PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Venous thromboembolism in adults screened for Sickle Cell Trait: a population based cohort study with nested case-control analysis
AUTHORS	Little, Iain; Vinogradova, Yana; Orton, Elizabeth; Kai, Joe; Qureshi, Nadeem

VERSION 1 - REVIEW

REVIEWER	Simon Dyson De Montfort University United Kingdom
REVIEW RETURNED	27-May-2016

GENERAL COMMENTS	**Review of:-** **Venous thromboembolism in adults screened for Sickle Cell Trait: a population based cohort study with nested case control analysis** **Caveat:** This review is written by a non-clinician. In recommending publication after revision the assumption is made that clinical, statistical and epidemiological reviewers are satisfied with those aspects of the study**.** There are some statistical results that do not immediately make sense to me as a non-specialist but that may be my lack of knowledge. **Overall:** This is a retrospective observational study of those screened for sickle cell, comparing rates of venous thromboembolism in those identified with SCT and those not identified as carriers. As the authors themselves note, given the extensive screening for sickle cell currently taking place, and the standard public health advice that, except in certain extreme circumstances, SCT is essentially benign, this is a paper with important public health, ethical and social implications. Subject to addressing some concerns I support the publication of this paper. **Specific points:** **P3 (and also p 12)** ***"****Some people had a record of screening but no result recorded and these participants were assumed to be non-carriers in our main analysis."* I am unsure why these records were not excluded from the study. It obviously introduces a bias of some kind if assumptions have to be made and in this respect the NHS Screening Programme shows an opposite bias (in relation to those who fail to complete a Family Origins Questionnaire, a tool used as part of the sickle cell screening) in that missing data is assumed to place the person in the high risk group (i.e. a sickle cell carrier), with the partner to be offered a blood test (i.e. in practice missing data is

	assumed to be a carrier, here the authors assume missing data equals a non-carrier). An additional development might be to treat missing-SCT-screening-results cases as a third group to be compared. Thus the reader would be given an explicit comparison not only of those who have been screened with a definite SCT result and confirmed non-carriers (Supplementary Table 1), but also to those who have been screened with a no SCT result and confirmed non-carriers. **If this is possible, I would suggest this analysis be included and commented upon**. In this respect, and in a paper very carefully dealing with large numbers, it is surprising to see (p12) the lack of precision in referring to "some" people had a screening recorded but no result, when that "some" is actually a very large majority indeed. I think a comparison of non-carriers (known and assumed) would be an important centrepiece of this paper, both in terms of the presented table and in terms of commentary. This might help decide if there is anything about the (ethnically-focussed) screening in the UK that is having any influence on the results. On page 25 and p 26 (are these the same tables?), Supplementary Table 1, we are given results of a sensitivity analysis for "confirmed non-carriers". ***None of these reaches statistical significance?*** This seems an extremely important finding which is not strongly commented on the text, but I think should be commented upon. In commentary, at least as much attention should be drawn to these non-statistically significant results, as to the statistically significant ones that can be derived by assuming missing data to be non-carriers. P4 There is no controversy as to whether or not screening **without any arrangements for counselling and with a financial inducement to simultaneously waive screening and one's legal rights** (both the case with US athletics) will lead to discrimination. Duster (2003) has demonstrated historically that in such contexts discrimination does happen, not might happen. To state that stigma "might" emerge is to seriously underestimate the known effects. It has further been argued that, certainly in the US, SCT has been used as a key resource in effecting and extending discrimination, whilst simultaneously denying that such discrimination is occurring (Carter and Dyson, 2015). As such links to (genuine) clinical concerns should I think, acknowledge the extent and strength of the politicized framework within which such work will inevitably be apprehended. Given where such discrimination on SCT can end up (Dyson and Boswell, 2009), and that we know that UK clinicians routinely incorrectly include SCT on death certificates where it has no place (Lucas et al, 2009), my view is that it is better to acknowledge that the science is nested within political situations that scientists have little or no control over. In short, because it has the potential to be misused, I think this paper should signal up far more strongly the nature and content of the political context to SCT information. P9 I realize the research team will have been dealing with recorded data for ethnicity that will be of variable quality, especially historically going back to 1998, but I'm surprised they did not attempt to map ethnic data onto categories derived from the NHS Screening Family Origin Questionnaire. P9 working with sickle cell patient groups ….. this is a strength of the paper, as the authors will be aware that sickle cell community groups assert symptoms associated with SCT in contradiction to received medical advice. Enquiries about ostensibly SCT-related

symptoms form part of the range of enquires fielded by support groups and good quality community-orientated information is vital.

P11 “There were 27 VTE events in the sub-group of 7,343 Black patients” This phrase prompts me to think that somewhere the authors should comment on the issue that, whilst the relative odds risk may appear raised (at least for those assumed to be non-carriers because they have no formal test results recorded) , *the absolute numbers of events remain quite small*. This was also the case with Kark’s classic 1987 NEJM article on deaths from exertional heat illness associated with SCT.

P13 “future research” I think the authors might be anticipating a future study for themselves here. In which case they might reflect here on the fact that this paper looks (mainly?) at those screened ante-natally for SCT (where in principle anyway, consent to test specifically for SCT has been obtained) whereas in a cohort entirely of those screened neonatally, none of those identified have had permission sought to test. Ethically it’s one thing to undertake research on anonymized data where the person giving that data has consented to the generation of that knowledge. But even searching anonymized data raises some issues where the person: (1) never themselves gave permission for testing; (2) may not know that they have SCT; (3) and may not know that their medical record is being searched for links between something they neither know, nor consented to, and something like VTE relevant to their health. I’m not arguing against such a research enterprise, just that it raises some issues that need thinking about.

P14
In commenting on public health relevance of this research the authors confine themselves to a narrow range of “modifiable” (sic) risk factors such as obesity and smoking. First, the implication is that these are so-called lifestyle factors are within an individuals’ control (see Waitzkin, 1991 on how doctors’ talk turns social problems into individualized lifestyle ones) and not to do with, for example, the lack of a national food policy, the lack of a national transport policy, the lack of a national safe neighbourhood policy, or the increased precarity of neoliberal societies. Second, the range of exemplars held to be interactive with vte risk does not exhaust those likely to be relevant to Black patients in the UK, namely experience of racism (see the work of Nancy Krieger on racism and high blood pressure) or lack of status (see the work of Richard Wilkinson on the relationship between social status and health-damaging effects of flight or fight substances [substances which increase blood pressure and blood-clotting functions?]). The manner in which the authors frame the clinical relevance of the link between vte and SCT is currently very limited and should be opened up in both respects.

References

Carter, B and Dyson, SM (2015) Actor Network Theory, agency and racism: the case of sickle cell trait and US athletics *Social Theory and Health* 13: 62-77.

Duster, T. (2003) *Backdoor to Eugenics.* Second Edition. New

	York/London: Routledge. Dyson, SM and Boswell, GR (2009) *Sickle Cell and Deaths in Custody* London: Whiting and Birch Krieger, N., Chen, J.T., Waterman, P.D., Hartman, C., Stoddard, A.M., Quinn, M.M., Sorensen, G. and Barbeau, E.M. (2008) The inverse hazard law: blood pressure, sexual harassment, racial discrimination, workplace abuse and occupational exposures in US low-income black, white and Latino workers. *Social Science and Medicine*, 67(12): 1970-1981. Lucas, SB; Mason, DG; Mason, M and Weyman, D. (2008) *A Sickle Crisis? Report of the National Confidential Enquiry into Patient Outcome and Death* London: NCEPOD. Available: http://www.ncepod.org.uk/2008report1/Downloads/Sickle_report.pdf Waitzkin, H (1991) *The Politics of Medical Encounters: How Patients and Doctors Deal with Social Problems* New Haven: Yale University Press. Wilkinson, RG (2002) *Unhealthy Societies: The Afflictions of Inequality* London: Routledge.

REVIEWER	Matthew Bucknor University of California, San Francisco USA
REVIEW RETURNED	27-Jun-2016

GENERAL COMMENTS	This is an excellent paper, significantly broadening the scope of prior work with a number of careful and well thought-out analyses. The more diverse population included here compared to similar prior studies is incredibly important for moving this particular field forward. The inclusion of data from the several sensitivity analyses makes the essence of the results quite clear. Overall, the paper is incredibly well-written and reads as very complete. The only significant limitation is the high percentage (over 70%) of non-carrier cases which were non-confirmed. The authors acknowledge this limitation and have performed the appropriate secondary analysis, calculating incidence rates and rate ratios for a sample restricted to documented carrier and non-carrier status exclusively. While that restricted sample is underpowered, I truly feel like the authors have done their due diligence in this regard.

REVIEWER	Alejandro Lazo-Langner Western University, Canad
REVIEW RETURNED	03-Dec-2016

GENERAL COMMENTS	Comments for authors Manuscript BMJopen-2016-012665 Little and colleagues report the results of an interesting study evaluating the association of sickle cell trait and venous thromboembolism. They found a significant risk for VTE among

	sickle cell trait carriers, with this being higher for pulmonary embolism. Overall the study is well conducted and interesting. It also presents novel information. A few clarifications are needed. 1. Please provide information on the validity of the VTE codes in your databases. I am sure this has been done before. I am not certain the reference you cite addresses this issue specifically. 2. My main concern with this cohort study is that I wonder if there is some recall bias in the sickle population. The fact that there was a difference in VTE that was driven by the difference in the incidence of PE, makes me wonder if this is due to a higher use of CT scans among patients with sickle cell trait. It is well known that these patients develop pulmonary complications, including acute chest syndrome and pulmonary hypertension as a consequence of the sickling phenomenon. Thus, it is entirely possible that, knowing that a patient has a sickle cell trait might result in patients being subject to chest imaging more frequently than patients without sickle cell trait. An unintended consequence might be the more frequent recognition of thromboembolic events. A way of addressing this issue could be to adjust by number of CT or VQ studies performed if such information is available. If not, this limitation should be clearly identified in the discussion. Of course, a mechanistic explanation is also possible since chronic lung damage associated with the sickle cell trait might predispose patients to thrombotic phenomena, but this remains purely theoretical.

VERSION 1 – AUTHOR RESPONSE

Reviewer (1) - Simon Dyson
COMMENT (1): P3 (and also p 12) “Some people had a record of screening but no result recorded and these participants were assumed to be non-carriers in our main analysis.” I am unsure why these records were not excluded from the study. It obviously introduces a bias of some kind if assumptions have to be made and in this respect the NHS Screening Programme shows an opposite bias (in relation to those who fail to complete a Family Origins Questionnaire, a tool used as part of the sickle cell screening) in that missing data is assumed to place the person in the high risk group (i.e. a sickle cell carrier), with the partner to be offered a blood test (i.e. in practice missing data is assumed to be a carrier, here the authors assume missing data equals a non-carrier). An additional development might be to treat missing-SCT-screening-results cases as a third group to be compared. Thus the reader would be given an explicit comparison not only of those who have been screened with a definite SCT result and confirmed non-carriers (Supplementary Table 1), but also to those who have been screened with a no SCT result and confirmed non-carriers. If this is possible, I would suggest this analysis be included and commented upon.

RESPONSE: Thank you.We recognise (in the Discussion) that classifying unconfirmed records in this way is a limitation. This is, of course, why we undertook the sensitivity analysis described (Supplementary Table 1), which restricts the analysis to confirmed non-carriers only. We note Reviewer 2 supports our approach, “While that restricted sample is underpowered, I truly feel the authors have done their due diligence in this regard”. Further details on the relevant sensitivity analysis are provided in Response to Comment (3).

Secondly, in relation to the default policy of the antenatal screening programme Family Origins Questionnaire, it is unlikely that there is a correlation between patients’ failure to report ethnicity in the Family Origins Questionnaire and General Practitioners (GP) recording of their carrier status in the

primary care electronic health records.

Thirdly, if we have inadvertently misclassified carriers as non-carriers in our analysis, the result would be to reduce the overall effect size towards the null hypothesis. In this case our results, if anything, would be an underestimation of the true association. We have further made this point in the "Strengths and limitations of the study" section (1Last line on page 12 to 1st paragraph on page 13) with the following comment:

"The majority of people had a record of screening but no result recorded and these participants were assumed to be non-carriers in our main analysis, as this would be consistent with clinical practice. However some with no results recorded, may have been carriers. The presence of carriers in the unconfirmed non-carriers (no test) group would reduce the effect size of the main analysis. Further, GPs are more likely to document carrier state than non-carrier state introducing recall bias."

Further, an analysis of no SCT result and confirmed non-carriers groups would be difficult to interpret as the majority of the no SCT result group would be non-carriers.

COMMENT (2): In this respect, and in a paper very carefully dealing with large numbers, it is surprising to see (p12) the lack of precision in referring to "some" people had a screening recorded but no result, when that "some" is actually a very large majority indeed. I think a comparison of non-carriers (known and assumed) would be an important centrepiece of this paper, both in terms of the presented table and in terms of commentary

RESPONSE: We thank the Reviewer for pointing this out and agree that saying "some" is misleading. The last sentence on page 12 has been changed to read:

"The majority of people had a record of screening but no result recorded and these participants were assumed to be non-carriers in our main analysis".

COMMENT (3): On page 25 and p 26 (are these the same tables?), Supplementary Table 1, we are given results of a sensitivity analysis for "confirmed non-carriers". None of these reaches statistical significance? This seems an extremely important finding which is not strongly commented on the text, but I think should be commented upon. In commentary, at least as much attention should be drawn to these non-statistically significant results, as to the statistically significant ones that can be derived by assuming missing data to be non-carriers.

RESPONSE: In response to the question about the tables being the same, this may refer to the fact that Table 4 and Supplementary Table 1 both refer to sensitivity analyses and may therefore have caused confusion. To avoid this we have re-worded the title of Table 4 to say:

"Unadjusted and adjusted odds ratios of thrombotic events in patients with SCT, compared to patients without SCT, main and subgroup analyses".

Further in 4th paragraph on page 8 we have clarified that the case-control analysis against more stringent VTE criteria is a subgroup analysis rather than sensitivity analysis.

To further clarify, this was a sensitivity analysis and therefore not designed to be powered to detect a statistical difference. As noted above in our Response to Comment (1), the results are consistent with the main analysis and the limitations and interpretation of the sensitivity analysis are described in the Discussion on page 13 (1st paragraph):

“Restricting participants to only those with documented carrier and non-carrier status resulted in incidence rates and incidence rate ratios that were consistent with the main analysis, although underpowered due to the restricted number of events”.

COMMENT (4): P4 There is no controversy as to whether or not screening without any arrangements for counselling and with a financial inducement to simultaneously waive screening and one’s legal rights (both the case with US athletics) will lead to discrimination. Duster (2003) has demonstrated historically that in such contexts discrimination does happen, not might happen. To state that stigma “might” emerge is to seriously underestimate the known effects. It has further been argued that, certainly in the US, SCT has been used as a key resource in effecting and extending discrimination, whilst simultaneously denying that such discrimination is occurring (Carter and Dyson, 2015). As such links to (genuine) clinical concerns should I think, acknowledge the extent and strength of the 2 politicized framework within which such work will inevitably be apprehended. Given where such discrimination on SCT can end up (Dyson and Boswell, 2009), and that we know that UK clinicians routinely incorrectly include SCT on death certificates where it has no place (Lucas et al, 2009), my view is that it is better to acknowledge that the science is nested within political situations that scientists have little or no control over. In short, because it has the potential to be misused, I think this paper should signal up far more strongly the nature and content of the political context to SCT information.

RESPONSE: We thank Reviewer (1) for highlighting that discrimination does happen and have amended the relevant line in 2nd paragraph on page 4 accordingly:

“The US National Collegiate Athletic Association’s mandatory SCT screening program for student athletes has provoked considerable controversy about whether this will improve outcomes, whilst also leading to discrimination and confusion.[4 11 12]”

The objective of this clinical database study was to determine whether sickle cell trait is associated with venous thromboembolism. We have briefly referred to issues of discrimination and stigma in the paper. However, as its focus is applied primary care health service research, we have not made further sociological comment about the political context of sickle cell screening.

We do recognise it is important that individuals are able to make an informed choice about whether or not to be screened, based on the findings of our studies and those of others, which is why we have referred to this in the section on implications for clinical practice on page 14.

We thank the Reviewer for highlighting relevant references which we have incorporated in the statement about stigmatisation of communities in last paragraph on page 14 (Dyson and Boswell 2009) and the statement on discrimination in the introduction in 2nd paragraph on page 4 (Carter and Dyson 2015). .

COMMENT (5): P9 I realize the research team will have been dealing with recorded data for ethnicity that will be of variable quality, especially historically going back to 1998, but I’m surprised they did not attempt to map ethnic data onto categories derived from the NHS Screening Family Origin Questionnaire.

RESPONSE: This is a very good point, however the ethnicity data are derived from individual NHS IT systems using the standard NHS ethnicity coding classification. Ethnicity data from the antenatal Screening Family Origin Questionnaire is not coded in the primary care database. Further, researchers only have access to anonymised data and this is not linked to the NHS Screening Family Origin Questionnaires entered in other settings.

COMMENT (6): P9 working with sickle cell patient groups ….. this is a strength of the paper, as the authors will be aware that sickle cell community groups assert symptoms associated with SCT in contradiction to received medical advice. Enquiries about ostensibly SCT-related symptoms form part of the range of enquires fielded by support groups and good quality community-orientated information is vital.

RESPONSE: We thank the Reviewer for this comment. No response needed.

COMMENT (7): P11 “There were 27 VTE events in the sub-group of 7,343 Black patients” This phrase prompts me to think that somewhere the authors should comment on the issue that, whilst the relative odds risk may appear raised (at least for those assumed to be non-carriers because they have no formal test results recorded), the absolute numbers of events remain quite small. This was also the case with Kark’s classic 1987 NEJM article on deaths from exertional heat illness associated with SCT.

RESPONSE: We agree. We have amended the following sentence in the “Implications for clinical practice” section of the discussion (2nd paragraph on Page 14):

“Although the absolute numbers of VTE events were small, our results indicate that clinicians should make patients with SCT aware of their increased risk of VTE”.

COMMENT (8): P13 “future research” I think the authors might be anticipating a future study for themselves here. In which case they might reflect here on the fact that this paper looks (mainly?) at those screened ante-natally for SCT (where in principle anyway, consent to test specifically for SCT has been obtained) whereas in a cohort entirely of those screened neonatally, none of those identified have had permission sought to test. Ethically it’s one thing to undertake research on anonymized data where the person giving that data has consented to the generation of that knowledge. But even searching anonymized data raises some issues where the person: (1) never themselves gave permission for testing; (2) may not know that they have SCT; (3) and may not know that their medical record is being searched for links between something they neither know, nor consented to, and something like VTE relevant to their health. I’m not arguing against such a research enterprise, just that it raises some issues that need thinking about.

RESPONSE: Whilst the reviewer makes a very interesting ethical point, this would encompass all previous studies using electronic health records where the research is secondary to the primary reason for data collection. As with all CPRD/HES studies, the ethical safeguards are provided through necessary scientific approvals from MHRA and ethical approvals for the use of these data for health services research have already been sought by the MHRA from an NHS Research Ethics committee. Statements regarding ethical approvals are included in the manuscript on page 6 (2nd paragraph), page 10 (1st paragraph) and page 15.

COMMENT (9): P14 In commenting on public health relevance of this research the authors confine themselves to a narrow range of “modifiable” (sic) risk factors such as obesity and smoking. First, the implication is that these are so-called lifestyle factors are within an individuals’ control (see Waitzkin, 1991 on how doctors’ talk turns social problems into individualized lifestyle ones) and not to do with, for example, the lack of a national food policy, the lack of a national transport policy, the lack of a national safe neighbourhood policy, or the increased precarity of neoliberal societies. Second, the range of exemplars held to be interactive with vte risk does not exhaust those likely to be relevant to Black patients in the UK, namely experience of racism (see the work of Nancy Krieger on racism and high blood pressure) or lack of status (see the work of Richard Wilkinson on the relationship between social status and health-damaging effects of flight or fight substances [substances which increase blood pressure and blood-clotting functions?]). The manner in which the authors frame the clinical

relevance of the link between vte and SCT is currently very limited and should be opened up in both respects.

RESPONSE: As a primary care database study, we have limited our discussion in the “Implications for clinical practice” section to possible other risk factors for VTE that are both identifiable in primary care and amenable to clinical intervention, hence term “modifiable risk factors”. This corresponds to the revised Abstract conclusion. We acknowledge that there are many social determinants of these and other risk factors for VTE but that was not the focus of this paper. Further, we are not able to take racism and social status into account in our analyses as these are not routinely recorded in the electronic healthcare record. However, we have acknowledged this in the discussion at the end of 1st paragraph on page 13:

“We also only used patient data that was considered to be of sufficient quality (in terms of completeness and accuracy) as determined by CPRD (i.e. identified as ‘up to standard’ within the database). However, we were only able to take account of confounding factors that are recorded in the electronic health record.”

Reviewer (2) Matthew Bucknor

We are grateful to Reviewer (2) for his positive comments. No responses are required.

Reviewer (3) Alejandro Lazo-Langner
COMMENT (1): Please provide information on the validity of the VTE codes in your databases. I am sure this has been done before. I am not certain the reference you cite addresses this issue specifically.

RESPONSE: Thank you. We have amended the methods section to address this by clarifying that the code list was validated by Lawrenson. Similarly, other studies that have identified VTEs in primary care databases have cited Lawrenson as the source for validated VTE codes (e.g. Grainge et al. 2010; Walker et al. 2013).The relevant sentence in the last paragraph of page 6 now reads:

“Patients were considered to have had a VTE if they had a validated diagnostic medical code for VTE in their record during the observational period (February 1988 to May 2013).[31]”

COMMENT (2): My main concern with this cohort study is that I wonder if there is some recall bias in the sickle population. The fact that there was a difference in VTE that was driven by the difference in the incidence of PE, makes me wonder if this is due to a higher use of CT scans among patients with sickle cell trait. It is well known that these patients develop pulmonary complications, including acute chest syndrome and pulmonary hypertension as a consequence of the sickling phenomenon. Thus, it is entirely possible that, knowing that a patient has a sickle cell trait might result in patients being subject to chest imaging more frequently than patients without sickle cell trait. An unintended consequence might be the more frequent recognition of thromboembolic events. A way of addressing this issue could be to adjust by number of CT or VQ studies performed if such information is available. If not, this limitation should be clearly identified in the discussion. Of course, a mechanistic explanation is also possible since chronic lung damage associated with the sickle cell trait might predispose patients to thrombotic phenomena, but this remains purely theoretical.

RESPONSE: Thank you: we now comment on this in the Discussion. As with other studies using healthcare data for secondary research purposes, it is not possible to rule out ascertainment biases associated with limited documentation of certain characteristics of the individuals in their primary care health records. In other words, we are only able to ascertain if an investigation has been performed if

this is medically coded in the primary care electronic healthcare records. Further, the information is not available to researchers if recorded as free-text. Although we are not aware that patients with sickle cell trait, in the UK, are more likely to have diagnostic imaging, we have added this as a limitation in the discussion. An additional sentence has been added at the end of the 1st paragraph on page 13:

"Similarly, while free-text information on diagnostic imaging is inconsistent and not accessible to researchers in electronic primary care records, the prevalence of PE in the carrier group could potentially reflect ascertainment bias, if, for example, clinicians had a lower index of suspicion for lung problems in carriers, with more frequent diagnostic imaging."

VERSION 2 – REVIEW

REVIEWER	Simon Dyson De Montfort University United Kingdom
REVIEW RETURNED	16-Jan-2017

GENERAL COMMENTS	Review of:- Venous thromboembolism in adults screened for Sickle Cell Trait: a population based cohort study with nested case control analysis Overall: This is a retrospective observational study of those screened for sickle cell, comparing rates of venous thromboembolism in those identified with SCT and those not identified as carriers. As the authors themselves note, given the extensive screening for sickle cell currently taking place, and the standard public health advice that, except in certain extreme circumstances, SCT is essentially benign, this is a paper with important public health, ethical and social implications. I continue to support the publication of this paper, though still feel it could be improved by attention to the points listed. Specific points: Abstract: Whilst the authors have recognized my point from the first review that, whilst the relative risks are increased the absolute numbers of events are small in the text (p14) I would like to see this point made in the abstract so that in the future this important subtlety is not lost on reviewers scanning abstracts Page 10 and Supplementary Table 1 The authors have attended to my comment on the importance of making explicit comparisons with non-confirmed carriers. I appreciate that the authors wish to have a clear message and that the lack of statistical significance here might be seen to dilute their argument. Rather than see this as any weakness on the part of the researchers (which I do not) but in order that this important feature of the findings is accorded due weight, I think we need to see this as other than something that needs to be downplayed in the discussion. To my mind what it does suggest in another very important implication for practice. If the association is significant for carriers v confirmed+imputed non-carriers and not significant for carriers v confirmed carriers only, then surely this has important implications for primary practice records. As a non-clinician I'm not familiar with

these but if there is a code for having been screened surely in an electronic record there should be a field linked automatically requiring a haemoglobin variant+thalassaemia status result. I don't share the author's confidence that post NHS Sickle Cell Screening Programme that recording of results in primary care will necessarily have improved. In short I would suggest that an important finding for practice should be that of improved record keeping so that no clinician (or researcher) has to impute a non-carrier result from the absence of a positive result. I also think that (a) the non-significant result of non-confirmed carriers and (b) the implications for primary care records should be signalled in the abstract.

In my first review I wrote……

"In commenting on public health relevance of this research the authors confine themselves to a narrow range of "modifiable" (sic) risk factors such as obesity and smoking. First, the implication is that these are so-called lifestyle factors are within an individuals' control (see Waitzkin, 1991 on how doctors' talk turns social problems into individualized lifestyle ones) and not to do with, for example, the lack of a national food policy, the lack of a national transport policy, the lack of a national safe neighbourhood policy, or the increased precarity of neoliberal societies. Second, the range of exemplars held to be interactive with vte risk does not exhaust those likely to be relevant to Black patients in the UK, namely experience of racism (see the work of Nancy Krieger on racism and high blood pressure) or lack of status (see the work of Richard Wilkinson on the relationship between social status and health-damaging effects of flight or fight substances [substances which increase blood pressure and blood-clotting functions?]). The manner in which the authors frame the clinical relevance of the link between vte and SCT is currently very limited and should be opened up in both respects".

The authors have included broad-brush data on level of material deprivation. As might be expected those research participant coded in the "Black" ethnic group are disproportionately located in the most deprived quintile. Although not modifiable by a lifestyle-orientated GP, this social location does make my comments completely apposite to the paper. Since the sickle cell carriers are (i) more likely to experience low social standing, Wilkinson's work applies and since sickle cell carriers are more likely to be "Black" and thus experience racism Krieger's work applies. I would still encourage some discussion of both deprivation and racism.

References

Krieger, N., Chen, J.T., Waterman, P.D., Hartman, C., Stoddard, A.M., Quinn, M.M., Sorensen, G. and Barbeau, E.M. (2008) The inverse hazard law: blood pressure, sexual harassment, racial discrimination, workplace abuse and occupational exposures in US low-income black, white and Latino workers. Social Science and Medicine, 67(12): 1970-1981.

Waitzkin, H (1991) The Politics of Medical Encounters: How Patients and Doctors Deal with Social Problems New Haven: Yale University Press.

Wilkinson, RG (2002) Unhealthy Societies: The Afflictions of Inequality London: Routledge.

REVIEWER	Alejandro Lazo-Langner Western University, Canada
REVIEW RETURNED	16-Jan-2017

GENERAL COMMENTS	Authors did a nice work at addressing the reviewers' concerns. I have no further comments

VERSION 2 – AUTHOR RESPONSE

Please find response to Reviewer (1)'s further recommendations. Additional text is highlighted in yellow. Tracked changes to Abstract are also included.

REVIEWER'S RECOMMENDATION (1): "Whilst the authors have recognized my point from the first review that, whilst the relative risks are increased the absolute numbers of events are small in the text (p14) I would like to see this point made in the abstract so that in the future this important subtlety is not lost on reviewers scanning abstracts"

Response: Please note the low incidence rate of venous thromboembolism is included in the Abstract Results (Carriers 14.9/10000 & Non-carriers 8.8/10,000 person-years) but we have explicitly added low absolute numbers to the Abstract Conclusion

REVIEWER'S RECOMMENDATION (2): "The authors have attended to my comment on the importance of making explicit comparisons with non-confirmed carriers. I appreciate that the authors wish to have a clear message and that the lack of statistical significance here might be seen to dilute their argument. Rather than see this as any weakness on the part of the researchers (which I do not) but in order that this important feature of the findings is accorded due weight, I think we need to see this as other than something that needs to be downplayed in the discussion. To my mind what it does suggest in another very important implication for practice. If the association is significant for carriers v confirmed+imputed non-carriers and not significant for carriers v confirmed carriers only, then surely this has important implications for primary practice records. As a non-clinician I'm not familiar with these but if there is a code for having been screened surely in an electronic record there should be a field linked automatically requiring a haemoglobin variant+thalassaemia status result. I don't share the author's confidence that post NHS Sickle Cell Screening Programme that recording of results in primary care will necessarily have improved. In short I would suggest that an important finding for practice should be that of improved record keeping so that no clinician (or researcher) has to impute a non-carrier result from the absence of a positive result. I also think that (a) the non-significant result of non-confirmed carriers and (b) the implications for primary care records should be signalled in the abstract."

Response: Reviewer provides an interesting observation. We agree a key step to improve analysis is better recording of non-carrier status. To achieve this would probably require better coding of results coming from pathology laboratories rather than try to tag results to primary care computer record code for sickle cell screening. This has been amended accordingly on page 14 of Discussion:

"If primary care records are to be used in future research, the coding of non-carrier status needs to be improved, for example, through direct coding of carrier status when results are transferred electronically to primary care records from pathology laboratories."

Considering expansion of the Abstract, although this is limited to 300 words, we have tried to incorporate details on small absolute numbers (see above), sensitivity analysis and primary care records.

We would like to restate our previous response: “if we have inadvertently misclassified carriers as non-carriers in our analysis, the result would be to reduce the overall effect size towards the null hypothesis. In this case our results, if anything, would be an underestimation of the true association” and Reviewer (2)’s comment: ““While that restricted sample is underpowered, I truly feel the authors have done their due diligence in this regard”. However, recognising the Reviewer (1)’s concerns, added the findings of the sensitivity analysis to the Abstract Results. Further, the Abstract conclusion ends with a statement on improving coding in primary care records.

REVIEWER’S RECOMMENDATION (3): “The authors have included broad-brush data on level of material deprivation. As might be expected those research participant coded in the “Black” ethnic group are disproportionately located in the most deprived quintile. Although not modifiable by a lifestyle-orientated GP, this social location does make my comments completely apposite to the paper. Since the sickle cell carriers are (i) more likely to experience low social standing, Wilkinson’s work applies and since sickle cell carriers are more likely to be “Black” and thus experience racism Krieger’s work applies. I would still encourage some discussion of both deprivation and racism.”

Response: Reviewer’s concerns are acknowledged. We would like to highlight that this is a GP database study with no surrogate measures of racism, and in the “Discussion” we have tried to avoid interpretation beyond the data in the article. However, on page 14-15, we have tried to incorporate some of the Reviewer’s observations about racism and deprivation.

“Previous researchers have observed the Black community, at genetic risk of sickle cell, are also disadvantaged in society. A situation exacerbated by racism. [58] Such issues also deserve further consideration.”

Thank you for allowing us the opportunity to revise these sections in light of reviewer (1)’s comments