PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Cardiovascular, antidepressant and immunosuppressive drug use in relation to risk of cutaneous melanoma: A protocol for a prospective case-control study
AUTHORS	Berge, Leon Alexander; Andreassen, Bettina; Stenehjem, Jo; Larsen, Inger; Furu, Kari; Juzeniene, Asta; Roscher, Ingrid; Heir, Trond; Green, Adele; Veierød, Marit; Robsahm, Trude

VERSION 1 – REVIEW

REVIEWER	Amelia K Smit The University of Sydney
REVIEW RETURNED	01-Aug-2018

GENERAL COMMENTS	This manuscript presents an interesting and well-designed prospective case-control study that aims to examine the associations between melanoma risk and cardiovascular, antidepressant and immunosuppressive drug use. The methods and analysis are well described and justified, and the benefits and limitations are identified. This study will make a timely contribution to the literature on melanoma risk factors and may help inform future improvements of melanoma prevention and early detection strategies.

REVIEWER	Caroline Watts The University of Sydney, Australia
REVIEW RETURNED	03-Aug-2018

GENERAL COMMENTS	Thank you for the opportunity to review this paper. It is pleasing to see research protocols published to know what is in the "pipeline". This topic is of interest given there are still research questions related to drug interactions and melanoma risk and using linked population-based data is a great way of addressing difficult questions. The protocol is comprehensive and for the most part clearly written. I have a few comments regarding the protocol and some minor comments where I feel clarification of text is required. 1. Given that UV exposure is a major risk factor for melanoma have the researchers considered calculating a lifetime cumulative UV dose based on address rather than using UV exposure based on place of residence at diagnosis? 2. In the introduction the authors note that there are several risk factors for melanoma however many of these risk factors will not be controlled for in the analysis. This limitation should be acknowledged. I agree that the timing of exposure regarding periods on drugs and latency time between medication use and melanoma diagnosis is also a limitation.

	3. Some people have more than one melanoma diagnosed. Could the authors explain how individuals with multiple reports of melanoma will be handled in the analysis. 4. I think examining interactions with immunosuppressive drugs will be the most challenging of the medication groups given there are many reasons for being immunosuppressed. Will your analysis of immunosuppressive drugs include cytokines? Will any information on any additional medications be collected to provide information on other concurrent medical conditions/ drug associations? Minor points 1. I was a little confused by the word parity on page 12 (52) and Page 15 (50) and wonder if the authors could clarify these statements. 2. Page 5 (33), “skin sensitivity”, could be better explained. I have provided several suggestions you might consider to describe this melanoma risk factor; sun sensitive skin, phenotypic characteristics or fair complexion. 3. Could the authors complete the sentence page 15 (41), Due to the skew distribution of …., and delete from Page 19 (37) “a running”, from the sentence “has received a running approval”

REVIEWER	Loes Hollestein Erasmus MC University Medical Center and Netherlands Comphrensive Cancer Organization, the Netherlands I work on a pharmacoepidemiological study regarding the use of anti-hypertensive drugs and keratinocyte cancer.
REVIEW RETURNED	23-Aug-2018

GENERAL COMMENTS	1.Is it possible to use an active comparator as control? i.e.use controls who were prescribed another type of drug, which is hypothesized not be associated with melanoma, but is administred for a similar indication. 2.The health care utilization between cases and controls is likely to be different and may also influence the probability of melanoma diagnosis. Could the authors match or control for health care utilization? E.g. number of different prescribed drugs, number of visits to medical specialist/GP or a comorbidity index? 3.The authors will perform lag time analyses, excluding 6 months of exposure time window before the development of melanoma. However, the lag time is unknown. I would recommend to test multiple latency periods, which are preferably longer. 4.Can the authors specify, which interaction terms they consider relevant? 5.Have the Norwegian Cancer Registry and Prescription database been transformed to the OMOP common data model? If so, the authors may consider to put the protocol on the OHDSI website in order to facilitate replication in different countries/databases. 6.The authors provide an overview of studies in supplementary tables. Was the search systematic? It seems that a few studies are missing, eg.: -McCourt C, Coleman H, Murray L et al. Beta-blocker usage after malignant melanoma diagnosis and survival: a population-based nested case–control study. Br J Dermatol 2014; 170:930–38. -Livingstone E, Hollestein LM, van Herk-Sukel MP et al. b-Blocker use and all-cause mortality of melanoma patients: results from a population-based Dutch cohort study. Eur J Cancer 2013; 49:3863–71. Both studies did not observe a statistically significant association.

	Please check if other studies are missing from the overviews presented in the supplementary tables and provide information regarding the literature search. 7.According to the RECORD statement, all codes that are used to define outcome, exposure, covariates should be reported. Possibly this can already be added as a supplement to the protocol.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:
This manuscript presents an interesting and well-designed prospective case-control study that aims to examine the associations between melanoma risk and cardiovascular, antidepressant and immunosuppressive drug use. The methods and analysis are well described and justified, and the benefits and limitations are identified. This study will make a timely contribution to the literature on melanoma risk factors and may help inform future improvements of melanoma prevention and early detection strategies.

Response: We sincerely thank for your positive comments.

Reviewer 2:
Thank you for the opportunity to review this paper. It is pleasing to see research protocols published to know what is in the "pipeline". This topic is of interest given there are still research questions related to drug interactions and melanoma risk and using linked population-based data is a great way of addressing difficult questions.
The protocol is comprehensive and for the most part clearly written. I have a few comments regarding the protocol and some minor comments where I feel clarification of text is required.

1. Given that UV exposure is a major risk factor for melanoma have the researchers considered calculating a lifetime cumulative UV dose based on address rather than using UV exposure based on place of residence at diagnosis?

Response: First, thank you first for your positive comments. Using data from the Norwegian Radiation Protection Authority, UV exposure will be calculated as a lifetime cumulative UV dose based on region-specific UV measurement stations in closest proximity to the address of each individual at time of diagnosis. This information is now given at page 13 (lines 4-6) in the revised manuscript, in addition to page 16 (lines 13-14). The relevant covariate is now termed as "residential ambient UV exposure", throughout the manuscript.

2. In the introduction the authors note that there are several risk factors for melanoma however many of these risk factors will not be controlled for in the analysis. This limitation should be acknowledged. I agree that the timing of exposure regarding periods on drugs and latency time between medication use and melanoma diagnosis is also a limitation.

Response: To more precisely acknowledge risk factors which will not be accounted for in the analysis, this sentence has been changed an now reads as follows: "Additionally, while we will adjust for residential ambient UV exposure, we will not be able to account for other UV exposure variables such as recreational sun exposure, sunburns (as a marker of episodes of severe acute UV exposure) or indoor tanning. Neither will we be able to take phenotypic characteristics (fair complexion, freckles and nevi), socioeconomic variables (e.g. education, occupation), postmenopausal hormone use and anthropometric factors into account,..." (see page 20, lines 5-11)

3. Some people have more than one melanoma diagnosed. Could the authors explain how individuals with multiple reports of melanoma will be handled in the analysis.

Response: Any case with two or more simultaneous diagnoses of melanoma will be removed from the main analysis alongside their respective controls. These cases and their respective controls can be subject to a separate additional analysis given that their number facilitates a statistical analysis of sufficient power. This information is given in the revised manuscript; see page 14 (lines 2-5).

4. I think examining interactions with immunosuppressive drugs will be the most challenging of the medication groups given there are many reasons for being immunosuppressed. Will your analysis of immunosuppressive drugs include cytokines?

Response: We agree with the reviewer, that this will be a challenging part of our study. Unfortunately, our material will not include information about cytokines. Neither will we have access to data that can indicate reasons for immunosuppression therapy. We are aware however; that there are many different indications for treatment with immunosuppressant drugs which may represent a source of confounding (assuming the disease itself may influence cancer risk). We have therefore included potential confounding by indication as an additional limitation, see page 19 (lines 13-14).

5. Will any information on any additional medications be collected to provide information on other concurrent medical conditions/ drug associations?

Response: The data on drug use that will be available for this study will only encompass cardiovascular, antidepressant and immunosuppressive drug types. While we will be able to account for use of these drug types in all analyses, we unfortunately do not have information pertaining to other drug types that could provide information on any concurrent medial conditions or drug associations relevant for the analysis. This is now emphasized in the revised manuscript on page 19 (lines 14-16).

Minor points
1. I was a little confused by the word parity on page 12 (52) and Page 15 (50) and wonder if the authors could clarify these statements.

Response: To clarify this, “number of births” has now replaced the word parity; this more descriptive terminology defines the number of births experienced up until the point of diagnosis (case)/index date (control). Changes have been made at page 2 (line 23), page 11 (lines 3-4), page 13 (lines 8-9) and page 16 (line 14 and 16).

2. Page 5 (33), “skin sensitivity”, could be better explained. I have provided several suggestions you might consider to describe this melanoma risk factor; sun sensitive skin, phenotypic characteristics or fair complexion.

Response: The term “skin sensitivity” is replaced with “phenotypic characteristics” on page 2 (lines 8-9), page 5 (line 13) and page 20 (lines 8-9).

3. Could the authors complete the sentence page 15 (41), Due to the skew distribution of …., and delete from Page 19 (37) “a running”, from the sentence “has received a running approval”

Response: The relevant sentence, now on page 16 (lines 11-12) has been revised to specifically mention Breslow thickness as the covariate in question. The words “a running” have been deleted from the relevant sentence on page 20 (line 17).

Reviewer: 3

1. Is it possible to use an active comparator as control? i.e. use controls who were prescribed another type of drug, which is hypothesized not be associated with melanoma, but is administered for a similar indication.

Response: Thank you for your valuable comment. For any given Anatomical Therapeutic Chemical (ATC) 2nd level, we also intend to categorize by pharmacological subgroups (ATC 4th level) and chemical substances (ATC 5th level). Thus, depending on the availability and statistical power, we will perform comparisons between drug subgroups. Where applicable, this will enable us to use active comparators as controls for specific agent of interest. This information is now given on page 15 (lines 1-7).

2. The health care utilization between cases and controls is likely to be different and may also influence the probability of melanoma diagnosis. Could the authors match or control for health care utilization? E.g. number of different prescribed drugs, number of visits to medical specialist/GP or a comorbidity index?

Response: Unfortunately, we do not have information on health care utilization, including the number of visits to medical specialist/GP. Lack of information about health care utilization and comorbidity has been emphasized as limitations, see page 20 (line 10).

3. The authors will perform lag time analyses, excluding 6 months of exposure time window before the development of melanoma. However, the lag time is unknown. I would recommend to test multiple latency periods, which are preferably longer.

Response: To account for reverse-causation bias due to drug latency effects we initially suggested to use 6 months, as the recent study by Pottegård & Hallas (Pharmacoepidemiology and drug safety 2017: 26: 223-7) estimated the duration of lag-time needed to be at least 6 months. However, we agree with the reviewer's assertion that the lag time is unknown. Therefore, in our effort to avoid reverse causation bias, we will conduct analyses with a lag-time of 1, 3 and 5 years. This information is given on page 15 (line 13).

4. Can the authors specify, which interaction terms they consider relevant?

Response: To extend upon the rather short sentence, potential interactions between covariates that are to be considered for the analyses have been suggested (sex/drugs, urban or rural residence/drugs and number of children/drugs) on page 16 (lines 17-18)

5. Have the Norwegian Cancer Registry and Prescription database been transformed to the OMOP common data model? If so, the authors may consider to put the protocol on the OHDSI website in order to facilitate replication in different countries/databases.

Response: The Norwegian Cancer Registry and Prescription Database have not been transformed to the OMOP data model.

6. The authors provide an overview of studies in supplementary tables. Was the search systematic? It seems that a few studies are missing, eg.:
-McCourt C, Coleman H, Murray L et al. Beta-blocker usage after malignant melanoma diagnosis and survival: a population-based nested case–control study. Br J Dermatol 2014; 170:930–38.
-Livingstone E, Hollestein LM, van Herk-Sukel MP et al. b-Blocker use and all-cause mortality of melanoma patients: results from a population-based Dutch cohort study. Eur J Cancer 2013; 49:3863–71.
Both studies did not observe a statistically significant association.

Please check if other studies are missing from the overviews presented in the supplementary tables and provide information regarding the literature search.

Response: The search was not systematic in nature (according to PRISMA etc.) and not akin to those featured in meta-analyses or systematic reviews. While interesting, the two articles mentioned by the reviewer concerns drug use after the cancer diagnosis and are thus not relevant as the study proposed considers pre-diagnostic drug use. We have however, seen fit to include two additional papers to the supplementary materials, concerning pre-diagnostic use of cardiovascular drugs (see supplementary table S1).

7. According to the RECORD statement, all codes that are used to define outcome, exposure, covariates should be reported. Possibly this can already be added as a supplement to the protocol.

Response: Additional codes that define outcome and exposure have been added to the supplementary section of the revised protocol manuscript (see supplementary table S4). These include ICD codes for the cancer diagnoses (including melanoma sub-types and anatomical location), as well as the ATC codes for the relevant drug types. Other covariates that will be included in the proposed analyses are not defined by any pre-determined code system.

VERSION 2 – REVIEW

REVIEWER	Caroline Watts University of Sydney, Australia and University of New South Wales, Australia
REVIEW RETURNED	27-Nov-2018

GENERAL COMMENTS	Thank you for addressing my comments, and I look forward to reading about your findings in the future.

REVIEWER	Dr. L.M. Hollestein dept. Dermatology, Erasmus University Medical Center, Rotterdam, The Netherlands
REVIEW RETURNED	10-Dec-2018

GENERAL COMMENTS	I suggested to adjust for health care utilization, but the authors state that they do not have such a measurement, such as number of visits to a doctor. However, the prescription database contains all prescriptions. Therefore, I think that they can use number of different ATC codes (any ATC code) prescribed as a proxy for health care utilization. (Number of different drugs prescribed and number of health care visits are likely highly correlated). I think that this will remove at least some part of the confounding. Therefore I advise the authors to include number of different ATC codes (any) within a fixed period before indexdate as covariate. The authors responded sufficiently to all my other questions.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
Thank you for addressing my comments, and I look forward to reading about your findings in the future.

Response: We are happy we were able to answer all your questions satisfactorily; we sincerely thank you for your positive comments.

Reviewer: 3

I suggested to adjust for health care utilization, but the authors state that they do not have such a measurement, such as number of visits to a doctor. However, the prescription database contains all prescriptions. Therefore, I think that they can use number of different ATC codes (any ATC code) prescribed as a proxy for health care utilization. (Number of different drugs prescribed and number of health care visits are likely highly correlated). I think that this will remove at least some part of the confounding. Therefore I advise the authors to include number of different ATC codes (any) within a fixed period before indexdate as covariate.

The authors responded sufficiently to all my other questions.

Response: Thank you for your comment. Based on this, we applied and have now been granted permission to acquire information about additional drug use, which can be used as a covariate in the statistical analyses. This new variable will also act as proxy indicator for general health care usage. Additional information about this has been given in the revised manuscript on page 12 (lines 19-22), page 15 (lines 4-7) and page 19 (lines 10-15).