PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Cohort profile: The Finnish Genetics of Pre-eclampsia Consortium (FINNPEC)
AUTHORS	Jääskeläinen, Tiina; Heinonen, Seppo; Kajantie, E; Kere, Juha; Kivinen, Katja; Pouta, Anneli; Laivuori, Hannele

VERSION 1 - REVIEW

REVIEWER	Reynir Tómas Geirsson, prof.em. Univ. Dept. of Obstetrics and Gynecology, Landspitali University Hospital/University of Iceland, Hringbraut, 101 Reykjavik, Iceland None direct and none financial, but I am a member of a collaborating group in Iceland (Interpreggen. org).
REVIEW RETURNED	12-Jul-2016

GENERAL COMMENTS	The objective of this manuscript/article is to introduce an ongoing study, and thus also to serve as a basic reference for future articles that may come out of the FINNPEC study and possibly through collaborative national and international studies. The study has advantages, in particular through a largely prospective design and reasonably clear definitions used, and by the emphasis of collecting triads and material for biobanking. There are established links to two major data collection efforts already in existence for the study of genetics in pregnancy hypertension and there are also inbuilt possibilities to pursue the currently prevalent interests in associations with cardiovascular and medical complications in later life. Such wider collaborative efforts are necessary because the data collection in the FINNPEC study is as yet not of sufficient strength for much of what it is proposed to achieve on it´s own, - this will only materialize through international collaboration. Cross-linking possibilities to the well established and well run Finnish national databases on health and to sociologic determinants are good. The personal identification number is though not unique to Finland as it is also in use in all the 27 million populations of the Nordic countries. There are already articles published where use of this material has been included and thus the contents of this article may have been at least partly described. The results given in this study overview are of a general and epidemiological nature and are contained in the description of the material. As such they do not encompass new information. The objective here is to describe the currently collected material, but "currently" could be described better, i.a. to what date the material extends.

	There are limitations, which are to some extent discussed by the authors. They rightly mention a skewness produced by the cases only coming from university hospitals. This means that there is a predelection for more severe cases as seen from the high number of HELLP cases, but at the same time there is an overlap with the controls (some of which are excluded case selections = borderline cases). This will tend to lessen distinction between cases and controls. One wonders why there was not an attempt to include all cases in Finland and to at least double the number of controls clearly selected on the basis of normality. However, there are some further concerns. Why were the ACOG and not the ISSHP criteria used in principle? Why is the retrospective part included and not kept as a separate material? Are the cases well enough categorized to allow necessary subdivision (such as with regard to underlying medical diseases/conditions)? It seems so at first glance, but much of the present information is based on questionnaires and thus open to recall bias, since as yet verification through the actual patient records has not been completed. Publication might have been deferred until this is complete. It could be clearer how the controls (next patient delivering after the case) are selected, such as with regard to parity, age and BMI. Some stratification for factors such as these might have been justifiable, i.a. because the controls might be a rather mixed group. To have objective measures of weight and height (BMI) would have been valuable. The definition of small-for-gestational age is based on an old Finnish reference standard where gestational age was probably largely based on last menstrual period recall. Third trimester blood sampling really includes much of the second trimester which will reduce the value of some of the blood samples collected as they will be more difficult to interpret. So on the one hand it would have been an advantage to include the whole Finnish population for the case selection and double the controls (more of a work input), perhaps at the expense of collecting fewer and more reliable variables by questionnaire (= lesser collection and evaluation work), and standardizing the blood collections better. The blood is collected for genetic studies, but perhaps also for measuring predictive factors, angiogenic and blood pressure determinants and so on, when timing matters. Yet it must be acknowledged that a large unselected material can also have epidemiological advantages. The English can in places be improved (has Finnish hallmarks). The manuscript could be shortened and focused better on description of the study and study material, on results of the present initial comparison of cases and controls and on keeping discussion elements better separate.

REVIEWER	János Rigó Jr. Semmelweis University 1st Department of OB/GYN Hungary
REVIEW RETURNED	15-Jul-2016

GENERAL COMMENTS	A very interesting paper aiming to summarize a big amount of clinical information in PE: As the authors mention in their paper, it is a strength of this study that patients were recruited in five different tertiary centers in Finland.

	The data are represented in excellent tables, and the text itself tries to give a mostly detailed background for the analysis of the results. The Introduction communicates the most important information about PE, though it misses to concentrate on the significance of clinical data, which are interpreted in the Results section without highlighting their importance. The greatest problem of this paper, that a plenty of data, which are interpreted in the Tables, may yield an excellent opportunity to discuss them, to make hypotheses based on them or at least to show directions for further research on the area of PE. Also screening protocols could be based on these wide-scale results, which could be useful in the daily clinical practice. Unfortunately the authors miss this opportunity, so it would worth to reconsider this issue. Detailed remarks: In the Intro section the authors highlight the etiological role of immunologic and angiogenetic factors in PE, though they miss to give more information about them. I think a few more sentence would lift the worth of the paper. Generally a bit more about the genetic components of the complex etiology in PE would make sense. In the Cohort description it is not perfectly clear, what were the exclusion criteria. The authors do not state, whether other pathological conditions in pregnancy (e.g. gestational diabetes), or prepregnancy conditions (endocrine problems etc.) had influenced their inclusion into the study sample or not. On page 6 the authors mention more than 500 variables concerning clinical data; I think a few of them, or at least the most important data-groups should be mentioned in this section. On page 7 the authors write about blood sampling in the first and third trimester. It must be declared in which gestational age range were the blood samples collected. The authors must also be clear whether they made a differentiation of the placenta samples coming from vaginal deliveries vs. C-sections or not. I think the frequently associating IUGR should be also discussed in this study. What was its prevalence, which group of PE patients were strongly predisposed for IUGR etc. Which are the candidate genes mentioned on page 10? In summary: a promising paper with numerous strengths, which could be considered for publication after a revision based on the suggestions.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Reynir Tómas Geirsson, prof.em.
Institution and Country: Univ. Dept. of Obstetrics and Gynecology, Landspitali University Hospital/University of Iceland, Hringbraut, 101 Reykjavik, Iceland Competing Interests: None direct and none financial, but I am a member of a collaborating group in Iceland (Interpreggen. org).

The objective of this manuscript/article is to introduce an ongoing study, and thus also to serve as a basic reference for future articles that may come out of the FINNPEC study and possibly through collaborative national and international studies. The study has advantages, in particular through a largely prospective design and reasonably clear definitions used, and by the emphasis of collecting triads and material for biobanking. There are established links to two major data collection efforts already in existence for the study of genetics in pregnancy hypertension and there are also inbuilt possibilities to pursue the currently prevalent interests in associations with cardiovascular and medical complications in later life. Such wider collaborative efforts are necessary because the data collection in the FINNPEC study is as yet not of sufficient strength for much of what it is proposed to achieve on it´s own, - this will only materialize through international collaboration. Cross-linking possibilities to the well established and well run Finnish national databases on health and to sociologic determinants are good. The personal identification number is though not unique to Finland as it is also in use in all the 27 million populations of the Nordic countries.
There are already articles published where use of this material has been included and thus the contents of this article may have been at least partly described. The results given in this study overview are of a general and epidemiological nature and are contained in the description of the material. As such they do not encompass new information. The objective here is to describe the currently collected material, but "currently" could be described better, i.a. to what date the material extends.
There are limitations, which are to some extent discussed by the authors. They rightly mention a skewness produced by the cases only coming from university hospitals. This means that there is a preselection for more severe cases as seen from the high number of HELLP cases, but at the same time there is an overlap with the controls (some of which are excluded case selections = borderline cases). This will tend to lessen distinction between cases and controls. One wonders why there was not an attempt to include all cases in Finland and to at least double the number of controls clearly selected on the basis of normality.

Response: We kindly thank Prof. Geirsson for the careful review and constructive feedback about our manuscript. Please find our detailed point-by-point responses below.

However, there are some further concerns. Why were the ACOG and not the ISSHP criteria used in principle?
Response: Indeed this was a difficult decision, because there has never been a definite consensus of the diagnostic criteria. ACOG 2002 was chosen, because it was the most recent definition at the time when the study was designed.

Why is the retrospective part included and not kept as a separate material?
Response: Recruitment for the prospective arm of the FINNPEC was already ongoing when the decision to start the retrospective arm was made. Aim was to increase the number of pre-eclamptic women and DNA samples. It is certainly possible to study these two arms separately in the future studies when indicated.

Are the cases well enough categorized to allow necessary subdivision (such as with regard to underlying medical diseases/conditions)? It seems so at first glance, but much of the present information is based on questionnaires and thus open to recall bias, since as yet verification through

the actual patient records has not been completed. Publication might have been deferred until this is complete.
Response: We consider data on pregnancy and medical diseases/conditions very reliable since each diagnosis was ascertained from hospital records and confirmed independently by a research nurse and a study physician (lines 166-67 in the highlighted version). We think that the most essential questionnaire based information to be verified is personal history of PE. This work is still ongoing and unfortunately data is not available yet.

It could be clearer how the controls (next patient delivering after the case) are selected, such as with regard to parity, age and BMI. Some stratification for factors such as these might have been justifiable, i.a. because the controls might be a rather mixed group.
Response: The controls were recruited from the same hospital as soon as possible after a pre-eclamptic woman was recruited. The only exclusion criteria were multiple pregnancy, maternal age less than 18 years and inability to provide an informed consent based on information in Finnish or Swedish. Thus, the controls indeed were a mixed group of patients. However, the detailed phenotyping of controls makes possible to distinguish important non-pre-eclamptic subgroups, e.g. women with gestational hypertension or chronic hypertension without superimposed pre-eclampsia.

To have objective measures of weight and height (BMI) would have been valuable.
Response: We have concentrated on pre-pregnancy BMI and thus we need to rely on self-reported information. For the prospective arm we now compared the information obtained from the maternity cards and background questionnaires and mean BMI for maternity cards was 24.8±4.9 and 24.6±4.8 from questionnaires.

The definition of small-for-gestational age is based on an old Finnish reference standard where gestational age was probably largely based on last menstrual period recall.
Response: At the time when the cohort was recruited (1990-2008), Pihkala et al. (1989) was the only Finnish reference standard available. We are aware of recently published new references (Sankilampi U et al./Ann Med 2013;45:446-54) and we will compare these two references in the FINNPEC cohort.

Third trimester blood sampling really includes much of the second trimester which will reduce the value of some of the blood samples collected as they will be more difficult to interpret.
Response: There were only five samples drawn at second trimester (below 27+6 weeks of gestation). These mothers suffered from severe form of the disease and delivered before third trimester. Gestational weeks at sampling will be taken into account in future studies as a confounding factor e.g. in relation to angiogenic markers.

So on the one hand it would have been an advantage to include the whole Finnish population for the case selection and double the controls (more of a work input), perhaps at the expense of collecting fewer and more reliable variables by questionnaire (= lesser collection and evaluation work), and standardizing the blood collections better.
The blood is collected for genetic studies, but perhaps also for measuring predictive factors, angiogenic and blood pressure determinants and so on, when timing matters. Yet it must be acknowledged that a large unselected material can also have epidemiological advantages.
Response: We agree that the collection of all cases in Finland would have provided more informative approach to study the diversity of the pathology presented in pre-eclampsia. Furthermore, a large unselected material would have had more epidemiological advantages. However, the available resources were limited and it was decided to focus on all five university hospitals. Particularly the ascertainment of the outcome based on hospital records was very laborious method for a research nurse and study physicians. This has now been commented on lines 332-33.
Angiogenic markers have now been analysed and manuscript is under preparation. Furthermore, metabolomics analyses are currently undergoing. Please see lines 259-62 in the manuscript.

The English can in places be improved (has Finnish hallmarks). The manuscript could be shortened and focused better on description of the study and study material, on results of the present initial comparison of cases and controls and on keeping discussion elements better separate.
Response: We apologise for the grammatical errors. Language review has now been performed. We hope that the changes made in the manuscript clarify the description of study material and methods. Since Reviewer 2 asked to deepen the Discussion section, we have not shortened that part.

Reviewer: 2
Reviewer Name: János Rigó Jr.
Institution and Country: Semmelweis University, 1st Department of OB/GYN, Hungary Competing Interests: None declared

A very interesting paper aiming to summarize a big amount of clinical information in PE: As the authors mention in their paper, it is a strength of this study that patients were recruited in five different tertiary centers in Finland.
The data are represented in excellent tables, and the text itself tries to give a mostly detailed background for the analysis of the results.

Response: We would like to thank Dr. Rigó for constructive comments and careful review of the manuscript. Please find our point-by-point responses below and the changes in the manuscript.

The Introduction communicates the most important information about PE, though it misses to concentrate on the significance of clinical data, which are interpreted in the Results section without highlighting their importance.
Response: We have now modified the Introduction section (please see lines 89-95) and underscored the various clinical manifestations of the disease.

The greatest problem of this paper, that a plenty of data, which are interpreted in the Tables, may yield an excellent opportunity to discuss them, to make hypotheses based on them or at least to show directions for further research on the area of PE. Also screening protocols could be based on these wide-scale results, which could be useful in the daily clinical practice. Unfortunately the authors miss this opportunity, so it would worth to reconsider this issue.
Response: Aim of this paper as a cohort description is to serve as a reference for the future studies. We agree with the Reviewer and hope that future papers of FINNPEC will cover deeper discussion (e.g. the manuscript on angiogenic markers is under preparation and is expected to be submitted soon).

Detailed remarks:

In the Intro section the authors highlight the etiological role of immunologic and angiogenetic factors in PE, though they miss to give more information about them. I think a few more sentence would lift the worth of the paper.
Generally a bit more about the genetic components of the complex etiology in PE would make sense.
Response: We have now modified Introduction section and provided more information on the role of angiogenic and immunologic factors in pre-eclampsia, please see lines 100-105. Furthermore, we have now described the role of genetic components in pre-eclampsia in more detail, on lines 110-15.

In the Cohort description it is not perfectly clear, what were the exclusion criteria. The authors do not state, whether other pathological conditions in pregnancy (e.g. gestational diabetes), or prepregnancy conditions (endocrine problems etc.) had influenced their inclusion into the study sample or not.
Response: The only exclusion criteria were multiple pregnancy, maternal age less than 18 years and

inability to provide an informed consent based on information in Finnish or Swedish.
Thus, the controls indeed were a mixed group of patients. However, the detailed phenotyping of controls makes possible take into account pathological conditions.

On page 6 the authors mention more than 500 variables concerning clinical data; I think a few of them, or at least the most important data-groups should be mentioned in this section.
Response: The most important data categories are: medical history, family history, obstetric history, pregnancy complications, pregnancy outcome, proteinuria, blood pressure, laboratory measurements, information on delivery and newborn. We have added these data-groups also on lines 174-76.

On page 7 the authors write about blood sampling in the first and third trimester. It must be declared in which gestational age range were the blood samples collected.
Response: We have now added the ranges of sampling weeks on lines 202-3 Furthermore, we have separate number of antepartum, at delivery and postpartum serum samples from third trimester in Table 1

The authors must also be clear whether they made a differentiation of the placenta samples coming from vaginal deliveries vs. C-sections or not.
Response: We have very detailed information on delivery and sampling of placenta, e.g. contractions and medication. There were no differences in sample handling according to the mode of delivery. However, it will be taken account in placental studies. Please see below the summary.

Vaginal delivery (including vacuum extraction):
Pre-eclampsia (PE): 35
Control: 41
Elective C-section with labour:
PE: 13
Control:18
Acute C-section*:
PE:52
Control:18
Emergency C-section*:
PE:1
Control:1
*with or without contractions

I think the frequently associating IUGR should be also discussed in this study. What was its prevalence, which group of PE patients were strongly predisposed for IUGR etc.
Response: There were 302/1148 (26.3%) pre-eclamptic mothers who had SGA newborn. We thank reviewer for excellent suggestion to study further this subgroup.

Which are the candidate genes mentioned on page 10?
Response: We have now added the gene names on line 254-55.

VERSION 2 – REVIEW

REVIEWER	Reynir Tómas Geirsson prof. em. Univ. Dept. of Obstetrics and Gynecology, Landspitali University Hospital/University of Iceland, Hringbraut, 101 Reykjavik, Iceland None direct and none financial, but I am a member of a collaborating

	group in Iceland (Interpreggen. org).
REVIEW RETURNED	28-Sep-2016

GENERAL COMMENTS	In general the manuscript has seen notable improvements and it´s publication would be a benefit after some additional considerations and corrections as detailed here below. The English still has hallmarks of Finnish where in the latter language definite and indefinite articles do not exist in the same form as used in English. In manuscripts from Finland this is often the case. Here either the authors should provide a new version read through by a native English speaker with knowledge of medical English, or the journal may elect do this. Introduction, line 91-92 "....led to inconsistent results in studies that have attempted to understand PE on the basis of a single pathogenetic hypothesis" = studies do not attempt to understand anything by themselves, so this should be phrased better. In lines 124-126 it is also too much to say that "The study represents a prospective cohort design with detailed clinical outcome information allowing to define accurately the subphenotypes of PE", because the authors have yet to show that their study will allow better phenotype definitions, let alone allow subphenotype definitions to be made (it is characterization, not definition). But on the whole the Introduction reads better and is better constructed. On the material: In lines 135-136 it says "...University Hospitals in ..." = small capitals should be used unless one is naming a particular university hospital. Lines 137-139 = I still find it insufficient to just say of the control group that "the next woman with a non-pre-eclamptic pregnancy attending the same clinic was recruited as a control subject". This is lacking in detail and thus open to suspicion of selection bias. If that was the case then the authors should make the existence of such a bias clear. Who selected and how? "Next" is imprecise. Then I do not like to call women or people for that matter, "subjects". This word is usually unnecessary and to me rather degrading when discussing study participants (women, individuals, patients are accepable alternatives where needed). Line 140: here IUGR is not defined when it should be. Line 148: does the journal not require the authors to state the ethical approval number ? Line 157: here it says that control women were "...all other pregnant women...." when above it says "the next". Please make sure this is aligned and information is not duplicated. Either it is "all" or "next". Lines 185-186: Here SGA is defined and if this equates to IUGR it should be stated here. Line 193: state whether "...all subjects..." refers to all mothers, all babies and all fathers as appropriate, in order to clarify who had blood samples and who did not, including presumably cord blood. Lines 212-213: "As expected, older age, obesity, and preexisting medical conditions (e.g. chronic hypertension, type1 diabetes, and gestational diabetes) place women at increased risk for PE (table 2)." Is this not a Result or as the authors call it "Findings to date"? If it is not then such a statement might need a reference and the use of the past tense. The same goes for this whole section on Basic characteristics, which really is a mix of Results and Discussion elements. The manuscript would benefit from separating this fully, but the journal editors must also advise what is acceptable format

	here. In lines 239-241 the authors say that "There is a robust body of literature that consistently has demonstrated a reduced risk of PE in women who smoke when they are pregnant. Accordingly, in the FINNPEC Study, controls were more often smokers". Here again is this mix of results and a discussion element. The word "literature" in English has a somewhat different meaning in English than in Scandinavian langauges (in English this refers to what in Swedish would be called "skönlitteratur" or prose in English). It is surely clear in enough to talk about "published articles" or just articles or use similar terminology). "Accordingly etc...." does not follow directly from the former sentence, as this is unrelated and the "robust" in line 239 contrasts with the "trend" in line 244. This can easily be adjusted. Findings to date: I think the authors still have to show how "valuable" (line 250) their data will be. It is not necessary to use this adjective as all knowledgable readers will realize the value of the material as a future resource for research in PE. Line 266: "those participants that..." should be "those participants who...". Line 282: Again I object to "...the unique Finnish personal identification numbers", since they are not unique, - they are also used in Denmark, Iceland, Norway and Sweden, i.e. by another 22+ million people. Line 297: "excellent" and similar adjectives are often used by authors to try to enhance interest in what they are writing about. This is usually not necessary and presumes that the reader can not by himself/herself realize the value of what is being said. The reader will be able to decide for himself/herself on what is excellent, interesting, valuable and so on. Modesty often pays off in the long run, not least when something unknown and set in the future is being discussed. Describing the study as "large/llarger/largest" is, however, often justified and here it is. Line 307-308: "These findings suggest that demands for diagnostic criteria are different for the purpose....and purpose" Is this not more than the data collections described by the authors can suggest at this point in time?

REVIEWER	János Rigó Jr. Semmelweis University, Budapest, 1st Department of OB/GYN
REVIEW RETURNED	25-Sep-2016

GENERAL COMMENTS	Based on the performed changes according the suggestions, the paper is now acceptable for publication.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Reynir Tómas Geirsson prof. em.
Institution and Country: Univ. Dept. of Obstetrics and Gynecology, Landspitali University Hospital/University of Iceland, Hringbraut, 101 Reykjavik, Iceland
Competing Interests: None direct and none financial, but I am a member of a collaborating group in Iceland (Interpreggen. org).
In general the manuscript has seen notable improvements and it´s publication would be a benefit after

some additional considerations and corrections as detailed here below.
The English still has hallmarks of Finnish where in the latter language definite and indefinite articles do not exist in the same form as used in English. In manuscripts from Finland this is often the case. Here either the authors should provide a new version read through by a native English speaker with knowledge of medical English, or the journal may elect do this.
Response: A native English speaker with knowledge of medical English has now read the article and we've modified the manuscript further.

Introduction, line 91-92 "....led to inconsistent results in studies that have attempted to understand PE on the basis of a single pathogenetic hypothesis" = studies do not attempt to understand anything by themselves, so this should be phrased better.
Response: We've now rephrased the sentence, please find lines 89-91.

In lines 124-126 it is also too much to say that "The study represents a prospective cohort design with detailed clinical outcome information allowing to define accurately the subphenotypes of PE", because the authors have yet to show that their study will allow better phenotype definitions, let alone allow subphenotype definitions to be made (it is characterization, not definition). But on the whole the Introduction reads better and is better constructed.
Response: We have now replaced "define" with "characterise".

On the material: In lines 135-136 it says "...University Hospitals in ..." = small capitals should be used unless one is naming a particular university hospital.
Response: This has now been corrected.

Lines 137-139 = I still find it insufficient to just say of the control group that "the next woman with a non-pre-eclamptic pregnancy attending the same clinic was recruited as a control subject". This is lacking in detail and thus open to suspicion of selection bias. If that was the case then the authors should make the existence of such a bias clear. Who selected and how? "Next" is imprecise.
Response: Recruitment of control subjects was done at the antenatal ward after pre-eclamptic mother was recruited. Study nurse approached for non-pre-eclamptic mother whose condition was rather stable (e.g. no severe bleeding or life-threatening fetal diagnosis). Obviously this could have caused selection bias but as described in the manuscript controls had various other conditions, like gestational diabetes etc. We have now deleted "next" in the manuscript.

Then I do not like to call women or people for that matter, "subjects". This word is usually unnecessary and to me rather degrading when discussing study participants (women, individuals, patients are acceptable alternatives where needed).
Response: "Subject(s)" has now been replaced by other expression

Line 140: here IUGR is not defined when it should be.
Response: We have now deleted "IUGR" in the manuscript since the recruitment was actually done based on placental insufficiency.

Line 148: does the journal not require the authors to state the ethical approval number?
Response: 149/EO/2007 has now been added, please see line 147.

Line 157: here it says that control women were "...all other pregnant women...." when above it says "the next". Please make sure this is aligned and information is not duplicated. Either it is "all" or "next".
Response: This has now been rephrased, please see line 155-8.

Lines 185-186: Here SGA is defined and if this equates to IUGR it should be stated here.
Response: Please see response above, "IUGR" has been deleted now.

Line 193: state whether "...all subjects..." refers to all mothers, all babies and all fathers as appropriate, in order to clarify who had blood samples and who did not, including presumably cord blood.
Response: “All subjects have” now been replaced by “mothers and fathers”. Cord blood and cord plasma have been mentioned on line 202.

Lines 212-213: "As expected, older age, obesity, and preexisting medical conditions (e.g. chronic hypertension, type1 diabetes, and gestational diabetes) place women at increased risk for PE (table 2)." Is this not a Result or as the authors call it "Findings to date"? If it is not then such a statement might need a reference and the use of the past tense. The same goes for this whole section on Basic characteristics, which really is a mix of Results and Discussion elements. The manuscript would benefit from separating this fully, but the journal editors must also advise what is acceptable format here. In lines 239-241 the authors say that "There is a robust body of literature that consistently has demonstrated a reduced risk of PE in women who smoke when they are pregnant. Accordingly, in the FINNPEC Study, controls were more often smokers". Here again is this mix of results and a discussion element. The word "literature" in English has a somewhat different meaning in English than in Scandinavian langauges (in English this refers to what in Swedish would be called "skönlitteratur" or prose in English). It is surely clear in enough to talk about "published articles" or just articles or use similar terminology). "Accordingly etc...." does not follow directly from the former sentence, as this is unrelated and the "robust" in line 239 contrasts with the "trend" in line 244. This can easily be adjusted.
Response: We have now modified the paragraph and avoided to include Discussion elements in the Results section. The word “literature” does not exist anymore.

Findings to date: I think the authors still have to show how "valuable" (line 250) their data will be. It is not necessary to use this adjective as all knowledgable readers will realize the value of the material as a future resource for research in PE.
Response: “Valuable” has now been deleted.

Line 266: "those participants that..." should be "those participants who...".
Response: This has now been corrected.

Line 282: Again I object to "...the unique Finnish personal identification numbers", since they are not unique, - they are also used in Denmark, Iceland, Norway and Sweden, i.e. by another 22+ million people.
Response: “Unique” has now been deleted.

Line 297: "excellent" and similar adjectives are often used by authors to try to enhance interest in what they are writing about. This is usually not necessary and presumes that the reader cannot by himself/herself realize the value of what is being said. The reader will be able to decide for himself/herself on what is excellent, interesting, valuable and so on. Modesty often pays off in the long run, not least when something unknown and set in the future is being discussed. Describing the study as "large/llarger/largest" is, however, often justified and here it is.
Response: Use of superlatives has now been diminished.

Line 307-308: "These findings suggest that demands for diagnostic criteria are different for the purpose....and purpose" Is this not more than the data collections described by the authors can suggest at this point in time?
Response: The reviewer is right and we have removed the text.