Body Mass Index, Surgery, and Risk of Venous Thromboembolism in Middle-Aged Women

A Cohort Study

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Background—Obesity and surgery are known risk factors for venous thromboembolism (VTE), but there is limited information about the independent effects of obesity on the incidence of postoperative VTE. We linked questionnaire data from the Million Women Study with hospital admission and death records to examine the risk of VTE in relation to body mass index (BMI) both in the absence of surgery and in the first 12 weeks following an operation.

Methods and Results—Overall, 1,170,495 women (mean age, 56.1 years) recruited in 1996 to 2001 through the National Health Service Breast Screening Programme in England and Scotland were followed for an average of 6 years, during which time 6,438 were admitted to hospital or died of VTE. The adjusted relative risks of VTE increased progressively with increasing BMI and women with a BMI $\geq$ 35 kg/m$^2$ were 3–4 times as likely to develop VTE as those with a BMI 22.5 to 24.9 (relative risk 3.45 [95% CI 3.09–3.86]). Overweight and obese women were more likely than lean women to be admitted for surgery and also to develop postoperative VTE. During a 12-week period without surgery, the incidence rates of VTE per 1000 women with a BMI $<25$ and $\geq 25$ were 0.10 (0.09–0.10) and 0.19 (0.18–0.20); the corresponding rates in the 12 weeks following day and inpatient surgery were, respectively, about 4 and 40 times higher.

Conclusions—VTE risk increases with increasing BMI and the associated excess risk is much greater after surgery than without surgery. (Circulation. 2012;125:1897-1904.)

Key Words: obesity ■ surgery ■ deep vein thrombosis ■ pulmonary embolism ■ cohort study

Venous thromboembolism (deep vein thrombosis and/or pulmonary embolism) accounts for a large burden of potentially preventable morbidity and death in the United Kingdom and elsewhere. Surgery is a strong risk factor for venous thromboembolism, with substantially elevated incidence rates persisting for up to 12 weeks following both inpatient and day surgery. Excess body weight, which is becoming increasingly common in many populations, is another important risk factor for venous thromboembolism. Although clinical guidelines usually state that obesity increases the risk of postoperative venous thromboembolism, the few studies that have explored the independent effects of excess body weight on venous thromboembolism risk in the postoperative period have focused on specific types of surgery, most commonly of the lower limb. Similarly, although obesity is an established risk factor for many conditions that often require surgery (such as gall bladder disease, osteoarthritis, coronary heart disease, and cancer), the overall relationship between excess body weight and the risk of being admitted to hospital for surgery has not been directly examined.

Clinical Perspective on p 1904

We linked questionnaire data from a large prospective study, the Million Women Study, with hospital admission and death records to examine whether women who were overweight or obese were more likely to undergo surgery than women who were a healthy weight, and also to describe the relation of body mass index to the incidence of venous thromboembolism in the absence of surgery and in the first 12 weeks following an operation.

Methods

Study Population

The Million Women Study has been described in detail elsewhere. In brief, it is a prospective cohort study that recruited 1.3 million women (mean age, 56.1 years) between 1996 and 2001, through the National Health Service (NHS) Breast Screening Pro-
gramme in England and Scotland. At recruitment, women completed a questionnaire that enquired about current weight and height, use of hormone replacement therapy, smoking status, physical activity, alcohol consumption, medical and reproductive history, history of oral contraceptive use, and educational attainment (questionnaire available from www.millionwomenstudy.org).

All study participants were flagged on the NHS Central Registers in England and Scotland, permitting the ongoing identification of women who had new cancer registrations and those who emigrated or died. Admissions (as day or inpatients) to NHS hospitals during follow-up were identified by linkage to the English Hospital Episode Statistics and the Scottish Morbidity Records. For each admission, information was obtained about the main and secondary diagnoses (coded to the International Classifications of Diseases) and any surgical procedures or interventions that were undertaken (coded to the Tabular List of the Classification of Surgical Operations and Procedures of the Office of Population Censuses and Surveys, fourth revision, codes (other than those related to the diagnoses and treatment of venous thromboembolism admission or death (as an inpatient or in the community)), had surgery in the previous 12 weeks, or had a diagnosis of venous thromboembolism (see online-only Data Supplement Appendix). A sample of the study participants (~5%) were recruited in England in the year before the Hospital Episode Statistics database was complete (April 1997). For these women, the date of entry into the study (start of follow-up) was set at April 1, 1997. For all other women, follow-up began on the date the recruitment questionnaire was completed.

Body mass index was calculated from weight and height (as kg/m²) reported at recruitment. For a randomly selected subset of cohort members (n = 3591), weight and height were measured by their general practitioners 8 years after recruitment. These measured data were used to calculate a mean value for each category of body mass index, because this approach allows for calibration of the estimates against changes in body mass index over the follow-up period and takes into account measurement error associated with the self-reported data. Incidence rates for the complete cohort were subsequently reported with the mean measured values for each body mass index category by use of methods described previously.

Million Women Study participants were excluded from the present analysis if they reported a history of blood clots or treatment for clotting problems at recruitment; or if, before recruitment, they had a hospital admission for venous thromboembolism (see online-only Data Supplement Appendix). Women who had surgery in the previous 12 weeks, or had a previous cancer registration (excluding nonmelanoma skin cancer). Women were classified as having had surgery during follow-up if the hospital data included 1 or more Classification of Surgical Operations and Procedures of the Office of Population Censuses and Surveys, fourth revision, codes (other than those related to the diagnosis and treatment of venous thromboembolism and those identified as nonoperative procedures in NHS coding guidelines, as listed in the online-only Data Supplement Appendix).

Statistical Analysis
Relative risks of undergoing surgery during follow-up, and of a venous thromboembolism admission or death (as an inpatient or in the community), according to body mass index at recruitment were estimated from hazard ratios with use of Cox regression models; attained age was the underlying time variable. Age was measured in days and was incremented over time during follow-up so that age at each point in time, rather than age at recruitment, was taken into account in the analyses. The proportional hazards assumption was assessed by using tests based on Schoenfeld residuals; no evidence of a violation of the assumption was found for any of the analyses. Analyses were stratified by region of recruitment, and we adjusted for socioeconomic group (quintiles of Townsend deprivation index), frequency of strenuous exercise (rarely/never, ≤1 time a week, >1 time a week), use of hormone replacement therapy (never, past, current), smoking status (never; past; current <9, 10–19, ≥20 cigarettes per day), history of hypertension, and history of diabetes, as reported at recruitment. For each adjustment variable, an “unknown” category was created to deal with missing values (data missing for ≤5% women per covariate).

The association between body mass index and the risk of venous thromboembolism was explored separately in 2 circumstances: in the absence of surgery and postoperatively in the first 12 weeks after surgery. In analyses relating to the period without surgery, women were followed up from their entry date until the earliest of the following: any day or inpatient surgery; a registered diagnosis of cancer; emigration, death, or other loss to follow-up in the NHS Central Registers; or the end of hospital record follow-up (the latest date for which complete hospital discharge data were available, March 31, 2008 in England and December 31, 2008 in Scotland).

In analyses relating to the postoperative period, person-time at risk for women who had at least 1 operation during follow-up was accrued from the date of the first recorded surgery until the earliest of the following: emigration, death, or other loss to follow-up; the end of hospital record follow-up; or 12 weeks since surgery. The duration of hospital stay was used to classify operations as day surgery (women admitted and discharged on the same day) or inpatient surgery (at least 1 overnight stay). Women who had a diagnosis of venous thromboembolism and surgery on the same day were counted as a postoperative case only if the classification of Surgical Operations and Procedures of the Office of Population Censuses and Surveys, fourth revision, codes indicated that major surgery had been undertaken (because it was considered unlikely that such surgery would have been conducted immediately following the diagnosis of venous thromboembolism, and, therefore, the surgery was likely to have preceded the thrombotic event). The remaining women, in whom the temporal sequence was unclear, were included as cases in the absence of surgery analysis.

The incidence of hospital admission with, or death from, venous thromboembolism per 1000 women per 12-week period was estimated in relation to body mass index in the absence of surgery, and following day and inpatient surgery separately. Incidence rates in women undergoing surgery were calculated for the 12-week period immediately following an operation; in women not undergoing surgery, the incidence rates were calculated for 12-week periods over the entire follow-up period until a woman had surgery or exited from follow-up for other reasons.

All analyses were undertaken using STATA version 11.1.

Ethical Approval
The Million Women Study has been approved by the Cambridge South Research Ethics Committee (formerly Oxford and Anglia Multi-Centre Research Ethics Committee) and is sponsored by the University of Oxford. Access and linkage to hospital records was approved by the Information Centre for Health and Social Care in England and the Information and Statistics Division in Scotland. Participants gave written consent for inclusion and follow-up.

Results
Overall, 1 170 495 women were included in the study after the exclusion of women with previous venous thromboembolism, clotting disorders, cancer, or surgery in the 12 weeks before recruitment (n = 129 178) and 5% (n = 64 591) of eligible women who did not report weight and/or height at recruitment. Table 1 shows the characteristics of the population included in these analyses in relation to body mass index category at recruitment. According to World Health Organization criteria, 46.8% of participants were a normal weight or less (body mass index <25 kg/m²), 35.7% were overweight (body mass index 25–29.9 kg/m²), and 17.5% were obese (body mass index ≥30 kg/m²). The mean body mass index was 26.2 kg/m² (standard deviation, 4.6). There was an excellent correlation between measured body mass index and that estimated from self-reported data (correlation coefficient = 0.9). Figure 1 shows body mass index assessed from self-reported data for the randomly selected sample of women, plotted against their measured body mass index about 8 years after recruitment. Although mean measured values 8 years later were slightly higher than those assessed at baseline, the ranking of individuals did not change substantially.
The mean age at recruitment was 56.1 years (standard deviation, 4.8) for all women combined (Table 1). All differences in baseline characteristics between the body mass index categories were statistically significant ($P<0.001$), and we draw attention to the differences that are clinically significant. The proportion of women in the lowest socioeconomic tertile increased with increasing body mass index, as did the proportions of women who reported a history of diabetes or hypertension at recruitment. Conversely, the proportions of women who reported they were current users of hormone replacement therapy, were current smokers, and undertook regular strenuous exercise decreased with increasing body mass index.

The 5% of eligible women who were excluded from the study because of unknown body mass index at baseline had some, but not all, characteristics similar to those of women with a body mass index $\geq 30$ kg/m$^2$, because they were of a similar age (mean $=56.1$ years) and a similar proportion came from the lowest socioeconomic tertile (42%). However, they were significantly ($P<0.05$) more likely to be current smokers (26%) and less likely to have a history of diabetes (4%) or hypertension (25%).

During 7.33 million person-years of follow-up in the absence of surgery (an average of 6 years of follow-up per woman), 4585 women had a hospital admission with, or died from, venous thromboembolism (Table 1). Overall, 641 056 women (55% of the study population) underwent 1 or more operations during the average 6 years of follow-up and 1853 of them were diagnosed with nonfatal or fatal venous thromboembolism during the first 12 postoperative weeks. The surgery was undertaken as a day case for 367 512 women, as an inpatient case for 272 776 women, and for a small number (768, none of whom had venous thromboembolism) it was not possible to determine whether they had day surgery or an inpatient operation. Hence, 640 288 women were included in the surgery analyses. The most common types of surgery (classified as described previously) were for gastrointestinal

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**Table 1. Baseline Characteristics and Follow-Up of Women Included in the Analyses, by Body Mass Index**

<table>
<thead>
<tr>
<th>Characteristics and Follow-Up</th>
<th>All Women (n=1 170 495)</th>
<th>$&lt;25$ (23.9)* (n=548 158)</th>
<th>$25–29.9$ (28.6)* (n=418 073)</th>
<th>$\geq 30$ (34.5)* (n=204 264)</th>
<th>$P$†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>56.1 (4.8)</td>
<td>55.9 (4.9)</td>
<td>56.3 (4.9)</td>
<td>56.1 (4.7)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Lowest socioeconomic tertile, %</td>
<td>32.5</td>
<td>28.8</td>
<td>33.2</td>
<td>41.1</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Current user of hormone replacement therapy, %</td>
<td>34.0</td>
<td>36.7</td>
<td>33.2</td>
<td>28.5</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Strenuous physical activity &gt;1 time a week, %</td>
<td>21.3</td>
<td>25.3</td>
<td>19.5</td>
<td>14.2</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>20.2</td>
<td>22.4</td>
<td>19.1</td>
<td>16.4</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>History of diabetes, %</td>
<td>2.5</td>
<td>1.2</td>
<td>2.4</td>
<td>6.5</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>History of hypertension, %</td>
<td>23.9</td>
<td>16.5</td>
<td>25.8</td>
<td>40.0</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Follow-up: without surgery‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of women</td>
<td>1 170 495</td>
<td>548 158</td>
<td>418 073</td>
<td>204 264</td>
<td></td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>7 330 843</td>
<td>3 561 282</td>
<td>2 585 024</td>
<td>1 184 537</td>
<td></td>
</tr>
<tr>
<td>No. of venous thromboembolism cases</td>
<td>4585</td>
<td>1485</td>
<td>1687</td>
<td>1413</td>
<td></td>
</tr>
<tr>
<td>Follow-up: after surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of women with $\geq 1$ hospital admissions for surgery during follow-up</td>
<td>640 288</td>
<td>282 405</td>
<td>233 784</td>
<td>124 099</td>
<td></td>
</tr>
<tr>
<td>Person-years of follow-up during 12 wk after first operation</td>
<td>145 297</td>
<td>64 085</td>
<td>53 057</td>
<td>28 155</td>
<td></td>
</tr>
<tr>
<td>No. of venous thromboembolism cases during 12 wk after first operation</td>
<td>1853</td>
<td>615</td>
<td>755</td>
<td>483</td>
<td></td>
</tr>
</tbody>
</table>

Values are percentages of women with reported characteristics unless stated otherwise.

*Mean measured body mass index 8 y after recruitment.
†$P$ values for comparisons of baseline characteristics according to body mass index category.
‡Includes the incident cases and person-years of follow-up for women who did not have surgery during the entire follow-up period (n=530 207), and the incident cases and person-years of follow-up in the period before the first operation for women who had surgery, as well (n=640 288).

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![Figure 1. Body mass index calculated from self-reported data at baseline plotted against body mass index 8 years after recruitment based on measured weight and height. BMI indicates body mass index.](https://example.com/image1.png)
(23%), orthopaedic (13%), gynecological (9%), cancer (8%), and vascular disease (7%), and each of these were associated with an increased risk of venous thromboembolism in the first 12 postoperative weeks.

We first investigated the relative risks, by body mass index category, for a first hospital admission with, or death from, venous thromboembolism in the absence of surgery (Table 2). There is a clear trend of increasing risk of venous thromboembolism with increasing body mass index \((P<0.0001)\); for example, women with a body mass index of \(\geq 35\) kg/m\(^2\) were 3–4 times as likely as women with a body mass index of 22.5 to 24.9 kg/m\(^2\) to develop venous thromboembolism (relative risk 3.45 [95% CI 3.09–3.86]). Of the 4585 women with venous thromboembolism, 2047 had a recorded diagnosis of pulmonary embolism, and similar patterns of increasing risk were seen both for day and inpatient surgery, and for women with and without a diagnosis of pulmonary embolism (Table 2).

We also looked at the risk of being admitted to hospital for surgery in relation to body mass index, and then looked at the effect of body mass index on the incidence of venous thromboembolism during the first 12 weeks postoperatively (Table 3). Women who were overweight (body mass index 25–29.9 kg/m\(^2\)) and obese (body mass index \(\geq 30\) kg/m\(^2\)) were more likely to be admitted to hospital for day or inpatient surgery than women with a body mass index \(<25\) kg/m\(^2\) \((P<0.0001)\); the relative risks were 1.10 (95% CI 1.09–1.11) and 1.22 (95% CI 1.22–1.23), respectively. Among those who underwent surgery, overweight and obese women also had higher risks of postoperative venous thromboembolism than women of a healthy weight; the relative risks were 1.46 (95% CI 1.31–1.63) and 1.78 (95% CI 1.57–2.01), respectively. This increased risk of postoperative venous thromboembolism was seen for both day and inpatient surgery; the relative risks for overweight and obese women following day surgery were 1.32 (95% CI 0.98–1.78) and 1.72 (95% CI 1.21–2.45), respectively. The corresponding relative risks following inpatient surgery were 1.43 (95% CI 1.27–1.61) and 1.58 (95% CI 1.38–1.81).

Incidence rates of venous thromboembolism per 1000 women during a 12-week period with no surgery, and following day and inpatient surgery are shown, by body mass index, in Table 4. In all 3 circumstances, the incidence of venous thromboembolism was significantly higher among

### Table 2. In the Absence of Surgery, Adjusted Relative Risks by Body Mass Index Of Hospital Admission With, or Death From, Venous Thromboembolism (and Separately for Pulmonary Embolism and for Venous Thrombosis Without Pulmonary Embolism)

<table>
<thead>
<tr>
<th>Body Mass Index Category (Mean Measured Body Mass Index)*</th>
<th>No. of Cases</th>
<th>Adjusted Relative Risks (95% CI)</th>
<th>No. of Cases</th>
<th>Adjusted Relative Risks (95% CI)</th>
<th>No. of Cases</th>
<th>Adjusted Relative Risks (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;22.5 (22.2)</td>
<td>565</td>
<td>0.84 (0.76–0.93)</td>
<td>251</td>
<td>0.81 (0.69–0.94)</td>
<td>314</td>
<td>0.87 (0.75–1.00)</td>
</tr>
<tr>
<td>22.5–24.9 (25.1)</td>
<td>920</td>
<td>1.0</td>
<td>427</td>
<td>1.0</td>
<td>493</td>
<td>1.0</td>
</tr>
<tr>
<td>25–27.4 (27.6)</td>
<td>963</td>
<td>1.32 (1.20–1.44)</td>
<td>405</td>
<td>1.19 (1.03–1.36)</td>
<td>558</td>
<td>1.43 (1.26–1.61)</td>
</tr>
<tr>
<td>27.5–29.9 (30.2)</td>
<td>724</td>
<td>1.57 (1.42–1.73)</td>
<td>316</td>
<td>1.47 (1.27–1.70)</td>
<td>408</td>
<td>1.66 (1.45–1.89)</td>
</tr>
<tr>
<td>30–32.4 (32.5)</td>
<td>555</td>
<td>2.18 (1.96–2.43)</td>
<td>230</td>
<td>1.94 (1.65–2.28)</td>
<td>325</td>
<td>2.40 (2.08–2.76)</td>
</tr>
<tr>
<td>32.5–34.9 (34.7)</td>
<td>332</td>
<td>2.28 (2.00–2.58)</td>
<td>174</td>
<td>2.56 (2.14–3.07)</td>
<td>158</td>
<td>2.02 (1.69–2.43)</td>
</tr>
<tr>
<td>(\geq 35) (38.9)</td>
<td>526</td>
<td>3.45 (3.09–3.86)</td>
<td>244</td>
<td>3.47 (2.95–4.09)</td>
<td>282</td>
<td>3.44 (2.95–4.00)</td>
</tr>
</tbody>
</table>

Population at risk = 1 170 495 women. Relative risks are adjusted for age, use of hormone replacement therapy, frequency of strenuous exercise, smoking, socioeconomic group, history of hypertension, history of diabetes, and stratified by region.

*Body mass index (kg/m\(^2\)) category derived from self-reported weight and height at recruitment (mean measured body mass index 8 years later in a random sample [see Methods]).

†Diagnosis of deep vein thrombosis and/or pulmonary embolism.

‡Pulmonary embolism with or without a recorded diagnosis of concurrent deep vein thrombosis.

### Table 3. Relative Risks of Hospital Admission for Surgery During Follow-Up, by Body Mass Index; and, Among Women Admitted to Hospital, Relative Risks of Subsequent Hospital Admission With, or Death From, Venous Thromboembolism in 12 wk Following Surgery, by Body Mass Index

<table>
<thead>
<tr>
<th>Body Mass Index Category (Mean Measured Body Mass Index)*</th>
<th>Relative Risk of Hospital Admission for Surgery During Follow-Up</th>
<th>Relative Risk of Venous Thromboembolism in 12 wk Period Following Surgery†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Population at Risk</td>
<td>Adjusted Relative Risks (95% CI)</td>
</tr>
<tr>
<td>(&lt;25) (23.9)</td>
<td>548 158</td>
<td>282 405 1.0</td>
</tr>
<tr>
<td>25–29.9 (28.6)</td>
<td>418 073</td>
<td>233 784 1.10 (1.09–1.11)</td>
</tr>
<tr>
<td>(\geq 30) (34.5)</td>
<td>204 264</td>
<td>124 099 1.22 (1.22–1.23)</td>
</tr>
</tbody>
</table>

Relative risks are adjusted for age, use of hormone replacement therapy, frequency of strenuous exercise, smoking, socioeconomic group, history of hypertension, history of diabetes, and stratified by region.

*Body mass index (kg/m\(^2\)) category derived from self-reported weight and height at recruitment (mean measured body mass index 8 years later in a random sample [see Methods]).

†Diagnosis of deep vein thrombosis and/or pulmonary embolism.
women who were overweight or obese than among those with a lower body mass index. In the absence of surgery, the incidence rates for women with a body mass index <25 kg/m² and ≥25 kg/m² were, respectively, 0.10 (95% CI 0.09–0.10) and 0.19 (95% CI 0.18–0.20) per 1000 women per 12 weeks; the corresponding rates were about 4 times higher following day surgery (0.51 [95% CI 0.41–0.63] and 0.75 [95% CI 0.64–0.88]), and about 40 times higher following inpatient surgery (4.77 [95% CI 4.38–5.19] and 7.00 [95% CI 6.60–7.43]). In Figure 2, the incidence rates for a hospital admission with, or death from, venous thromboembolism in the absence of surgery, and following day and inpatient surgery, are shown by body mass index category.

Discussion

In this large prospective study of middle-aged women in the United Kingdom, we found that increasing body mass index was associated with an increasing risk of a hospital admission with, or death from, venous thromboembolism. We also found that the risk of being admitted to hospital for surgery increased with increasing body mass index. Incidence rates of venous thromboembolism were substantially increased in the 12 weeks after inpatient surgery, and the increase in disease incidence among overweight and obese women was greatest after inpatient surgery.

Findings in Relation to Previous Studies

Our findings of an increase in the relative risks of venous thromboembolism with increasing body mass index are consistent with the results of a 2008 meta-analysis and with subsequent reports from cohort studies. Overall, previous prospective studies have reported a 2- to 3-fold increased risk of venous thromboembolism associated with a body mass index ≥30 kg/m² in comparison with women who were not overweight or obese. These studies included far fewer participants and cases of venous thromboembolism than this study and consequently their power to undertake detailed explorations of risk was limited; the study with the largest number of cases, the Iowa Women’s Health Study, included only 463 events that did not occur after surgery, a recent cancer diagnosis, or another acute precipitating event (compared with >4000 events included here).

The few studies that have explored the independent effects of body mass index on venous thromboembolism following surgery have generally been restricted to risk following particular types of surgery. The largest study, which used data from the National Hospital Discharge Survey in the United States and was based on 25 127 cases of pulmonary embolism that developed in hospital following a primary or revised total hip or knee arthroplasty, found that obese patients were almost 3 times as likely to develop pulmonary embolism as the nonobese. Two smaller studies of elective hip replacement found relative risks of ∼2.0 in overweight and obese patients relative to those of a healthy weight, and a third study of hip and knee arthroplasty reported a relative risk of 1.5 for every 5 kg/m² increase in body mass index. Independent effects of excess body weight on postoperative venous thromboembolism risk have also been reported following colorectal, podiatric, and bariatric surgery.

Obesity is known to increase the risk of certain common conditions that often require surgical treatment, such as gall bladder disease, osteoarthritis, coronary heart disease, and cancer. Therefore, our finding that the risk of undergoing surgery increases with increasing body mass index is not entirely unexpected. However, to our knowledge, no other study has looked directly at this relationship. Nor have the absolute risks of venous thromboembolism by body mass index, been compared previously within the same study population, both in the absence of surgery and following day surgery and inpatient operations.

The biological mechanism by which obesity increases the risk of venous thromboembolism is not fully understood, but raised levels of fibrinogen and some clotting factors, low-grade systemic inflammation, and raised intra-abdominal pressure and reduced venous return from the lower limbs are thought to be involved.

Obesity is one of several acquired and inherited risk factors for venous thromboembolism and it is important for several reasons. First, it is a potentially avoidable and reversible condition that is steadily increasing in prevalence in many

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**Table 4. Incidence Rates of Venous Thromboembolism per 1000 Women per 12 wk Period, Without Surgery, After Day Surgery, and Inpatient Surgery, by Body Mass Index**

<table>
<thead>
<tr>
<th>Body Mass Index Category (Mean Measured Body Mass Index)*</th>
<th>No. of Cases (n=4585)</th>
<th>Incidence Rate (95% CI)</th>
<th>No. of Cases (n=232)</th>
<th>Incidence Rate (95% CI)</th>
<th>No. of Cases (n=1621)</th>
<th>Incidence Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25 (23.9)</td>
<td>1485</td>
<td>0.10 (0.09–0.10)</td>
<td>85</td>
<td>0.51 (0.41–0.63)</td>
<td>530</td>
<td>4.8 (4.4–5.2)</td>
</tr>
<tr>
<td>≥25 (30.1)</td>
<td>3100</td>
<td>0.19 (0.18–0.20)</td>
<td>147</td>
<td>0.75 (0.64–0.88)</td>
<td>1091</td>
<td>7.0 (6.6–7.4)</td>
</tr>
</tbody>
</table>

*Body mass index (kg/m²) category derived from self-reported weight and height at recruitment (mean measured body mass index 8 years later in a random sample [see Methods]).

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**Figure 2. Venous thromboembolism incidence per 1000 women per 12-week period with and without surgery, by body mass index.**
parts of the world. Second, in addition to independent effects on postoperative venous thromboembolism risk, it has been suggested that obesity interacts with other risk factors for venous thromboembolism, including inherited prothrombotic mutations and acquired risk factors such as pregnancy, oral contraceptive use, and hormone replacement therapy. Third, excess body weight has been reported to be associated with a higher risk of recurrent venous thromboembolism. Fourth, the risk of postthrombotic syndrome also appears to be higher in heavier patients. Finally, obesity presents particular challenges for prescribers, with some uncertainty about the appropriate anticoagulant doses to be used both for prophylaxis and for treatment of venous thromboembolism in overweight and obese patients.

### Strengths and Limitations

Strengths of this study include the large number of participants and the virtually complete follow-up for hospital admissions and deaths. This allowed a more detailed examination of the associated risks than was possible in previous prospective studies. It also permitted an exploration of the independent effects of body mass index on both the likelihood of undergoing surgery and the subsequent risk of a postoperative venous thromboembolic event. The linkage of questionnaire data with hospital admission, cancer registration, and death and emigration records enabled the exclusion of women with a history of venous thromboembolism or cancer before recruitment, provided information on a wide range of potential confounders, and ensured close to complete follow-up. Previous investigations have found a high degree of accuracy in the linkage between NHS data sets, and in the identification of Million Women Study participants within those data sets. In addition, high accuracy rates have been reported for the coding of diagnoses and operations in NHS hospital admission data. Furthermore, an underlying cause of death was recorded for 99.9% of cohort members who died during follow-up, and the number of women for whom there was no information about cause of death was extremely small (n = 35). Hence, it is exceedingly unlikely that our results were distorted by a failure to identify fatal cases of venous thromboembolism. Finally, measured weight and height were obtained for a random sample of participants and this enabled us to allow for misclassification of body mass index based on self-reported data and changes in body mass index over time, by presenting estimates of relative and absolute risks with the mean measured values for each body mass index category derived from self-reported data.

Several aspects of this study warrant further discussion. We estimated both the relative and absolute risks of a first hospital admission with, or death from, venous thromboembolism in relation to body mass index. It is probable that our reported absolute risks are underestimates of the true incidence of venous thromboembolism events in the study population, because uncomplicated deep vein thrombosis was increasingly diagnosed and treated in outpatient settings during the follow-up period and would not have been identified in hospital data. Conversely, the serious nature of pulmonary embolism means that virtually all cases are likely to have been identified by using hospital admission and death data. When we examined the association between body mass index and pulmonary embolism and deep vein thrombosis as separate outcomes, we found similar patterns of increasing risk with increasing body mass index. This suggests that our relative risk estimates are unlikely to have been distorted by the exclusion of outpatient cases of deep vein thrombosis.

Asymptomatic episodes of deep vein thrombosis and pulmonary embolism were, by definition, not included here, because the focus of this report is on clinically significant disease. We did not have information about the use of postoperative anticoagulation, and because women who were obese might have been more likely to receive prophylaxis than women in a healthy weight range (if the clinical guidelines in existence during the study period were followed), it is possible that the excess incidence of postoperative venous thromboembolism associated with obesity might be even higher than was found in this study.

We were able to minimize the potential for confounding by major risk factors for venous thromboembolism: we excluded women with a history of venous thromboembolism or cancer before recruitment; age was accounted for, and we adjusted for socioeconomic group, physical activity, hormone replacement therapy, smoking, hypertension, and diabetes; in the absence of surgery analysis we censored follow-up at any cancer diagnosis or surgery (which included operations to treat fractures and other trauma); and oral contraceptive use and pregnancy are not plausible confounders in this study of middle-aged women. We did not have information about inherited prothrombotic mutations, but body mass index is not known to differ in patients with thrombophilic disorders, so confounding is unlikely. Obese women are less active than thinner women (Table 1), and we adjusted for physical activity reported at baseline. The only information we had about subsequent immobility, a known risk factor for venous thrombosis, was whether women had had surgery during follow-up, so we were unable to take into account any other periods of immobility.

Our study was confined to women, but other prospective studies have found a similar relationship between increasing body size and venous thromboembolism risk for men in the absence of surgery, as have studies in which sex-adjusted estimates were reported. Previous studies that explored the independent effects of obesity on venous thromboembolism risk following surgery have not reported sex-specific analyses so it is not known whether the relationship differs between women and men. This would be interesting to explore in future studies.

### Implications

During a 12-week period without surgery, an estimated 0.1 in 1000 middle-aged United Kingdom women with a healthy weight (body mass index <25 kg/m²) had a first hospital admission with, or died from, venous thromboembolism in comparison with 0.2 in 1000 who were overweight or obese (body mass index ≥25 kg/m²). We also found that women who were overweight or obese were more likely to undergo surgery than women with a body mass index <25 kg/m², and that subsequently they were more likely to have a postoperative venous thromboembolic event. In the first 12 weeks following inpatient surgery, an estimated 4.8 in 1000 women of a healthy weight developed venous thromboembolism in comparison with 7.0 in 1000 who were overweight or obese.
The corresponding figures for the 12 weeks following day surgery were 0.5 in 1000 and 0.8 in 1000, respectively. The incidence of postoperative venous thromboembolism varies considerably by surgery type, and the numbers of cases of postoperative venous thromboembolism attributable to excess body weight are likely to be much greater following high-risk operations, such as orthopaedic and cancer surgery.

The 2010 United Kingdom National Institute for Clinical Excellence guidelines on the prevention of venous thromboembolism identify several additional risk factors in surgical patients, including a body mass index ≥30 kg/m² and surgical and anesthetic times of >90 minutes (or 60 minutes for lower limb or pelvic surgery). Our findings suggest that venous thromboembolism prophylaxis is important not only for obese patients, but also for overweight patients, who are undergoing both inpatient and day surgery.

In addition, our finding of a progressive increase in venous thromboembolism incidence with increasing body mass index, both in the absence of surgery and postoperatively, suggests that the avoidance of weight gain and the loss of even small amounts of weight are likely to be beneficial for those who are overweight and obese.

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References
Obesity and surgery are established risk factors for venous thromboembolism, but there is limited information about the independent effects of excess body weight on the incidence of postoperative venous thromboembolism. We linked questionnaire data from a large cohort study (the Million Women Study) with hospital admission and death records to examine the risk of venous thromboembolism in relation to body mass index, both in the absence of surgery and in the first 12 weeks following surgery. In the absence of surgery, there was a clear trend of increasing risk of venous thromboembolism with increasing body mass index. We also found that the risk of being admitted to hospital for surgery increased with increasing adiposity. Following surgery, both overweight and obese women had higher risks of venous thromboembolism, when compared with women of a healthy weight. This relationship between adiposity and postoperative venous thromboembolism risk was seen for both day and inpatient surgery, although the excess incidence was much greater following inpatient surgery. Clinical guidelines identify obesity as an additional risk factor for postoperative venous thromboembolism. Our findings suggest that venous thromboembolism prophylaxis is important for overweight, as well as obese, women undergoing either day or inpatient surgery. The observed progressive increase in venous thromboembolism incidence with increasing body mass index also suggests that the avoidance of further weight gain and even small reductions in body size are likely to be beneficial for those who are overweight and obese.
Body Mass Index, Surgery, and Risk of Venous Thromboembolism in Middle-Aged Women: A Cohort Study
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for the Million Women Study Collaborators

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SUPPLEMENTAL MATERIAL

Appendix

ICD codes used to identify venous thromboembolism before study entry and during follow-up:
ICD-9: 415.1, 451, 452, 453, 997.2, 671.3, 671.4, 671.9, 673.2, 634.6, 635.6, 636.6, 637.6, 638.6, and 639.6.
ICD-10: I26, I80, I81, I82, I97.8, I97.9, O22.3, O22.9, O87.1, O87.9, O88.2, O08.7, and O08.2.

OPCS-4 codes excluded from definition of surgery:
Variations de la prévalence de l’hypercholestérolémie à travers le monde, chez les patients présentant une maladie vasculaire avérée ou 3 facteurs de risque cardiovasculaire, en fonction des indices nationaux de développement économique et de performance des systèmes de santé

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Contexte—L’hypercholestérolémie est à l’origine d’une très large part des événements cardiovasculaires survenant de par le monde. La connaissance du lien unissant les facteurs économiques et sanitaires à l’hypercholestérolémie au sein d’un pays donné pourrait permettre de mieux définir les actions à mener en priorité dans le cadre des programmes de prévention des maladies cardiovasculaires.

Méthodes et résultats—En nous appuyant sur des modèles hiérarchiques, nous avons examiné, chez 53 570 patients ambulatoires répartis dans 36 pays, les relations existant entre l’hypercholestérolémie (taux supérieur à 2,0 g/l) et les territoires de plusieurs indices nationaux, à savoir (1) le produit intérieur brut (PIB), (2) le pourcentage du PIB consacré aux dépenses globales de santé, (3) la part de ces derniers assumée par les pouvoirs publics, (4) le reste à charge des frais médicaux pour les patients en pourcentage de leurs dépenses privées ainsi que les indicateurs utilisés par l’Organisation Mondiale de la Santé (OMS) pour évaluer les systèmes de santé en termes (5) de niveau de développement et (6) d’efficience. Globalement, 38 % des patients avaient une cholestérolémie totale supérieure à 2,0 g/l (5,18 mmol/l), 9,3 % de la variabilité totale de l’hypercholestérolémie s’étant révélée liée au pays d’appartenance ; le pourcentage était toutefois plus élevé pour les patients qui avaient des antécédents d’hyperlipidémie (12,1 %) que pour ceux qui en étaient exemptés (7,4 %). En limitant l’analyse aux patients ayant des antécédents d’hyperlipidémie, le risque d’hypercholestérolémie est apparu plus faible dans les pays dont le PIB ou le niveau de développement du système de santé tel que défini par l’OMS s’inscrivait dans le tertile le plus haut que dans ceux pour lesquels ces indicateurs se situaient dans les tertiles les plus bas (p <0,001, pour les deux indices). De même, le risque d’hypercholestérolémie était plus élevé pour les pays dans lesquels le reste à charge des frais médicaux pour les patients se situait dans le tertile le plus élevé que pour ceux dans lesquels cet indice relevait du tertile le plus faible (p <0,001). Aucune corrélation significative n’a été mise en évidence pour les patients qui n’avaient pas d’antécédent d’hyperlipidémie.

Conclusions—Les variations mondiales de la prévalence de l’hypercholestérolémie chez les patients ayant des antécédents d’hyperlipidémie sont corrélées avec le niveau de développement économique des pays et avec les indicateurs de performance de leurs systèmes de santé. Ces données montrent qu’il y a lieu de renforcer les mesures de prévention et de traitement des maladies cardiovasculaires et peuvent servir d’éléments d’orientation aux politiques nationales de santé publique.

Mots clés : maladie cardiovasculaire ■ hypercholestérolémie ■ tendances mondiales ■ performance des systèmes de santé ■ dépenses de santé nationales

Indice de masse corporelle, chirurgie et risque d’événement thromboembolique veineux chez la femme d’âge moyen

Une étude de cohorte

Lianne Parkin, MB, ChB, PhD ; Siân Sweetland, DPhil ; Angela Balkwill, MSc ; Jane Green, MB, ChB, DPhil ; Gillian Reeves, PhD ; Valerie Beral, MD, FRS, pour les investigateurs du Million Women Study

Contexte—L’obésité et la chirurgie sont des facteurs de risque connus d’événement thromboembolique veineux (ETV), mais peu de données sont disponibles sur l’influence spécifique exercée par l’obésité sur la survenue d’un ETV postopératoire. Nous avons donc confronté les données fournies par le questionnaire de la Million Women Study (étude sur un million de femmes) aux comptes rendus d’hospitalisation et aux certificats de décès afin d’évaluer le risque d’ETV encouru en fonction de l’indice de masse corporelle (IMC) en l’absence d’intervention chirurgicale et dans les 12 premières semaines qui suivent une opération.

Méthodes et résultats—Au total, 1 170 495 femmes (âge moyen : 56,1 ans) incluses dans l’étude entre 1996 et 2001 par l’intermédiaire du programme de dépistage du cancer du sein mis en place par le National Health Service britannique en Angleterre et en Ecosse ont été suivies pendant une durée moyenne de 6 ans, période pendant laquelle 6 438 de ces femmes ont été hospitalisées pour un ETV ou sont décédées des suites d’un tel événement. Nous avons pu établir que le risque relatif ajusté d’ETV avait augmenté proportionnellement à l’IMC et qu’il avait été 3 ou 4 fois plus élevé chez les femmes dont l’IMC atteignait 35 kg/m² ou plus que chez celles qui avaient un IMC compris entre 22,5 et 24,9 kg/m² (risque relatif : 3,45 [IC à 95 % : 3,09–3,86]). Les femmes en surcharge pondérale ou obèses se sont révélées plus exposées que les femmes minces à être hospitalisées en vue d’être opérées mais aussi à présenter un ETV postopératoire. Sur une période de 12 semaines libre d’intervention chirurgicale, les taux d’ETV pour 1 000 femmes ont été de 0,10 (0,09–0,10) lorsque l’IMC était inférieur à 25 kg/m² et de 0,19 (0,18–0,20) lorsqu’il atteignait 25 kg/m² ou plus ; les taux correspondants enregistrés au cours des 12 semaines ayant suivi un acte chirurgical pratiqué en ambulatoire ou dans le cadre d’une hospitalisation ont été, respectivement, près de 4 et 40 fois plus élevés.


Mots clés : obésité ■ chirurgie ■ thrombose veineuse profonde ■ embolie pulmonaire ■ étude de cohorte