of overall VTE. However, our findings suggest that obesity when jointly present with some prothrombotic genotypes may have a supra-additive effect on the risk of DVT or unprovoked VTE because of biological interaction in these subgroups.

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## Conflicts of interest

There are no conflicts of interest reported by any of the authors.

## Author contributions

T. Frischmuth analyzed data, interpreted the results and drafted the manuscript. K. Hindberg provided statistical support, interpreted the results, and revised the manuscript. M.E. Gabrielsen, B. Brumpton and K. Hveem organized data collection and revised the manuscript. S.K. Brækkan designed the study, organized data collection, interpreted the results, contributed to the manuscript draft, and revised the manuscript. J-B Hansen designed the study, organized data collection, interpreted the results, and revised the manuscript. V.M. Morelli designed the study, interpreted the results, contributed to the manuscript draft, and revised the manuscript. All authors reviewed and approved the final version of the manuscript.

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## Figures

**Figure 1** Study population. Participants were recruited from the fourth survey of the Tromsø Study (1994-2012), and from the second survey of the Trøndelag Health Study (HUNT) (1995-2008). BMI, body mass index; SNPs, single nucleotide polymorphisms; VTE venous thromboembolism.

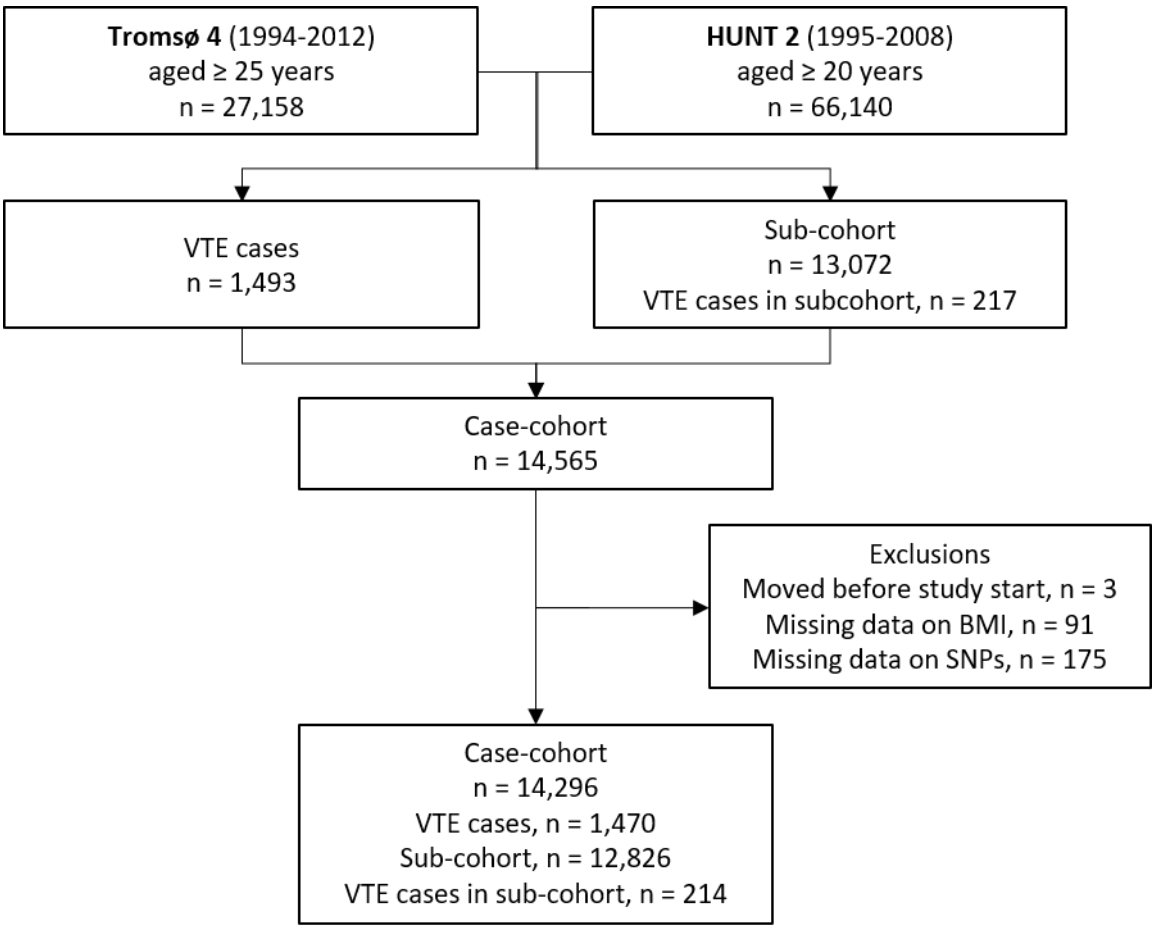


**Figure 2** Distribution (%) of individuals across number of risk alleles in the genetic risk score and categories of body mass index defined according to cutoff values of the World Health Organization.

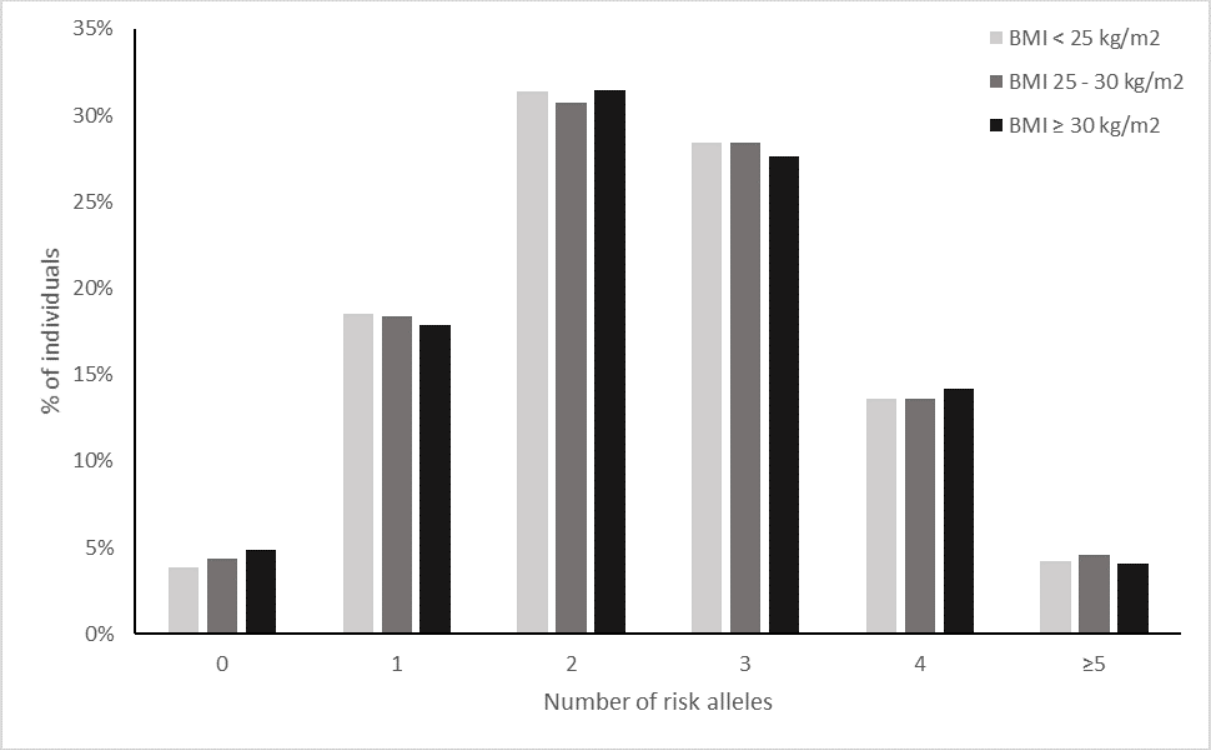
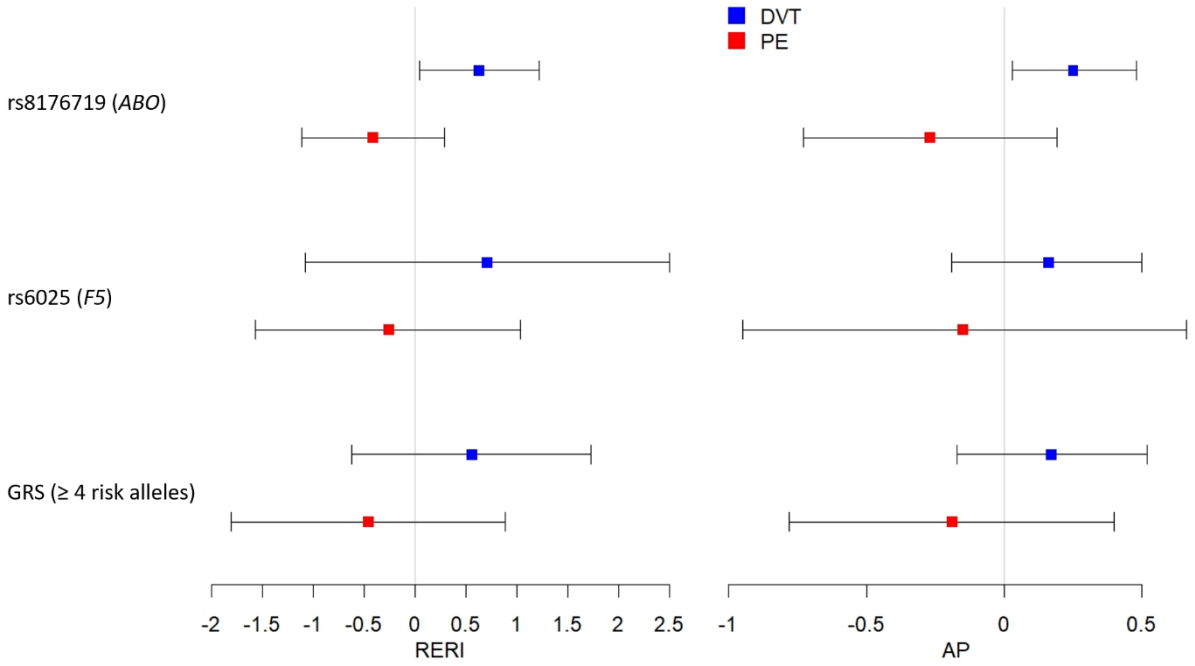


**Figure 3** Forest plot. Measures of biological interaction for the joint effect of obesity (body mass index ≥30 kg/m$^2$) and the single nucleotide polymorphisms (SNPs) in *ABO* and *F5* or the high-risk category of the genetic risk score (GRS) for deep vein thrombosis (DVT) and pulmonary embolism (PE). Point estimates in blue refer to DVT and in red to PE. Abbreviations: AP, attributable proportion; RERI, relative excess risk due to interaction.



## Tables

**Table 1** Baseline characteristics according to categories of body mass index (BMI).

| | **BMI <25 kg/m$^2$** | **BMI 25 - 30 kg/m$^2$** | **BMI ≥30 kg/m$^2$** |
|---|---|---|---|
| Number of subjects | 5,780 | 6,141 | 2,375 |
| Age (years), mean ± SD | 48 ± 17 | 53 ± 16 | 56 ± 16 |
| Male sex, % (n) | 42.1 (2,434) | 54.8 (3,368) | 39.2 (930) |
| CVD[a], % (n) | 5.8 (333) | 10.0 (611) | 12.2 (290) |
| rs8176719 (*ABO*) , ≥ 1 risk alleles, % (n) | 61.9 (3,579) | 62.4 (3,829) | 62.6 (1,487) |
| rs6025 (*F5*) , ≥ 1 risk alleles, % (n) | 7.4 (427) | 7.9 (484) | 7.2 (170) |
| rs1799963 (*F2*), ≥ 1 risk alleles, % (n) | 1.4 (82) | 1.3 (77) | 1.8 (42) |
| rs2066865 (*FGG) ,* ≥ 1 risk alleles, % (n) | 43.3 (2,502) | 42.4 (2,606) | 41.0 (973) |
| rs2036914 (*F11*), ≥ 1 risk alleles, % (n) | 78.8 (4,552) | 78.3 (4,806) | 79.1 (1,879) |

Abbreviations: CVD, cardiovascular disease; BMI, body mass index; SD, standard deviation.
BMI categories were defined according to cutoff values of the World Health Organization.
[a] Self-reported history of arterial cardiovascular disease (myocardial infarction, angina pectoris, stroke).

**Table 2** Hazard ratios with 95% confidence intervals for overall venous thromboembolism according to single nucleotide polymorphisms and categories of body mass index.

| **Risk alleles** | **BMI < 25 kg/m$^2$** | | **BMI 25 – 30 km/m$^2$** | | **BMI ≥ 30 kg/m$^2$** | |
|---|---|---|---|---|---|---|
| SNP (*gene*) | Events | HR (95% CI) | Events | HR (95% CI) | Events | HR (95% CI) |
| rs8176719 (*ABO*) | | | | | | |
| 0 | 136 | 1 (reference) | 220 | 1.28 (1.03 - 1.59) | 105 | 1.49 (1.16 - 1.93) |
| ≥ 1 | 296 | 1.42 (1.16 - 1.74) | 478 | 1.73 (1.43 - 2.09) | 235 | 2.07 (1.68 - 2.56) |
| rs6025 (*F5*) | | | | | | |
| 0 | 360 | 1 (reference) | 595 | 1.27 (1.11 - 1.45) | 295 | 1.53 (1.31 - 1.78) |
| ≥ 1 | 72 | 2.51 (1.95 - 3.23) | 103 | 2.82 (2.26 - 3.51) | 45 | 3.30 (2.42 - 4.50) |
| rs1799963 (*F2*) | | | | | | |
| 0 | 420 | 1 (reference) | 684 | 1.25 (1.11 - 1.42) | 336 | 1.51 (1.30 - 1.74) |
| ≥ 1 | 12 | 2.27 (1.28 - 4.03) | 14 | 1.93 (1.13 - 3.29) | 4 | 1.16 (0.43 - 3.11) |
| rs2066865 (*FGG*) | | | | | | |
| 0 | 224 | 1 (reference) | 377 | 1.25 (1.06 - 1.48) | 194 | 1.53 (1.26 - 1.86) |
| ≥ 1 | 208 | 1.20 (1.00 - 1.45) | 321 | 1.49 (1.26 - 1.77) | 146 | 1.72 (1.39 - 2.12) |
| rs2036914 (*F11*) | | | | | | |
| 0 | 77 | 1 (reference) | 133 | 1.27 (0.96 - 1.68) | 55 | 1.33 (0.94 - 1.88) |
| ≥ 1 | 355 | 1.20 (0.94 - 1.53) | 565 | 1.48 (1.17 - 1.88) | 285 | 1.81 (1.40 - 2.33) |

Abbreviations: BMI, body mass index; CI, confidence interval; HR, Hazard ratio; SNP, single nucleotide polymorphism.
BMI categories were defined according to cutoff values of the World Health Organization.
HR adjusted for age as a time scale and sex.

**Table 3** Hazard ratios with 95% confidence intervals for overall venous thromboembolism according to categories of the genetic risk score and body mass index.

| Number of risk alleles | Events | HR (95% CI)[a] | HR (95% CI)[b] |
|---|---|---|---|
| BMI < 25 kg/m$^2$ | | | |
| 0 - 1 | 67 | 1 (reference) | 1 (reference) |
| 2 | 111 | 1.16 (0.85 - 1.56) | 1.15 (0.85 - 1.56) |
| 3 | 134 | 1.55 (1.15 - 2.08) | 1.55 (1.15 - 2.07) |
| ≥ 4 | 120 | 2.21 (1.64 - 2.97) | 2.19 (1.62 - 2.95) |
| BMI 25 - 30 kg/m$^2$ | | | |
| 0 - 1 | 115 | 1 (reference) | 1.25 (0.93 - 1.70) |
| 2 | 191 | 1.23 (0.98 - 1.55) | 1.55 (1.17 - 2.05) |
| 3 | 210 | 1.49 (1.19 - 1.87) | 1.87 (1.42 - 2.47) |
| ≥ 4 | 182 | 2.07 (1.64 - 2.62) | 2.59 (1.96 - 3.43) |
| BMI ≥ 30 kg/m$^2$ | | | |
| 0 - 1 | 58 | 1 (reference) | 1.55 (1.09 - 2.21) |
| 2 | 87 | 1.09 (0.78 - 1.51) | 1.65 (1.20 - 2.27) |
| 3 | 119 | 1.69 (1.23 - 2.31) | 2.61 (1.93 - 3.53) |
| ≥ 4 | 76 | 1.83 (1.30 - 2.58) | 2.85 (2.05 - 3.96) |

Abbreviations: BMI, body mass index; CI, confidence interval; HR, Hazard ratio.
BMI categories were defined according to cutoff values of the World Health Organization.
[a] 0 – 1 risk allele as reference category in each BMI category.
[b] BMI <25 kg/m$^2$ and 0 – 1 risk allele as reference category.
HR adjusted for age as a time scale and sex.

**Table 4** Hazard ratios with 95% confidence intervals for venous thromboembolism in subgroups according to categories of the genetic risk score and body mass index.

| Number of risk alleles | Events | HR (95% CI)[a] | Events | HR (95% CI)[a] |
|---|---|---|---|---|
| | | ***DVT*** | | ***PE*** |
| BMI < 25 kg/m$^2$ | | | | |
| 0 - 1 | 38 | 1 (reference) | 29 | 1 (reference) |
| 2 | 66 | 1.21 (0.81 - 1.81) | 45 | 1.07 (0.67 - 1.71) |
| 3 | 77 | 1.58 (1.07 - 2.33) | 57 | 1.50 (0.96 - 2.34) |
| ≥ 4 | 68 | 2.19 (1.47 - 3.26) | 52 | 2.19 (1.39 - 3.44) |
| BMI 25 - 30 kg/m$^2$ | | | | |
| 0 - 1 | 68 | 1.33 (0.89 - 1.98) | 47 | 1.16 (0.73 - 1.84) |
| 2 | 111 | 1.62 (1.12 - 2.35) | 80 | 1.46 (0.95 - 2.24) |
| 3 | 123 | 1.97 (1.36 - 2.83) | 87 | 1.75 (1.15 - 2.67) |
| ≥ 4 | 110 | 2.79 (1.93 - 4.04) | 72 | 2.33 (1.51 - 3.59) |
| BMI ≥ 30 kg/m$^2$ | | | | |
| 0 - 1 | 30 | 1.45 (0.90 - 2.34) | 28 | 1.68 (1.00 - 2.82) |
| 2 | 53 | 1.80 (1.18 - 2.73) | 34 | 1.46 (0.89 - 2.40) |
| 3 | 80 | 3.16 (2.14 - 4.65) | 39 | 1.92 (1.19 - 3.11) |
| ≥ 4 | 48 | 3.20 (2.09 - 4.90) | 28 | 2.40 (1.43 - 4.05) |
| | | ***Unprovoked VTE*** | | ***Provoked VTE*** |
| BMI < 25 kg/m$^2$ | | | | |
| 0 - 1 | 23 | 1 (reference) | 44 | 1 (reference) |
| 2 | 40 | 1.20 (0.72 - 2.01) | 71 | 1.12 (0.77 - 1.64) |
| 3 | 54 | 1.81 (1.11 - 2.94) | 80 | 1.41 (0.98 - 2.04) |
| ≥ 4 | 54 | 2.85 (1.75 - 4.65) | 66 | 1.84 (1.26 - 2.70) |
| BMI 25 - 30 kg/m$^2$ | | | | |
| 0 - 1 | 50 | 1.56 (0.95 - 2.56) | 65 | 1.10 (0.75 - 1.61) |
| 2 | 87 | 2.03 (1.28 - 3.21) | 104 | 1.30 (0.91 - 1.86) |
| 3 | 95 | 2.42 (1.53 - 3.82) | 115 | 1.59 (1.12 - 2.25) |
| ≥ 4 | 91 | 3.71 (2.35 - 5.87) | 91 | 2.00 (1.39 - 2.87) |
| BMI ≥ 30 kg/m$^2$ | | | | |
| 0 - 1 | 18 | 1.38 (0.75 - 2.56) | 40 | 1.65 (1.07 - 2.53) |
| 2 | 42 | 2.29 (1.38 - 3.81) | 45 | 1.31 (0.86 - 1.99) |
| 3 | 58 | 3.68 (2.27 - 5.97) | 61 | 2.05 (1.39 - 3.02) |
| ≥ 4 | 35 | 3.82 (2.25 - 6.47) | 41 | 2.35 (1.53 - 3.59) |

Abbreviations: BMI, body mass index; CI, confidence interval; DVT, deep vein thrombosis; HR, Hazard ratio; PE, pulmonary embolism; VTE, venous thromboembolism.
BMI categories were defined according to cutoff values of the World Health Organization.
[a] BMI < 25 kg/m$^2$ and 0 – 1 risk allele as reference category.
HR adjusted for age as a time scale and sex.