PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Are familial factors underlying the association between socio-economic position and prescription medicine? A register-based study on Danish twins
AUTHORS	Madsen, Mia; Andersen, Per; Gerster, Mette; Andersen, Anne-Marie; Osler, Merete; Christensen, Kaare

VERSION 1 - REVIEW

REVIEWER	Karin Modig, Phd, Postdoc Institute of Environmental Medicine Division of Epidemiology Karolinska Institutet Sweden No conflict of interest
REVIEW RETURNED	13-Jun-2013

GENERAL COMMENTS	It is an interesting and mostly well written paper with a suitable approach to study the research question. The results are thoroughly and well presented in the results section. My concern is related to the discussion of the paper which I find rather poor in relation to the findings. The discussion consists almost completely of a long discussion about potential weaknesses and strength with twin design (mostly in general). I lack a discussion about the findings, what they mean and what conclusions can be drawn from them. There is nothing new about an association with low SEP and health status, the question is what mechanisms explain this association. Also if prescription of medication is used as a proxy of health status, more discussion about this would be interesting. The potential reverse causality is mentioned briefly but I would like this to be extended, and perhaps should certain medications related to health outcomes occurring early in life be excluded? Since these outcomes may affect SEP rather than the opposite (which is of interest in this study). The authors conclude that at least part of the observed social inequality in prescription fillings is explained by shared familiar factors since the association was attenuated within twin pairs. It was however more attenuated in MZ pairs suggesting genetic factors – this is not discussed much. To me it does not seem very surprising that MZ twins would share common genetics explaining both heath status and SES. But can one draw the conclusion from that so that SES differences in health in general is

	explained (partly) by genetic factors? In such case – what does that mean in terms of prevention and implications? Minor or more specific comments related to sections in the manuscript: Introduction First section, row 23-25 “Many studies have shown…” I find this interesting and it could perhaps be brought up in the discussion again with some more information. How much were the social differences reduced – if not fully, what does it mean in terms of residual confounding in the relation of SES and prescription filling? Methods Regarding the SEP indicators. Education was measured in 1995 but with a classification starting in 1997? Further, what about missing information on education, I guess that would be more of a problem for the older cohorts, born in 1920-ies than in the younger cohorts? For income I assume that the quartiles would be fairly similar for the older cohorts that are retired than the younger cohorts. How may that reflect the results? Also what the authors do when setting quartiles within each birth cohort is a relative comparison of income assuming it is the relative position and not an absolute level of income that matters – perhaps could this be clearer in the manuscript. Why was the period 1995 to 2005 chosen? An alternative could have been to go further back and compare cohorts at the same age (or perhaps was the register not available before?). Results Just a question for clarification, discordant meant that they belonged to a different educational groups or income quartiles? I found the discordant rate for both income and education to be surprisingly high in MZ twins. I also found the proportion of twins having no prescribed drug during the 10-year period low, 1.9% considering at least half of them (how many?) can be considered relatively young (below 50). Is this figure in accordance with previous findings? Table 4, it would be nice to have the number of individuals in each group. For example, could the attenuated result for MZ twins be a result of low power (considering a fairly wide CI?). Discussion I would like to see more discussion about the findings, how to interpret them and implications. The finding itself that lower SEP consume more drugs/ have a worse health status is no news. If drugs are used as a proxy for health, some discussions about which health outcomes that are captured within the different medication groups would be interesting. For example what is within the nervous system that seems to stick out in number of prescription, depression? Section 6 row 27-29, “We examined this concern by…”, What is meant by this? Wasn’t the previous analyses also made on discordant twins?

	Section 7, last part. I find this section rather weak. I don't really follow the discussion about correlated confounders, and whether income and education are less correlated than other highly correlated variables are not very informative. Such correlations vary over time and context. It would be better to state the correlation in this specific study. Further, even if in most cases one would expect a negative association between education and prescription fillings one can as well think of the opposite since educated people could be more likely to visit the doctor for regular heath checks, understand symptoms, and live in urban areas where people in general visit the doctor more often. The potential reverse causality must be discussed and handled more carefully – potentially by selecting drugs related to diseases occurring only/mainly in older ages.

REVIEWER	Øyvind Næss Norwegian Institute of Public Health
REVIEW RETURNED	05-Jul-2013

THE STUDY	Use of medicines/prescription should be more clearlty linked to clinical outcomes. Which clinical conditions are these most used for in the Danish population? The authors should express more clearly what they mean by "familial factors" both in the introduction and in the conclusion of the abstract.
RESULTS & CONCLUSIONS	1. There is no theoretical discussion on how genetical factors may explain socioeconomic inequalities in health in general and with respect to the chosen outcomes in which prescription medicine are used as proxy for. I would guess these medicines are used for many well known chronic diseases in adulthood. The study is a bit at odd with theoretical papers on genetical explanations of socioeconomic inequalities in chronic diseases with complex genetical origin, see Holtzman or Mackenbach. The increased attenuation in MZ compared to DZSS could just as equally be explained by the equal environment assumption being not valid here rather than genetical explanations having an important role for complex and chronic diseases such as CVD etc. This is not clearly discussed in the paper. 2. The study lacks a fundamental life course theoretical approach. In relation to this, the concept "familial factors" appears unprecise, though necessary given the chosen twin/sibling design. 3. Table 4. It would be advantageous to have per unit increase estimates for both education and income for all outcomes. Also, p-values for intereaction on zygosity should be presented in table 4 and not only in the text.
REPORTING & ETHICS	I have not seen the STROBE statement here.
GENERAL COMMENTS	The study is potentially very interesting and clearly written. The study seems to be analysed appropriately and is clearly written. It has a technically sofisticated approach, but I would welcome a clearer theoretical discussion and motivation. The concept "familial factors" including "shared" "unshared" and "genetical factors" should be contextualized with respect to specific diseases and their life

	course origin. There is hardly any reference to the large body of literature on childhood socioeconomic environment and chronic diseases in adulthood. Page 18. The authros report intra-pair correlation among twins and the population with reference to Frisell et al. How much was this intra-pair correlation?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Karin Modig

This study examines the association between adult SEP measured by education and income and prescription fillings among Danish twin pairs. The objective was to understand to what extent familial factors may explain an association between SEP and prescription of drugs (as a proxy of health status).

General comments

It is an interesting and mostly well written paper with a suitable approach to study the research question. The results are thoroughly and well presented in the results section.
My concern is related to the discussion of the paper which I find rather poor in relation to the findings. The discussion consists almost completely of a long discussion about potential weaknesses and strength with twin design (mostly in general). I lack a discussion about the findings, what they mean and what conclusions can be drawn from them. There is nothing new about an association with low SEP and health status, the question is what mechanisms explain this association.
Also if prescription of medication is used as a proxy of health status, more discussion about this would be interesting.
The potential reverse causality is mentioned briefly but I would like this to be extended, and perhaps should certain medications related to health outcomes occurring early in life be excluded? Since these outcomes may affect SEP rather than the opposite (which is of interest in this study).
The authors conclude that at least part of the observed social inequality in prescription fillings is explained by shared familiar factors since the association was attenuated within twin pairs. It was however more attenuated in MZ pairs suggesting genetic factors – this is not discussed much. To me it does not seem very surprising that MZ twins would share common genetics explaining both heath status and SES. But can one draw the conclusion from that so that SES differences in health in general is explained (partly) by genetic factors? In such case – what does that mean in terms of prevention and implications?

Response: Thanks, we completely agree with the reviewer that manuscript would profit from a more elaborated discussion of the findings and their implications. The discussion has now been extensively revised and restructured to address the concerns of the reviewer. Main changes include:
- More explicit link between drug prescriptions and potential clinical outcomes
- Reporting of intra-pair correlations
- Closer examination and discussion of potential reverse causation underlying the association between income and drugs targeting the nervous system
- Extended literature review
- Subheadings

We have decided to keep much of the discussion on measurement error, “social interaction”, selection issues, confounding from unshared factors, and Equal Environment Assumption in the beginning of the discussion section because we feel that it is not only a question of “strengths and limitations”, but that it is crucial to our interpretation of the findings, i.e. to justify 1) why we believe that the findings do suggest that shared family factors explain part of the association between SEP and drugs, although

we cannot fully exclude alternative explanations, and 2) why we do not put too much emphasis on genetic factors, although we observed a greater attenuation of effect in MZ twins. We have aimed discuss the general concerns of the twin approach in relation to this particular study.

Minor or more specific comments related to sections in the manuscript:

Introduction
First section, row 23-25 “Many studies have shown…” I find this interesting and it could perhaps be brought up in the discussion again with some more information. How much were the social differences reduced – if not fully, what does it mean in terms of residual confounding in the relation of SES and prescription filling?

Response: An extended review of the existing literature has now been included in the revised discussion, but unfortunately the nature of the literature makes it difficult to go much beyond association or no association.

Methods
Regarding the SEP indicators. Education was measured in 1995 but with a classification starting in 1997?

Response: Education was indeed measured in 1995, but the classification of different specific types of education into the categories: “primary”, “secondary” and “tertiary” education has been applied after words in accordance with the referenced guidelines.

Further, what about missing information on education, I guess that would be more of a problem for the older cohorts, born in 1920-ies than in the younger cohorts?

Response: As mentioned in the methods section on the study population missing information is generally not a huge problem in this data, but as suggested by the reviewer, we have now examined if the amount of missing information varied according to birth cohort. There was no clear indication of this. However, it is possible that the quality of the information on the older birth cohorts might be poorer, but this concern is difficult to prove or disprove.

For income I assume that the quartiles would be fairly similar for the older cohorts that are retired than the younger cohorts. How may that reflect the results?

Response: The reviewer is right: the income contrasts between quartiles varies over the life course being smallest for the oldest birth cohorts, somewhat bigger for the youngest birth cohorts, and largest for the birth cohorts born around 1940. We have previously considered to include a table corresponding to table 4, but stratified on groups of birth cohorts. This table showed that the association between SEP and fillings of prescriptions was weakest for the oldest births cohorts and strongest for the youngest birth cohorts. However, this is true for both education and income, and the same pattern was seen when we used income as an absolute measure (i.e. <100,000 DKK, <200,000, <300,000, <400,000 <500,000, 500,000+). We therefore think it reflects a greater health effect of SEP in younger cohorts, which may have to do with the health issues requiring prescription drugs among younger people (e.g. fillings of ATC-N drugs). Although this modification of effect by birth cohort is a very interesting finding, we had to focus the paper and prioritize, and the table was left out eventually. We are, however, willing to reconsider this, if the reviewers and editors think so. Due to the fact the older birth cohorts account for the greatest proportion of prescription fillings (table

3), the combined estimate is closer to the estimate for older cohorts, which may be an underestimation of the true effect for younger birth cohorts.

Also what the authors do when setting quartiles within each birth cohort is a relative comparison of income assuming it is the relative position and not an absolute level of income that matters – perhaps could this be clearer in the manuscript.

Response: The reviewer is right. Making quartiles within each birth cohort makes it a relative rather than an absolute measure of income. Part of the reason for doing this is that age differences can be a little tricky because older people may have lower incomes but larger wealth due to other assets not fully captured by household income. The underlying assumption has now been made clearer in the text.

Why was the period 1995 to 2005 chosen? An alternative could have been to go further back and compare cohorts at the same age (or perhaps was the register not available before?).

Response: Data from Danish Registry of Medicinal Products only exists from 1996 and onwards. Therefore, this follow-up period was chosen. This has now been explicated in section on prescription medicine.

Results
Just a question for clarification, discordant meant that they belonged to a different educational groups or income quartiles? I found the discordant rate for both income and education to be surprisingly high in MZ twins.

Response: Yes, the reported discordances refer to the proportion of twin pairs belonging to different educational groups and income quartiles, respectively. We agree with the reviewer that discordances of 30% (education) and 61% (income) among MZ twins is perhaps surprising, but as appears from table 2, large discordance contrasts are rare, which we think makes the findings credible.

I also found the proportion of twins having no prescribed drug during the 10-year period low, 1.9% considering at least half of them (how many?) can be considered relatively young (below 50). Is this figure in accordance with previous findings?

Response: To our knowledge, no direct comparable data have been published on this point, but a Swedish study based on the entire Swedish population found that 59% of all men and 76% of all women were dispensed at least one prescription during 2010 (Loikas et al., BMJ Open 2013) So with this in mind, we do not find it unlikely that most people during a period of ten years have filled at least one prescription.

Table 4, it would be nice to have the number of individuals in each group. For example, could the attenuated result for MZ twins be a result of low power (considering a fairly wide CI?).

Response: The number of individuals is already reported in table 4. We think the reviewer might mean the number of prescription fillings for each group instead. However, we have decided to leave out this number in order not to compromise the readability of the table too much. Since fillings of prescription medicine are fairly frequent, numbers are generally large and take up a lot of space. If, however, the editors would like us to include this information, we are of course willing to do so.

Discussion
I would like to see more discussion about the findings, how to interpret them and implications. The finding itself that lower SEP consume more drugs/ have a worse health status is no news.

If drugs are used as a proxy for health, some discussions about which health outcomes that are captured within the different medication groups would be interesting. For example what is within the nervous system that seems to stick out in number of prescription, depression?

Response: As mentioned earlier, we acknowledge that the discussion could be improved in several ways (please see revision). In addition, we have now included a supplementary table in order to make explicit which clinical outcomes might be related to the investigated categories of drugs. In the discussion section, we additionally mention a post hoc analysis carried out to shed further light on the findings of a persistent association of income with ATC-N drugs in the intra-pair analysis.

Section 6 row 27-29, “We examined this concern by…”, What is meant by this? Wasn’t the previous analyses also made on discordant twins?

Response: The unpaired twin analyses were based on all MZ and DZSS twins regardless of discordance. In the subanalysis - referred to above – the study population was restricted only to include exposure-discordant pairs. It seems that this stepwise analytical approach is widely accepted.

Section 7, last part. I find this section rather weak. I don’t really follow the discussion about correlated confounders, and whether income and education are less correlated than other highly correlated variables are not very informative. Such correlations vary over time and context. It would be better to state the correlation in this specific study.

Response: This discussion has been revised and the correlations are now being reported.

Further, even if in most cases one would expect a negative association between education and prescription fillings one can as well think of the opposite since educated people could be more likely to visit the doctor for regular heath checks, understand symptoms, and live in urban areas where people in general visit the doctor more often.

Response: We completely agree with the reviewer that SEP may have a complicated influence on the filling of prescriptions. We have elaborated a bit on this in the discussion section.

The potential reverse causality must be discussed and handled more carefully – potentially by selecting drugs related to diseases occurring only/mainly in older ages.

Response: We agree with the reviewer that reverse causality is a likely explanation with respect to drugs targeting the nervous system. For the other outcomes we think that this concern is less relevant. The fact that the association was attenuated for education but not for income supports this notion. The post hoc analysis of the association between SEP and subcategories of ATC-N drugs was carried to give some idea of what might be driving this particular association. It seems, however, that the association persisted for more or less all of the subcategories of ATC-N drugs.

Reviewer 2
Øyvind Næss

Use of medicines/prescription should be more clearlty linked to clinical outcomes. Which clinical conditions are these most used for in the Danish population?

Response: We completely agree with the reviewer that the organ-system classification of drugs is somewhat abstract. We have therefore included a supplementary table 1 that shows the most incident drug prescriptions in more detail in order to get a better idea of the related clinical outcomes.

The authors should express more clearly what they mean by "familial factors" both in the introduction and in the conclusion of the abstract.

Response: This is a good point. We have now explicated the term both in the abstract and in the introduction.

There is no theoretical discussion on how genetical factors may explain socioeconomic inequalities in health in general and with respect to the chosen outcomes in which prescription medicine are used as proxy for. I would guess these medicines are used for many well known chronic diseases in adulthood. The study is a bit at odd with theoretical papers on genetical explanations of socioeconomic inequalities in chronic diseases with complex genetical origin, see Holtzman or Mackenbach.

Response: The reviewer addresses an important point. In the introduction, we have now added a bit about how genetics and childhood environment might influence the association between SEP and health.

The increased attenuation in MZ compared to DZSS could just as equally be explained by the equal environment assumption being not valid here rather than genetical explanations having an important role for complex and chronic diseases such as CVD etc. This is not clearly discussed in the paper.

Response: Please see the revised discussion. We hope that the implications of the equal environment assumption are clearer now.

The study lacks a fundamental life course theoretical approach. In relation to this, the concept “familial factors” appears unprecise, though necessary given the chosen twin/sibling design.

Response: We completely agree with the reviewer that the life course approach is a fundamental assumption in this study. We have tried to make this more explicit both in the introduction and discussion section.

Table 4. It would be advantageous to have per unit increase estimates for both education and income for all outcomes. Also, p-values for intereaction on zygosity should be presented in table 4 and not only in the text.

Response: We have now made trend analyses (per unit increase). However, since linearity of the income variable was not supported by the data (Wald test: $p<0.000001$), estimates are not reported in table 4. In order not to compromise the readability of the table, we have also decided not to include the interaction parameters. We hope that the reviewer will appreciate this prioritisation.

The study is potentially very interesting and clearly written. The study seems to be analysed appropriately and is clearly written. It has a technically sofisticated approach, but I would welcome a clearer theoretical discussion and motivation. The concept "familial factors" including "shared" "unshared" and "genetical factors" should be contextualized with respect to specific diseases and their life course origin. There is hardly any reference to the large body of literature on childhood socioeconomic environment and chronic diseases in adulthood.

Response: Hopefully, the reviewer will find that the revised paper shows a more explicit link between the analysed drug prescriptions and potential clinical outcomes. In addition, references to the life course literature on early life factors and chronic diseases in adulthood have been added. This, however, is on a fairly general level, since a detailed discussion of each specific outcome seems to be beyond the scope of this more general paper.

Page 18. The authros report intra-pair correlation among twins and the population with reference to Frisell et al. How much was this intra-pair correlation?

Response: The intra-pair correlations have now been reported in the discussion.