PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Long-term impact of pregnancy-related venous thrombosis on quality of life, general health and functioning: results of a cross-sectional, case-control study
AUTHORS	Wik, Hilde; Jacobsen, Anne; Sandvik, Leiv; Sandset, Per Morten

VERSION 1 - REVIEW

REVIEWER	Dr.Susan Solymoss Division of Hematology The McGill University Health Center, Montreal General Hospital Montreal, Quebec, Canada. I have no competing interests.
REVIEW RETURNED	25-Sep-2012

RESULTS & CONCLUSIONS	The current study is a part of the authors' VIP study, already in part published, and listed as references 2 and 9 in the current submission. The connection to the previous publications, and that this is the same group of patients being studied, is not explicit. No justification is given to the change of focus, from a disease specific to a generic quality of life questionnare administered to the group. No analysis or discussion is included to put this work in context of the two prior publications on the same population.
REPORTING & ETHICS	this manuscript is part of the authors' previously published work with this group of patients. Some of the detail included in the current manuscript could simply be referred to as "as previously published" with a reference, to reduce redundancy. It would also enhance the current manuscript to explicitly compare and contrast the findings, now reported in three separate publications.

REVIEWER	Prof. F.R. Rosendaal Department of Clinical Epidemiology Leiden University Medical Center The Netherlands no conflicts of interest
REVIEW RETURNED	26-Sep-2012

RESULTS & CONCLUSIONS	This is a paper reporting a study on 559 women with venous thrombosis during pregnancy, and 1229 women with a pregnancy uncomplicated by thrombosis. Pregnancies took place three to 16 years before filling in the questionnaire, which was in 2006. The questionnaire contained mainly generic Quality of Life measures, and was filled in by 311 cases and 353 controls. No differences were found, either in crude analyses or analyses adjusted for

	confounding, except for women with self-reported postthrombotic syndrome, who reported more pain in the legs, and exhaustion after work. Strengths of this study are that is much larger than previous studies, and deals with an important subject. There are several severe limitations, however, that render it difficult to reach firm conclusions. 1. There was a major loss-to-follow-up, with participation proportions of 56% in cases and 28% in controls. Since for the majority of individuals it remains unknown why they did not participate, the representativeness and comparibility of cases and controls is highly questionable. Possibly for some of the measures, such as GHC-20, population figures are available. 2. This is not a cross-sectional case-control study, but a cohort study. 3. Data were collected three to 16 years after the event. Firstly, it would make sense to analyse time since event as a covariate. Secondly, anything may have happened in that long time, including comorbidity and recurrence, for which there are no data. Obviously, that does not invalidate the results, since recurrence is a consequence of thrombosis, but it would be helpful to study such data to obtain more insight. The lack of data on comorbidity at the time of the thrombosis, however, is likely to invalidate the results, since sich comorbidities could have confounded the findings. 4. This observational study should be reported using the STROBE guidelines. 5. The women with thrombosis differed markedly from those without on factors that shoud be expected to affect QoL, such as income, SES, smoking, BMI. Therefore, it is odd that adjustment for these factors did not change the estimates. It would indicate that the measures used were too insensitive.
REPORTING & ETHICS	1. This paper should have been written according to STROBE guidelines, presenting point estimates with confidence intervals 2. Why was this observational study registered in a trial registry? 3. Questionnaires were filled in in 2006: why the 6 year delay? 4. The flow diagram mentions blood draws: why?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Dr.Susan Solymoss
Division of Hematology
The McGill University Health Center,
Montreal General Hospital
Montreal, Quebec, Canada.

Q(uestion) 1: The current study is a part of the authors' VIP study, already in part published, and listed as references 2 and 9 in the current submission. The connection to the previous publications, and that this is the same group of patients being studied, is not explicit. No justification is given to the change of focus, from a disease specific to a generic quality of life questionnare administered to the group. No

analysis or discussion is included to put this work in context of the two prior publications on the same population.

R(esponse): We agree that reporting of disease specific QOL assessed by the VEINES-QOL/Sym questionnaire might have been reported with the generic QOL data and it would perhaps facilitated comparison of the findings. The two different publications regarding QOL were however pre-specified in the project protocol. We wanted both to report on predictors of reduced VEINES-QOL/Sym scores and on general health and functioning, and this was in our opinion too much for one article. Thus we followed the project protocol plan.

We disagree that the connection with our previous reports is not explicit. Both the VEINES-QOL/Sym publication and the main results were already mentioned in the Introduction of the current manuscript and we have discussed the discrepancy between our results in the Discussion section. The article on post-thrombotic syndrome and possible predictors in this population is in our opinion easier to read without the QOL data which also would have made it too long.

Q2: As detailed above, this manuscript is part of the authors' previously published work with this group of patients. Some of the detail included in the current manuscript could simply be referred to as "as previously published" with a reference, to reduce redundancy. It would also enhance the current manuscript to explicitly compare and contrast the findings, now reported in three separate publications.

R: We agree with this comment and have replaced some of the study details from the revised manuscript with a reference to our previously published work.

Reviewer 2: Prof. F.R. Rosendaal
Department of Clinical Epidemiology
Leiden University Medical Center
The Netherlands

This is a paper reporting a study on 559 women with venous thrombosis during pregnancy, and 1229 women with a pregnancy uncomplicated by thrombosis. Pregnancies took place three to 16 years before filling in the questionnaire, which was in 2006. The questionnaire contained mainly generic Quality of Life measures, and was filled in by 311 cases and 353 controls. No differences were found, either in crude analyses or analyses adjusted for confounding, except for women with self-reported postthrombotic syndrome, who reported more pain in the legs, and exhaustion after work.

Strengths of this study are that is much larger than previous studies, and deals with an important subject. There are several severe limitations, however, that render it difficult to reach firm conclusions.

Q(uestion) 1: There was a major loss-to-follow-up, with participation proportions of 56% in cases and 28% in controls. Since for the majority of individuals it remains unknown why they did not participate, the representativeness and comparibility of cases and controls is highly questionable. Possibly for some of the measures, such as GHC-20, population figures are available.

R(esponse): We agree that loss-to-follow-up is a limitation of the study, which is already acknowledged in the Discussion. However, we have previously reported in detail that the patients who answered and who did not answer the questionnaire were not different with regard to major clinical risk factors, and the appropriate references are already included. We are not aware of population norms for Ferrans&Powers QLI or GHQ-20.

Q2: This is not a cross-sectional case-control study, but a cohort study.

R: The study was originally a case-control study. But the questionnaire was answered by all of the participants in 2006, thus making the present report a cross-sectional study. In two recent publications in the Journal of Thrombosis and Haemostasis (listed as references number 2 and 9 in the current submission) concerning post-thrombotic syndrome and disease specific QOL in this population, the same terminology cross-sectional case-control study was used. We prefer to use the same terminology in the present report, but we will change the terminology if required by the Editor.

Q3a: Data were collected three to 16 years after the event. Firstly, it would make sense to analyse time since event as a covariate.

R: Done.

Q3b: Secondly, anything may have happened in that long time, including comorbidity and recurrence, for which there are no data. Obviously, that does not invalidate the results, since recurrence is a consequence of thrombosis, but it would be helpful to study such data to obtain more insight. The lack of data on comorbidity at the time of the thrombosis, however, is likely to invalidate the results, since sich comorbidities could have confounded the findings.

R: We agree with this comment. We have data on comorbidity at the time of the thrombosis from the hospital medical files. The comorbidity at the time of the index pregnancy was low in both groups. We therefore believe that such comborbidity not have confounded our findings. We have included a sentence about comborbidity at the time of index pregnancy in the first part of the Result section and we have also mentioned this in the Discussion of the revised manuscript.

Q4: This observational study should be reported using the STROBE guidelines.

R: We agree with this comment. See our response to Q6.

Q5: The women with thrombosis differed markedly from those without on factors that shoud be expected to affect QoL, such as income, SES, smoking, BMI. Therefore, it is odd that adjustment for these factors did not change the estimates. It would indicate that the measures used were too insensitive.

R: Even if smoking, BMI, education, employment, and income were statistically different between cases and controls, the real differences between these factors were small. The statistical difference is due to the rather large numbers of participants. As examples, mean BMI among cases and controls were 24.4 and 25.6, respectively and 26% versus 19% were smokers. This probably explains why adjustment of these factors did not change the estimates. Both Ferrans&Powers QLI and GHQ-20 are validated instruments that previously have shown to be sensitive for differences between groups. In our article concerning the disease specific QOL in the same population, only education was found to be a predictor for reduced QOL. The differences in self-reported general health, comorbidity, and functioning between cases and controls in the present report was also low and this is in line with the QOL results.

Q6: This paper should have been written according to STROBE guidelines, presenting point estimates with confidence intervals

R: We agree with this comment and point estimates with confidence intervals is now included in the Abstract, the Result section and Table 2 of the revised manuscript.

Q7: Why was this observational study registered in a trial registry?

R: We agree that this is not an interventional study, but at the time of planning the study, requirements for trial registration was not clear. Our study also included collection of blood samples and answering a questionnaire. It should also be noted that ClinicalTrials.gov includes both interventional and observational studies (http://clinicaltrials.gov/ct2/about-studies/learn).

Q8: Questionnaires were filled in 2006: why the 6 year delay?

R: The present report was a part of larger project, which included an analysis plan for different parts of the project. Due to the limited resources, reporting of the present data was delayed. Several articles from this project have been published during these 6 years. Despite the delay we believe that this data still are interesting for clinicians working in the field of venous thrombosis related to pregnancy.

Q9: The flow diagram mentions blood draws: why?

R: Thank you for this comment; it is obviously confusing that the flow diagram mentions blood draws when the article does not mention it. The participants did deliver a blood sample at the same time as filling out the questionnaire in 2006, but the results are not a part of the present manuscript. We have removed information regarding the blood samples from the flow diagram.