Lifestyle and venous thrombosis

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CHAPTER 2

Risk of venous thrombosis: obesity and its joint effect with oral contraceptive use and prothrombotic mutations

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SUMMARY

In the MEGA study we evaluated body weight, height and body mass index (BMI) as risk factors for venous thrombosis. Additionally we analyzed the joint effect of obesity together with oral contraceptive use and prothrombotic mutations on the risk of venous thrombosis. 3834 patients with a first venous thrombosis and 4683 control subjects were included, all non-pregnant and without active malignancies. Relative to those with a normal BMI (<25 kg/m^2), overweight (BMI≥25 and BMI<30 kg/m^2) increased the risk of venous thrombosis 1.7-fold (odds ratio (OR) $_{adj(age\ and\ sex)}$ 1.70, 95% confidence interval (95% CI) 1.55-1.87) and obesity (BMI≥30 kg/m^2) 2.4-fold (OR_{adj} 2.44, 95% CI 2.15-2.78). An increase in body weight and body height also individually increased thrombotic risk. Obese women who used oral contraceptives had a 24-fold higher thrombotic risk (OR_{adj} 23.78, 95% CI 13.35-42.34) than women with a normal BMI who did not use oral contraceptives. Relative to non-carriers of normal BMI, the joint effect of factor V Leiden and obesity led to a 7.9-fold increased risk (OR_{adj} 7.86, 95% CI 4.70-13.15); for prothrombin 20210A this was a 6.6-fold increased risk (OR_{adj} 6.58, 95% CI 2.31-18.69). Body height, weight and obesity increase the risk of venous thrombosis, especially obesity in women using oral contraceptives.

INTRODUCTION

Venous thrombosis has an average annual incidence of around 2 per 1000 individuals (Oger, 2000). The incidence rises exponentially with age, from 0.001% in childhood to nearly 1% per year in the very old (Rosendaal, 1997). Among venous thrombosis patients approximately two-thirds has deep venous thrombosis of the leg and one-third pulmonary embolism with or without deep venous thrombosis of the leg (Anderson, Jr. et al, 1991; White, 2003). The disease is potentially fatal when complicated by pulmonary embolism (White, 2003).

Venous thrombosis is a multicausal disease caused by both acquired and genetic factors. Recent studies indicate that obesity increases the risk of venous thrombosis (Abdollahi et al, 2003; Goldhaber et al, 1997; Oren et al, 2006; Samama, 2000; Stein et al, 2005; Tsai et al, 2002; Vaya et al, 2002; White et al, 2000). Biological support for the observed relationship between obesity and coagulation, and thus the risk of venous thrombosis, arises from studies showing an increase of procoagulant factors, such as factor VII, factor VIII, factor XII and fibrinogen, with increasing body mass index (BMI) (Bowles et al, 2003; Rosito et al, 2004; Chan et al, 1995; De Pergola et al, 1997). Obesity is also associated with venous stasis (Tsai et al, 2002) which may increase thrombotic risk.

Although BMI is the most widely used measure of obesity no single function of body height and weight is likely to capture fully the ways in which height and weight are related to venous thrombosis (Kronmal, 1993). For this reason we will also evaluate body weight and height as separate risk factors for venous thrombosis.

The multicausal nature of venous thrombosis dictates that risk factors are present simultaneously. We reported previously that oral contraceptives modified the effect of obesity on the risk of venous thrombosis, with a 10-fold increased risk among women with a BMI greater than 25 kg/m^2 compared to normal weight women not using oral contraceptives. A 4.6-fold increased risk was found for oral contraceptive use among women with a BMI below 25 kg/m^2 (Abdollahi et al, 2003). The Copenhagen City Heart Study led to reports on the joint effect of overweight and the factor V Leiden mutation and found a substantially increased risk in obese individuals with the mutation (Juul et al, 2004). Because obesity and oral contraceptive use are common in the general population and factor V Leiden and the prothrombin mutation are the two most frequent prothrombotic mutations, these are good candidates to investigate gene-environment interaction. Only a very large study will be able to do so.

To investigate the risk of venous thrombosis due to obesity, the separate risk contributions of body weight and body height and the combination of obesity with

other risk factors for venous thrombosis, we performed a large population-based case-control study.

METHODS

Study design

The Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA study) included consecutive patients with a first diagnosis of venous thrombosis. Between March 1999 and September 2004, patients were selected from the files of the anticoagulation clinics in Amsterdam, Amersfoort, The Hague, Leiden, Rotterdam and Utrecht. In the Netherlands, anticoagulation clinics monitor anticoagulation treatment of all patients in a geographically well-defined area. We included patients between the age of 18 and 70 years with a first deep venous thrombosis of the leg, a pulmonary embolism or a combination of these diagnoses. Idiopathic venous thrombosis was defined as venous thrombosis in patients without surgery, injury, plaster cast, immobilization in the year prior to the thrombosis or oral contraceptive use and hormone replacement therapy at the time of the event.

The diagnostic methods were verified in a random sample of the overall patient group (n=742). Within this group the diagnosis of 97% of deep venous thrombosis and 78% of pulmonary embolism was objectively confirmed. The tests included compression ultrasonography, Doppler ultrasound, impedance plethysmography and contrastvenography for diagnosis of deep venous thrombosis and perfusion and ventilation lung scanning, spiral computer tomography and pulmonary angiography for pulmonary embolism.

Patients with severe psychiatric problems or those unable to speak Dutch were considered ineligible. Of the 6331 eligible patients 276 died soon after the venous thrombosis. Of the remaining 6055 patients 5051 participated (83%). Of the non-participants 82 persons were in the end stage of disease and 922 refused to participate or could not be located. Of the participants, 4637 patients (92%) filled in and returned the questionnaire. Participants who did not return a questionnaire completed a short questionnaire by phone, which did not include questions on body weight and height, or only participated with a blood sample or buccal swab.

Partners of patients were asked to volunteer as control subjects. From January 2002 until September 2004, additional control subjects were recruited by using the random digit dialing (RDD) method (Hartge et al, 1984). Phone numbers were dialed at random within the geographical inclusion area of the patients. During

the phone call a specific person within a household (e.g. youngest woman between 20 and 50) was asked to participate. The random control subjects were frequency matched to the patients with respect to age and sex. RDD is an efficient method to collect a nearly random sample of all individuals in the population. Only control subjects with no recent history of venous thrombosis were included and the same exclusion criteria were applied as for the patients.

Of the 5051 participating patients, 3657 had an eligible partner. One partner died soon after the request for participation. Of the remaining 3656 partners 2982 participated (82%). Of the non-participants 18 were in end-stage disease, 649 refused to participate or could not be located and for 7 persons the reason for non-participation was unknown. A questionnaire was returned by 2821 participating partners (95%).

Of the 4350 eligible RDD control subject, four died before they were able to participate. Of the remaining 4346 persons 3000 participated (69%). Of the non-participants 15 were in the end stage of disease and 1331 refused to participate or could not be located. A questionnaire was returned by 2789 participants (93%). All participants gave written informed consent. The study was approved by the Medical Ethics Committee of the Leiden University Medical Center, Leiden, The Netherlands.

Data collection

Within a few weeks after diagnosis and registration at the anticoagulation clinics eligible patients received a letter with information about the MEGA study. Subsequently they were contacted by phone. If the patient was willing to participate a questionnaire was sent. The control subjects received the questionnaires immediately after inclusion by phone. The questionnaires included items on surgery, injury, plaster cast, immobilization, malignancies, pregnancy, use of oral contraceptives, hormone replacement therapy, body weight and body height. Most questions referred to a period of 12 months prior to the index date. For the patients and their partners, the index date was defined as the date of diagnosis of the thrombosis of the patient. The date of filling in the questionnaire was defined as the index date for the random control subjects.

Body mass index (BMI) was calculated by dividing body weight (kg) by squared height (m^2). BMI was categorized according to the criteria of the World Health Organization (1998), defining a BMI between 18.5 and 25 kg/m^2 in adults as normal, a BMI of 25 to 30 kg/m^2 as overweight and a BMI equal to or greater than 30 kg/m^2 as obesity (World Health Organisation, 2000).

Participants with missing data on body weight or body height were excluded from all analyses. In addition, individuals with malignancies diagnosed within 10 years prior to the index date and pregnant women or women that had been pregnant in the year before the index date were also excluded. In the analyses only partner controls with a participating patient were included leading to a total of 3834 patients, 2152 partner and 2531 random control subjects for the present analyses.

DNA collection

Within the patient group used for the analyses 3607 provided a blood sample or buccal swab (94%). In the combined control group 3830 blood samples or buccal swabs were obtained (82%). The factor V Leiden mutation was successfully determined in 3600 patients and 3809 control subjects, the prothrombin 20210A mutation in 3601 patient and 3810 control subjects. A detailed description of blood collection and DNA analysis for the factor V Leiden (G1691A) and the prothrombin mutation (G20210A) in the MEGA study has been published previously (Blom et al, 2005).

Statistical analysis

As estimates of relative risks we calculated odds ratios (ORs) and 95% confidence intervals (95% CI) according to the method of Woolf (Woolf, 1955). With a multiple logistic regression model we adjusted for age (continuous) and sex (categorical). Adjustment for age as a categorical variable resulted in the same risk estimates. In the analysis of body weight we also adjusted for body height (categorical). In the analyses with partners as control group, we performed a matched logistic analysis to adjust for similar lifestyle factors between patients and their partners (Cannegieter et al, 2006). In these matched analyses only patient-partner pairs were included (2152 pairs). In the analyses with the random control subjects an unmatched analysis including all patients and random control subjects was performed. Because the results of the matched and the unmatched analyses showed consistent elevated relative risks in all the analyses, we calculated our risk estimates with a method that combines the matched and the unmatched analyses. This analysis took into account the presence of 2152 patients in both the matched and the unmatched analysis (see appendix). When analyzing the risk in men and women separately it was not possible to perform a matched analysis with the partner controls, as control individuals were nearly always of the opposite sex to the cases. Therefore, risk estimates were calculated with an unmatched analysis with all patients and the

random control subjects. Statistical significance was considered for $P<0.05$. SAS 9.1 (SAS institute Inc, Cary, NC, USA) was used for all statistical analyses.

RESULTS

In the current analysis 3834 patients with a first venous thrombosis and 4683 control subjects were included. Mean age of 3834 patients was 48.3 (5^{th}-95^{th} percentiles, 25.9-67.5) and of 4683 control subjects 46.9 (5^{th}-95^{th} percentiles, 25.1-66.3) years. Fifty two percent (n=2008) of patients and 53% (n=2498) of control subjects were women. In the patient group 58% (n=2212) was diagnosed with deep venous thrombosis of the leg, 29% (n=1113) with a pulmonary embolism and 13% (n=509) with the combination of these diagnoses. In Table I relative risks of venous thrombosis with increasing body mass index are presented. The table presents the combined odds ratios for both control groups; the effects when each control group was used separately did not differ substantially (overweight, partner controls OR 1.45, 95% CI 1.26-1.67; overweight RDD controls OR 1.84, 95% CI 1.64-2.06; obesity partner controls OR 1.84, 95% CI 1.51-2.23; obesity RDD controls OR 2.88, 95% CI 2.47-3.37). Among patients 42% was overweight and 21% obese, which was 37% (overweight) and 13% (obese) among controls (Table I).

Overweight resulted in a 1.7-fold increased risk (OR_{adj} 1.70, 95% CI 1.55-1.87) and obesity in a 2.4-fold increased risk of venous thrombosis (OR_{adj} 2.44, 95% CI 2.15-2.78) compared to the reference category with a BMI below 25 kg/m^2 (Table I). Combining the overweight and obese categories, the odds ratio was 1.88 (95% CI 1.72-2.06).

In Figure 1 a more detailed relationship between body mass index and the risk of venous thrombosis is shown. Individuals with a body mass index between 22.5 and 25.0 kg/m^2 formed the reference category. In general the relation between BMI and thrombotic risk formed a J-shaped curve. In persons with the highest BMI (≥35 kg/m^2) the risk of venous thrombosis was 2.6 fold increased (OR_{adj} 2.62, 95% CI 2.06-3.33) compared to the reference group. With BMI as a continuous variable in the

Table I. Relative risk of venous thrombosis by categories of body mass index

BMI (kg/m^2)	Patients N=3834	Partners N=2152	RDD N=2531	OR*	95% CI
All VT					
<25	1393	948	1409	1	
≥25&<30	1629	880	848	1.70	1.55-1.87
≥30	812	324	274	2.44	2.15-2.78

VT, venous thrombosis; RDD, random digit dialing control subjects; OR, odds ratio; CI, confidence interval
*Combined OR, adjusted for age and sex

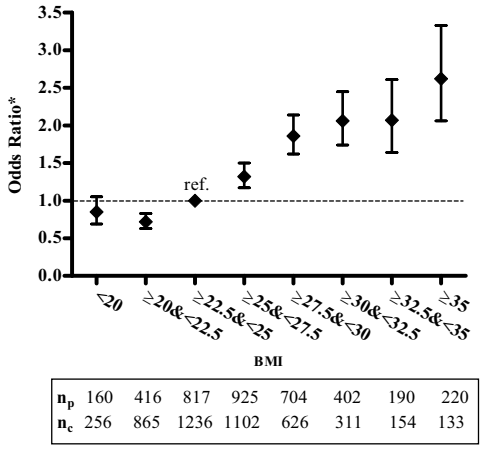

Figure 1. Relative risk of venous thrombosis by categories of body mass index (BMI) (kg/m^2).
I, 95% confidence interval; n_p, number of patients; n_c, number of control subjects; ref., reference category.
*Adjusted for age and sex

Table II. Relative risk of venous thrombosis by categories of body mass index in different subgroups

BMI (kg/m^2)	Patients	Control subjects	OR*	95% CI
DVT				
<25	772	2357	1	
≥25&<30	949	1728	1.83	1.63-2.06
≥30	491	598	2.80	2.41-3.26
PE				
<25	463	2357	1	
≥25&<30	458	1728	1.51	1.31-1.75
≥30	192	598	1.89	1.55-2.31
DVT+PE				
<25	158	2357	1	
≥25&<30	222	1728	2.05	1.64-2.57
≥30	129	598	3.77	2.89-4.93
Idiopathic VT				
<25	344	2357	1	
≥25&<30	549	1728	1.84	1.55-2.17
≥30	221	598	2.58	2.07-3.23
All VT_{women}†				
<25	823	867	1	
25-30	683	370	1.93	1.64-2.26
≥30	502	156	3.36	2.74-4.12
All VT_{men}†				
<25	569	542	1	
≥25&<30	944	478	1.72	1.46-2.03
≥30	310	118	2.32	1.82-2.97

DVT, deep venous thrombosis; PE, pulmonary embolism; OR, odds ratio; CI, confidence interval
*combined for both control groups and adjusted for age and sex; †three patients were not included in these analyses because two were transsexuals and one had Klinefelter syndrome, these analyses were performed with the random control subjects only.

logistic model a 1.1-fold increased risk (10% increase) per 1 kg/m^2 was observed (OR_{adj} 1.13, 95% CI 1.11-1.16).

Odds ratios were slightly higher for deep venous thrombosis than for pulmonary embolism and in women than in men (Table II). The odds ratio of idiopathic venous thrombosis with increasing BMI was approximately the same as the overall risk (Table II).

Table III shows the relative risk of venous thrombosis by categories of body weight (kg) and body height (m). As was to be expected, adjusted for body height, body weight again was associated with thrombotic risk, which was also evident without adjustment for body height, but less clearly. A 2.9-fold increased risk was found for body weights equal to or above 110 kg (OR_{adj} 2.93, 95% CI 2.28-3.77) relative to those between 70 to 79 kg. Body weights between 50 and 70 kg were associated with the lowest risk of venous thrombosis. Body weight was also assessed as a risk factor in men and women separately, with similar results (data not shown). Only individuals with a body height above 1.80 m had a slightly increased risk of venous thrombosis compared to those between 1.70 to 1.74 m. Short persons (<1.70 m) had a low risk of venous thrombosis. When analyzing men and women separately, the risk only appeared to be decreased for short men ($OR_{adj,\ \leq 1.79\ m}$ 0.77, 95% CI 0.64-0.94) and increased for very tall men ($OR_{adj,\ \geq 1.90\ m}$ 1.32, 95% CI 1.02-1.70) compared to men with a body height between 1.80 and 1.84 m (data not shown).

Table III. Relative risk of venous thrombosis by categories of body weight and body height

Body weight (kg)	Patients	Control subjects	OR*	95% CI
<50	27	38	0.68	0.40-1.16
50-59	206	396	0.60	0.49-0.73
60-69	595	1076	0.69	0.60-0.78
70-79	871	1209	1	
80-89	932	1038	1.43	1.26-1.62
90-99	676	586	1.88	1.63-2.17
100-109	308	212	2.45	2.01-2.99
≥110	219	128	2.93	2.28-3.77
Body height (m)				
<1.60	182	247	0.69	0.56-0.86
1.60-1.64	377	531	0.73	0.61-0.86
1.65-1.69	649	857	0.83	0.72-0.95
1.70-1.74	749	878	1	
1.75-1.79	662	809	1.01	0.87-1.16
1.80-1.84	571	671	1.14	0.98-1.33
1.85-1.89	373	438	1.17	0.98-1.41
≥1.90	271	252	1.56	1.27-1.92

OR, odds ratio; CI, confidence interval

*adjusted for age, sex and body height in body weight analyses, adjusted for age and sex in body height analyses

Joint effect of obesity with other risk factors for venous thrombosis

The combined effect of oral contraceptive use and obesity was examined in women aged 18 to 39 years (Table IV). Among women who did not use oral contraceptives the risk increased 2.5-fold for overweight women and 3.0-fold for obese women compared to normal weight women not using oral contraceptives. Relative to non-users of normal BMI, oral contraceptive users who were overweight had an 11.6-fold increased risk and those who were obese a 23.8-fold increased risk.

Among non-carriers of factor V Leiden, obesity led to a 2.5-fold increased risk (normal BMI as reference). The joint effect of factor V Leiden and obesity resulted in a 7.9-fold increased risk of venous thrombosis (Table V). For obese participants

Table IV. Combined effect of body mass index and oral contraceptive (OC) use on the risk of venous thrombosis in women aged 18 to 39

BMI (kg/m^2)	OC use	Patients	Control subjects	OR*	95% CI
<25	no	51	167	1	
≥25&<30	no	27	34	2.52	1.38-4.57
≥30	no	28	30	3.04	1.66-5.57
<25	yes	260	233	4.15	2.85-6.03
≥25&<30	yes	178	55	11.63	7.46-18.14
≥30	yes	132	19	23.78	13.35-42.34

OR, odds ratio; CI, confidence interval *analyses are performed with all patients and the random control subjects and adjusted for age

Table V. Combined effect of body mass index, the factor V Leiden (FVL) and the prothrombin (FII) 20210A mutation on the risk of venous thrombosis

BMI (kg/m^2)	FVL	Patients	Control subjects	OR*	95% CI
<25	no	1077	1631	1	
≥25&<30	no	1289	1244	1.72	1.54-1.93
≥30	no	643	423	2.48	2.13-2.88
<25	yes	217	69	4.18	3.12-5.61
≥25&<30	yes	250	58	5.77	4.20-7.93
≥30	yes	124	18	7.86	4.70-13.15
	FII 20210A	Patients	Control subjects	OR*	95% CI
<25	no	1225	1803	1	
≥25&<30	no	1455	1351	1.72	1.54-1.91
≥30	no	735	477	2.45	2.12-2.82
<25	yes	70	18	4.39	2.56-7.51
≥25&<30	yes	84	20	4.51	2.64-7.72
≥30	yes	32	4	6.58	2.31-18.69

OR, odds ratio; CI, confidence interval
*Adjusted for age and sex.
Note: The inclusion of matched case control pairs in the analyses was dependent on the category (BMI, FVL; BMI, FII 20210A) of both partners

with the prothrombin 20210A mutation the risk of venous thrombosis increased 6.6-fold (normal BMI, non-carriers as reference).

DISCUSSION

In this large population-based case-control study both overweight and obesity were associated with a two- to three-fold increased risk of venous thrombosis. Since the prevalence of obesity is increasing, this has a major impact (http://www.ic.nhs.uk/webfiles/publications/opan06/OPAN%20bulletin%20finalv2.pdf,http://www.cdc.gov/nchs/products/pubs/pubd/hestats/overweight/overwght_adult_03.htm). In this study 50% of the control subjects, who represent the general population, were overweight or obese. This suggests that almost one-third of all events of thrombosis are preventable by weight loss (population attributable risk=28%), assuming that weight loss reduces venous thrombotic risk (Ditschuneit et al, 1995; Hankey et al, 1997; Kopp et al, 2003). Prevalences of overweight and obesity reported from the UK and the USA of 60-65 percent lead to even higher preventable fractions (http://www.ic.nhs.uk/webfiles/publications/opan06/OPAN%20bulletin%20finalv2.pdf,http://www.cdc.gov/nchs/products/pubs/pubd/hestats/overweight/overwght_adult_03.htm).

We also evaluated body weight and height as separate risk factors for venous thrombosis. Body weight was positively associated with thrombotic risk in both men and women. For body height no substantial increased risks were found in women, but short men appeared to have a low risk and tall men a high risk of venous thrombosis. Particularly this latter is remarkable, since body height is not associated with the relative amount of fat, as body weight and BMI both are. The effect of obesity was more pronounced in women than in men, with high relative risks for overweight and obese women who used oral contraceptives. The joint effect of obesity with the factor V Leiden mutation or the prothrombin mutation appeared both slightly higher than the sum of the separate effects.

The association between BMI and venous thrombosis is likely to be causal because it is consistent over studies, shows a dose-response relation and is biologically plausible. Our results are consistent with previous studies demonstrating an increased risk of venous thrombosis with increasing body mass index. The Nurses Health Study found a three-fold increased risk of pulmonary embolism in women with obesity (Goldhaber et al, 1997). Another prospective follow-up study reported a hazard ratio of 2.3 for venous thrombosis among persons with a body mass index (BMI) above 30 kg/m^2 compared to persons with a BMI below 25 kg/m^2 (Tsai et al, 2002). Other studies also showed an elevated risk of venous thrombosis among

overweight persons (Abdollahi et al, 2003; Oren et al, 2006; Samama, 2000; Stein et al, 2005; Vaya et al, 2002; White et al, 2000). The magnitudes of the relative risks are largely similar. To our knowledge the only case-control study that did not found an increased risk of venous thromboses with BMI was a study with a very small sample size (n=90) performed in pregnant women and women during post partum (Danilenko-Dixon et al, 2001). It is not unlikely that BMI in these women is a poor marker for the relative amount of body fat.

There are several ideas about the mechanism behind the association between overweight and the risk of venous thrombosis. An increase in prothrombotic factors in obese persons may play a role (Bowles et al, 2003; Rosito et al, 2004; Chan et al, 1995; De Pergola et al, 1997), while obesity may also be associated with lack of exercise and venous stasis (Tsai et al, 2002). A high body mass index can be the result of excess body fat or abundant muscle development. 'The study of men born in 1913' evaluated waist circumference as a measure for abdominal obesity instead of BMI (Hansson et al, 1999). In this study, men in the highest decile of waist circumference (≥100 cm) had a relative risk for DVT of 3.9 compared to men with a waist circumference less than 100 cm. This result suggests that obesity caused by excess body fat is likely to be a risk factor for venous thrombosis.

We found a more pronounced excess risk for deep vein thrombosis than for pulmonary embolism. This is in accordance with results from the National Hospital Discharge Survey (Stein et al, 2005). An explanation may be the complexities of the diagnosis of pulmonary embolism, which may have led to misclassification, i.e. inclusion of some patients without a true pulmonary embolism (PIOPED, 1990). Alternatively, clots in obese individuals may be different from those in non-obese people and have less tendency to embolize, as has also been suggested as an explanation for the low risk of pulmonary embolism in individuals with factor V Leiden. Obesity and factor V Leiden both lead to APC resistance (Lowe et al, 1999), which lends further plausibility to a differential effect of deep venous thrombosis and pulmonary embolism. Oral contraceptive use also leads to APC-resistance, which helps to understand the syntergistic effect of obesity and factor V Leiden and obesity and oral contraceptive use. This is in line with the synergy between factor V Leiden and oral contraceptive use (Vandenbroucke et al, 1994) and a previous report on obesity and the factor V Leiden mutation (Juul et al, 2004).

A possible limitation of our study is that height and weight were self-reported. If there would be a difference between patients and control subjects in over- or underreporting body weight or height an incorrect estimate of risk would be the result. There is no reason to expect such a difference in reporting behaviour between the two groups. The number of individuals who failed to report their body weight

was similar in patients (2.2%) and control subjects (2.6%). In general, overweight individuals tend to underreport and underweight individuals tend to overreport their body weight (Gunnell et al, 2000). If this phenomenon occurred the actual relative risks would even be higher.

Control subjects were drawn from two different sources. Because partners have similar lifestyles that may result in similar body mass indices, we performed a matched analysis that takes these associations into account. The matched analysis adjusted for all similar lifestyle factors between partners, which may include some unknown, unmeasured confounders resulting in lower risk estimates for the matched analysis compared to the unmatched analysis using the random digit dialing controls. Both analyses show consistent results in terms of clearly increased risks.

In conclusion, overweight and obesity are risk factors for venous thrombosis in this large population-based case-control study. Especially obesity in women using oral contraceptives is associated with a very high risk. The 24-fold increased risk should be considered when prescribing oral contraceptives for obese women.

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APPENDIX: COMBINING THE ESTIMATES OF THE CONDITIONAL AND UNCONDITIONAL LOGISTIC REGRESSION

Combining two estimates of the odds ratio

In our approach the two estimates of the log-odds ratio are combined into one overall log-odds ratio. Since both estimates use the same subset of cases, the estimates are correlated. The correlation between the two estimates is estimated using a sandwich estimator which is the commonly used estimator in statistics (Kauermann & Carroll, 2001). Details about this calculation are given later on in this appendix. The correlation is used to combine the two estimates in the most efficient way and to calculate the correct standard errors.

We consider first the case when there is only one parameter to combine. Let $\hat{\beta}_1$ and $\hat{\beta}_2$ be the estimated log odds ratios in the two different analyses with respective standard errors s_1 and s_2 and let $\hat{\rho}$ be the estimated correlation coefficient between the two estimates. In this case the combined estimate is a weighted mean of $\hat{\beta}_1$ and $\hat{\beta}_2$: $\hat{\beta}_{com} = w\hat{\beta}_1 + (1-w)\hat{\beta}_2$ with standard error

$$s_{com} = se(\hat{\beta}_{com}) = \sqrt{w^2 s_1^2 + (1-w)^2 s_2^2 + 2w(1-w)\rho\, s_1 s_2}.$$

It is straightforward to show that the optimal weight is given by $w = (s_2^2 - \hat{\rho} s_1 s_2)/(s_1^2 + s_2^2 - 2\hat{\rho} s_1 s_2)$.

In general, there are two multidimensional parameters $\theta_1 = (\alpha_1, \beta)$ and $\theta_2 = (\alpha_2, \beta)$, respectively. The k-dimensional β-parameter is the shared part. The parameters α_1 and α_2 of dimension k_1 and k_2, respectively, are not shared, for example because of different confounding variables in the two analyses, or because the effect of a confounder is expected to act differently in the two models.

Suppose that $\hat{\beta}_1$ and $\hat{\beta}_1$ are the two correlated estimates of the shared part β with covariance matrices $\text{cov}(\hat{\beta}_1) = C_1$, $\text{cov}(\hat{\beta}_2) = C_2$ and $\text{cov}(\hat{\beta}_1, \hat{\beta}_2) = C_{12}$.

Then the most efficient estimate of β (the weighted least square estimate) is given by $\hat{\beta}_{com} = \left(\begin{pmatrix} I_k \\ I_k \end{pmatrix}^T \begin{pmatrix} C_1 & C_{12} \\ C_{21} & C_2 \end{pmatrix}^{-1} \begin{pmatrix} I_k \\ I_k \end{pmatrix} \right)^{-1} \begin{pmatrix} I_k \\ I_k \end{pmatrix}^T \begin{pmatrix} C_1 & C_{12} \\ C_{21} & C_2 \end{pmatrix}^{-1} \begin{pmatrix} \hat{\beta}_1 \\ \hat{\beta}_1 \end{pmatrix}$ with covariance matrix

$\text{cov}(\hat{\beta}_{com}) = \left(\begin{pmatrix} I_k \\ I_k \end{pmatrix}^T \begin{pmatrix} C_1 & C_{12} \\ C_{21} & C_2 \end{pmatrix}^{-1} \begin{pmatrix} I_k \\ I_k \end{pmatrix} \right)^{-1}$. Here I_k is the k-dimensional identity matrix.

Estimation of the correlation between the two estimated odds ratios

In the general situation, there are two multidimensional parameters $\theta_1 = (\alpha_1, \beta_1)$ and $\theta_2 = (\alpha_2, \beta_2)$, respectively. Assume that both parameters are estimated by multiple regression models (in our situation θ_1 is estimated by conditional logistic regression and θ_2 by unconditional logistic regression.) When fitting this models by maximum likelihood we obtain the estimated parameters $\hat{\theta}_1 = (\hat{\alpha}_1, \hat{\beta}_1)$ and $\hat{\theta}_2 = (\hat{\alpha}_2, \hat{\beta}_2)$, the Fisher-information matrices $\mathbf{I}_1$ and $\mathbf{I}_2$ and the score matrices $\mathbf{U}_1$ and $\mathbf{U}_2$, where, generally $\mathbf{I} = \frac{\partial^2 l}{\partial \theta^2}$ and $U_{ij} = \frac{\partial l_i(\hat{\theta})}{\partial \theta_j}$ is the derivative of the log-likelihood contribution of individual i with respect to parameter θ_j.

Due to the overlap the estimated parameters $\hat{\theta}_1 = (\hat{\alpha}_1, \hat{\beta}_1)$ and $\hat{\theta}_2 = (\hat{\alpha}_2, \hat{\beta}_2)$ are dependent. Their covariance matrix can be estimated by a sandwich estimator: $\text{cov}(\hat{\theta}_1, \hat{\theta}_2) = \mathbf{I}_1^{-1} \mathbf{U}_{1,overlap}{}^T \mathbf{U}_{2,overlap} \mathbf{I}_2^{-1}$ using only the rows of $\mathbf{U}_1$ and $\mathbf{U}_2$ that correspond to the overlapping observations. From the estimated covariance matrix $\text{cov}(\hat{\theta}_1, \hat{\theta}_2)$ we can obtain the covariance matrix of the common part $\text{cov}(\hat{\beta}_1, \hat{\beta}_2)$.