Author's response to reviews

Title: Factors affecting the uptake of prenatal screening tests for congenital anomalies; a multicentre prospective cohort study

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Author's response to reviews: see over
Dear Editor,

Thank you very much for the expert review of our manuscript entitled ‘Factors affecting the uptake of prenatal screening tests for congenital anomalies; a multicentre prospective cohort study’ MS: 1926747913119132.

We would like to thank the reviewers for their positive and constructive comments on our paper. We have used the reviewers comments to further improve our paper and we are pleased to hereby send you our revised manuscript. We were able to address all comments.

Hereafter we provide more detailed information on how we address the comments made by the two referees. We have copied the referees’ comments and provide our reactions after each comment in italics. The actual changes included in the manuscript are then provided in bold text.

**Referee 1**

Overall, this is a very well written paper with reasonable sample size involving multiple centers within a country.

*We thank the referee for this positive comment.*

Minor essential revisions for the following points:

1. Of 5216 participants, 23% had CT and 90% had FAS. Therefore, some women must have undergone both CT & FAS. It follows that the experience of women with CT and the result of CT (eg the numerical risk is borderline but the overall result is negative) could be an important factor affecting women's decision to undergo FAS. This was NOT addressed by the paper.

We thank the reviewer for this observation. Indeed, theoretically the experience and the result of the CT could influence women’s decision to undergo the FAS. From a clinical perspective, the FAS is not a confirming test for the CT. The CT is mainly focused on Down’s Syndrome as the FAS is focused on structural anomalies (e.g. spina bifida and heart disorders). Therefore,
it seems not likely that the result of the CT in our study strongly influenced women decision-making on opting for the FAS. We decided to leave this topic out of the paper.

2. The gestation at entry to pregnancy care was not mentioned. This is important because CT is not applicable to women seeking pregnancy care after the first trimester. These women might have completed all the questionnaires and be included in this study. It might turn out that the low CT uptake rate was due to women attending practices too late. ANY need for separate Chi square test?

We thank the referee for this observation. We did not ask the participants about the time of the first visit, so we do not know how many participants were too late in care to have the CT. A recent study showed that most pregnant women enter midwifery care around 9 weeks of gestation (Martin et al., 2013a). Therefore, we added a sentence in the second line of the second paragraph: An explanation for the lower uptake in our study could be, that some participants who indicated that they did not have the CT may have entered prenatal care after the first trimester and thus been ineligible for the test; on the other hand, pregnant women in the Netherlands enter midwifery care around 9 weeks of gestation [28]."

Furthermore, we moved the sentence “The mean FAS (90%) uptake in our study was comparable to the findings from earlier studies in the Netherlands [6,7].” to the sixth paragraph, which discussed the FAS uptake.

3. Line 76: add "the" between "about" and "factors".

We changed the sentence as suggested: “little is known about the factors influencing second-trimester FAS uptake.”

4. Lines 84-85: to replace "have the same options...diagnostic testing" by "are followed by the same diagnostic options for positive results"  
As suggested, we changed the mentioned sentence in text in: “…both the CT and the FAS screen for congenital anomalies and are followed by the same diagnostic options for positive results,…”

5. Line 101: change "is" to “was”

We changed the word ‘is’ into ‘was’: “A complete overview of the design of the DELIVER study was given by Manniën et al. [24].”
6. Line 102: change "the time" to "when"
We changed ‘the time’ into ‘when’: Depending on when clients started prenatal care relative to the timing of the study”, ...

7. Line 105: Second questionnaire was completed at around 34 weeks’
gestation? According to the design of the DELIVER study detailed in Mannien's paper, the second questionnaire was completed between 35 weeks of pregnancy and delivery.
We thank the referee for this important observation and changed the text into: “Questions regarding use of the CT and the FAS were asked in both the second questionnaire (completed between 35 weeks of gestation and birth) and the third questionnaire (completed six weeks post-partum). We used data from all participants who completed either questionnaire; in the case of women who completed both questionnaires, we used their responses to the questionnaire completed between 35 weeks and birth.”

8. Lines 118-119: I don't understand the message conveyed by "the classification used by of ethnicity (Dutch, non-Dutch) of Statistics Netherlands"
We thank the referee for this observation. This sentence is confusing. We changed the sentence into: “We used the classification of Statistics Netherlands to determine women’s ethnicity as Dutch or non-Dutch, that is: having at least one parent born in a country other than the Netherlands [25].”

9. Line 121: suggest to use "ascertained" in place of "measured".
The word ‘measured’ we used was not correct, so we changed I the word ‘into ‘ascertained’: “Consanguinity was ascertained by asking the question if her partner is a cousin, uncle or nephew.”

10. Line 136: Suggest to delete the word "highest".
We deleted the word ‘highest’: “We divided the highest level of education into three groups...”

11. Line 142: The disposable income is measured by total personal income after tax. Mind you that despite a low personal income for the woman, the disposable income could be high for other reasons (eg the partner, who is the sole
bread-winner of the family, earns a good salary.)

We thank the referee for this observation and we note that our description of income was incomplete. In the questionnaire, we asked for the income per household, including the eventually partner’s income. We changed the sentence into: “The demographic data collected included religious background, age, education and after tax income per household.”

12. Lines 147-150: Logistic regression analyses have been good enough. Any need for separate Chi square test?

We performed Logistic Regression Analyses to obtain OR’s for the effect size and then we interpreted a possible association between background characteristics and the uptake of the CT and FAS by means of the Chi square test. We thank the reviewer for this observation and this observation indicates that our text is confusing. In this respect, we turned the two sentences: “We used univariate logistic regression analyses to obtain odds ratios and 95% confidence intervals to determine if the background characteristics, pregnancy-related variables, Dutch languages skills among women of non-Dutch ethnic background significantly influenced test uptake. We performed \( \chi^2 \) tests in order to examine a possible association between the aforementioned factors and uptake of the CT and FAS.”

13. Line 160: I’m not in a position to comment on multilevel analysis as I have no experience using it. I suggest review by a statistician.

Three of the co-authors are familiar with multilevel analyses and one co-author is a statistician.

14. Line 172: There were 7907 participants mentioned there. But in the DELIVER study reported by Mannien, 7685 women returned at least one questionnaire.

We thank the referee for this observation. After accepting the paper about the design of the DELIVER study in BMC Health Serv Res, 222 questionnaires were added to the database. Therefore, we mentioned the 7907 participants. Furthermore, we changed two numbers in the first paragraph of the Results. The percentage of nulliparous women in our study should be 47% instead of 46%; The percentage of highly educated women in our study should be 51% instead of 49%. The first paragraph now is: “Of the 7907 participants in the DELIVER study, 5216 women completed questionnaires containing questions about CT and FAS. Comparison with the national perinatal registration revealed that our study population is representative for parity (nulliparous: 47% in our data versus 48% nationwide) and age (aged 34 or
younger: 79% versus 78%), but had more highly educated women (51% versus 42%) and fewer ethnic minority women (16% versus 27%) [24]."

**Referee 2**
I think this is relevant topic, but I do have some suggestions for major and minor revision of the paper:

>>>Major compulsory revision<<<

1. Introduction
- In the introduction it is explained that the FAS is performed around 12 weeks. Isn’t FAS performed around 20 weeks (so called SEO in Dutch)? Or are you talking about another type of test? This should be clarified in the introduction. As the referee mentioned, the FAS is performed around 20 weeks of gestation and this was in the text. To make it more clear, we added a comma between the information between the CT and the FAS.
- As described in the introduction, socio-demographic determinants of CT uptake are well known, but little is known about determinants of second trimester FAS uptake. Why focus on both tests in this study? Please explain this in the introduction. Although socio-demographic determinants of the CT uptake are well know, we mainly focused on Prenatal Anomaly Screening, that includes two tests: CT and FAS. First, the current study provides a baseline for this study population, which helps to understand this population. Therefore we added sentences in the first and in the third paragraph of the introduction.
- Please elaborate on why it is important to identify determinants of uptake. We thank the referee for this observation and we elaborated on the importance to identify determinants of uptake. The importance of identifying determinants of uptake is to understand the differences in uptake between subpopulations and to ensure, that all women have equal access to prenatal anomaly screening. We added a sentence to the text.

The introduction now is: Since 2007, all pregnant women in the Netherlands are informed about prenatal congenital anomaly screening tests. The available screening consists of two non-invasive tests: the Combined Test (CT) at around twelve weeks to determine the possibility of Down syndrome, and the Fetal Anomaly Scan (FAS) at around twenty weeks’ gestation to detect structural anomalies. **Both CT and FAS potentially require three**
decisions: 1) whether to have (one of) the screening test or not, 2) whether or not to follow up positive screens with diagnostic tests, which carry an associated 0.5% risk of miscarriage and 3) if diagnostic tests confirm a positive finding, whether to terminate the pregnancy before 24 weeks’ gestation or prepare for having a child with an anomaly. In contrast to other countries such as the United Kingdom, Denmark and Iceland, the tests are not routinely offered as part of prenatal care in the Netherlands [1-4]. Although both tests are part of a population screening programme, they are not offered on the same basis. The CT is free for women who are 36 or older, while younger women choosing to have the test pay approximately 150 euros; the FAS is free for all women.

The mean uptake of prenatal congenital anomaly screening tests in the Netherlands has been around 27% for some years for the CT but varies between different regions (12% to 52%) [5-8]; the mean uptake of the FAS has been around 91% (80% to 99%) [6,7]. Both tests’ uptake figures are considerably lower than in other European countries [1-4]; in Denmark and Iceland for example, the CT uptake is at least 90% and in Sweden the FAS uptake is up to 100% [3,4,9]. Earlier studies of the CT have shown that factors such as age, parity, ethnicity, socioeconomic status, immigrants’ language proficiency and religion can influence uptake decisions [8,10-19]. However, although both CT and FAS are part of the prenatal congenital anomaly screening programme, little is known about the factors influencing second-trimester FAS uptake. We were also interested in the sub-groups of western and of non-western women with a non-Dutch ethnic background getting care in the Netherlands. In 2010, women with a non-Dutch ethnic background were responsible for 27% of all live births [20] and it is known that immigrant women have made suboptimal use of prenatal care in the past [21,22].

To understand the differences in uptake and to use this knowledge to ensure that all women have equal access to prenatal anomaly screening, it is important to identify determinants influencing the uptake of the CT and the FAS. Therefore, the present nationwide study investigated factors influencing the uptake of the prenatal anomaly screening tests. Based on previous studies [8,10-19] and the fact that both the CT and the FAS screen for congenital anomalies and are followed by the same diagnostic options for positive results, we hypothesized that CT and FAS screening uptake would be associated with religious background, age, parity, socioeconomic status and ethnicity, and that (except for ethnicity) the same hypotheses plus an association with proficiency in Dutch language would hold for women with a non-Dutch background. Of all pregnant women in the Netherlands, more than 80% start their prenatal care in primary care midwifery and receive information and
counselling about prenatal screening from primary care midwives [23]. This study was therefore undertaken in primary care midwifery practices."

2. Methods
- Given the surprising findings on ethnic differences in uptake I think it is essential to provide more information about the non-Dutch group. For example: What exactly was their ethnic background? Or at least: Were they from non-Western ethnic background or Western ethnic background? Were they born in the Netherlands or in another country (first or second generation)? What is their educational attainment level? Other studies showed that women from Western ethnic background are more likely to participate in prenatal screening than women from non-Western background. It is therefore essential to make a distinction between these groups. We thank the referee for this important observation and we totally agree, that we had to make a distinction between western and non-western women with a non-Dutch ethnic background. Therefore, instead of the subgroup of women with a non-Dutch ethnic background, we performed subgroup analyses for western and for non-western women with a non-Dutch ethnic background. We added the background variable ‘generation’ (first or second) in the Method section: “We used the classification of Statistics Netherlands to determine women’s ethnicity as Dutch or non-Dutch, that is: having at least one parent born in a country other than the Netherlands [25]. For non-western with a non-Dutch ethnic background, we again used the classification of Statistics Netherlands and included those women from African, Latin-American, Asian (except for Indonesian and Japan) or Turkey [44]. A woman was of the first generation non-Dutch if she was born abroad, a woman was of the second generation non-Dutch if (one of) her parents was born abroad.”
- Especially the finding that limited Dutch language proficiency is positively associated with uptake of CT is unexpected. I would suggest to carefully check the data and analyses again. As suggested, performing the analyses for the subgroups western and non-western women with a non-Dutch ethnic background, we carefully checked the data and results of the analyses regarding limited Dutch language proficiency. We found that limited proficiency in Dutch indeed positively, independently is associated with the CT uptake among non-western women with a non-Dutch ethnic background. We discussed this finding in the Discussion.
- It would be interesting to know how language proficiency contributes to ethnic
differences in the model with ethnicity. Especially since language proficiency had an independent impact on the uptake in the non-Dutch group. So in other words:

To what extent can ethnic differences be explained by language proficiency?

Multivariate logistic regression analyses demonstrated that limited proficiency in Dutch is only independently associated with CT uptake of non-western women with a non-Dutch ethnic background. Furthermore, limited proficiency in Dutch is almost only seen in first generation non-Dutch women. Therefore, it is possible to explain the higher CT uptake by limited language proficiency more than by ethnicity.

3. Results

- Again it would be interesting if more information is provided about the non-Dutch group. How did uptake differ between ethnic groups, especially non-Western vs Western ethnic background. And did this differ between higher and lower educated women?

We described the results of the analyses among western and non-western women with a non-Dutch ethnic background in the Results and we discussed the most important outcomes in the Discussion. The description of the results among the subgroups in the text: “Finally, we performed subgroup analyses for the women with a western and women with a non-western non-Dutch ethnic background in the study population (respectively N=401 and N=400). The background characteristics of the women with a non-Dutch background that are related to the tests uptakes and information from the univariate logistic regression analyses are presented in Table 5. In comparison with the western women with a non-Dutch ethnic background, the non-western women were more religious, mostly Muslim, younger, had less education, were more likely to be from the western region of the Netherlands, multiparous, from the first generation, and have lower incomes. This subgroup had a higher percentage of limited proficiency in Dutch. The mean actual uptake among western non-Dutch women for the CT was 35% (141/401), and 94% for the FAS (377/401). The mean actual uptake among non-western non-Dutch women for the CT was 24% (94/401), and 84% for the FAS (337/400). Additionally, limited proficiency in Dutch among western non-Dutch women (28% (50/177)) were only found in the first generation. Limited proficiency in Dutch among non-western women were mostly found in the first generation (98% (118/121)). The results of the multivariate logistic regression subgroups analyses are presented in Table 6. In the CT model for western women of non-Dutch ethnic background ($\chi^2 (7, N=336)=367.41, p<0.001$), Women who were Protestant, or living in the eastern region
were significantly less likely to have the combined test (OR: 0.32 (95% CI=0.13-0.80) p =0.015; OR: 0.44 (95% CI=0.21-0.93) p=0.033 respectively). Older women, women with above average income, or women from the first generation were significantly more likely to have the CT (OR:2.00 (95% CI=1.44-2.78) p<0.001; OR:1.97 (95% CI=1.12-3.45) p=0.018; OR: 2.91 (95% CI=1.75-4.85) p<0.001 respectively). Being from the southern region and having limited proficiency in Dutch were not independently associated with the CT uptake. Regarding the FAS uptake ($\chi^2$ (2, N=399)=164.00, p<0.001), among western non-Dutch women, being Protestant, or Catholic had an independent impact on the uptake; women with these characteristics were significantly less likely to have the FAS (OR: 0.13 (95% CI=0.05-0.34) p<0.001; OR: 0.27 (95% CI=0.09-0.81) p=0.020 respectively).

In the CT model for non-western women of non-Dutch ethnic background ($\chi^2$ (3, N=392)=408.96, p<0.001), older women or women with a limited proficiency in Dutch were significantly more likely to have the CT (OR:1.73 (95% CI=1.25-2.39) p<0.001; OR: 2.18 (95% CI=1.34-3.56) p=0.002 respectively). Being from the first generation was not independently associated with the CT uptake. Regarding the FAS uptake ($\chi^2$ (3, N=395)=305.82, p<0.001), among non-western non-Dutch women, higher education had an independent positive impact on the uptake (OR: 1.47 (95% CI =1.02-2.14) p =0.041), while being Muslim or from the first generation had an independent negative impact on the uptake (OR: 0.37 (95% CI=0.19-0.72) p=0.003; OR: 0.27 (95% CI=0.13-0.59) p<0.001 respectively). Being Protestant, having an income above average, and having a limited proficiency in Dutch were not independently associated with the FAS uptake.”

4. Discussion
- The finding that non-Dutch women were more likely to have CT is indeed surprising. This is in contrast with other findings, please elaborate on possible reasons, including possible differences in study design that may explain this difference.

Western non-Dutch women were more likely to have the CT compared to women from Dutch ethnic origin. In a recent study Fransen et al. showed also a higher participation in the CT among western non-Dutch women, but found lower CT uptakes among non-western women [13]. However, we found a CT uptake among non-western non-Dutch comparable to the Dutch study population and not a lower uptake. The differences in results could probably be find in a different study design. See also the next remark.
- More likely to have CT if they had limited proficiency in Dutch is indeed very unexpected. Please refer to studies with contrary findings and discuss these differences.

We acknowledged, that the relatively higher uptake could also be caused through inadequate understanding of the test. Furthermore, we mentioned some possible other explanations of the unexpected uptake of non-western women with a limited proficiency in Dutch; not only limited proficiency played a role, religion for example played also a role. Together with the elaboration of the previous remark, the paragraph about non-western women is now:

“Notwithstanding a lower rate of access to healthcare amongst immigrant women [21,22], surprisingly, in our study non-western women with a non-Dutch background were more likely to have a CT compared to women from Dutch origin (respectively 24% and 22%). Contrary to our findings, Fransen et al. found a lower CT uptake among non-western women (around 12%) [13]. The differences in results could probably be find in a different study design. Fransen et al. used data of one specific Medical Diagnostic Centre in a high density immigrant area, and in our national study, we collected data by purposive sampling; furthermore, the percentage non-Dutch women in our sample was lower compared to the non-Dutch pregnant population and the other study (respectively 17% and 34%) [13]. Also surprisingly, in our study non-western women with a non-Dutch background with limited proficiency in Dutch were more likely to have a CT. An explanation of the higher uptake could be that the women did not have an adequate understanding of the CT [43]. A practical implication of inadequate understanding of the tests indicates that caregivers should make sure that all clients fully understand the information about the screening tests.

In addition to other plausible reasons, ninety-eight percent of the non-western women with a limited proficiency in Dutch were from the first generation and it could be that raising an disabled child may be viewed as complicating already complex lives and may be expensive. On the other hand, non-western women with limited proficiency had a significantly lower FAS uptake compared to non-western women with excellent proficiency (74% and 89% respectively). An explanation why more non-western women with limited Dutch proficiency choose early screening but fewer choose second-trimester screening could be found in the religious background. More than 50% of the non-western in our study were Muslim and from a religious perspective, Muslim women may prefer earlier screening because termination of pregnancy in the case of confirmed serious anomalies is permissible up to the 120th day after conception, that is at 19 weeks’ gestation, but not later in pregnancy [18,41,42].”
- Elaborate on implications for practice and further research. Knowing this, what should be the next step in research? What should we do with the finding (if indeed correct) that women from non-Dutch background with limited Dutch language proficiency are more likely to participate in CT? What should be further investigated?

As suggested, we elaborated on implications for practice and further research. Therefore, we added some words to the following sentence: A practical implication of inadequate understanding of the tests indicates that caregivers should make sure that clients with a (non-western and western) non-Dutch background fully understand the information about the screening tests.” We also added a few sentences at the end of the study limitations: “Because of the small numbers of the secondary analyses among the subgroups, the results should be interpreted cautiously, and further research among western and non-western non-Dutch women with a larger sample size will be important to enhance the generalizability of the results. Additional research is also needed on the different ways in which the prenatal anomaly tests are presented.”

5. General comments
The English writing could be improved, I would suggest to ask a native speaker to check the final manuscript.

Some language corrections were made by the native-English speaking co-author.

We would like to thank the referee for all abovementioned items to improve the paper.

>>>Suggestions for minor revision<<<
1. Methods
- Why call it operationalization? Why not measures?

We changed the word ‘operationalization’ into ‘measures’.

- Strange sentence: Women’s ethnicity was based on the classification used by Of ethnicity (Dutch, non-Dutch) of Statistics Netherlands.

We thank the referee for this observation; it is not a good sentence. We changed the sentence into: “We used the classification of Statistics Netherlands to determine women’s ethnicity
as Dutch or non-Dutch, that is: having at least one parent born in a country other than the Netherlands [25].”

2. Results
- Table 1: Table structure is sometimes invisible
To improve the visibility of the tables we changed the layout; now, the letters and numbers are 12-point type and the determinants in the tables 1 and 5 are shaded.

- Table 1: Please make clear that these are univariate analyses.
We added the word ‘univariate’ in the title of table in: “Background characteristics of the study population and univariate logistic regression analyses of the uptake of the combined test (CT) and the fetal anomaly scan (FAS) among pregnant women participating in the DELIVER study.”

- Table 2: Something wrong with layout. I don’t think international public is familiar with ‘bible belt’ explain in text.
We explained the ‘bible belt’ in the discussion and we agree with the referee, that we had to explain this earlier. Therefore, we added ‘a predominantly orthodox Protestant region’ to the footnote of table to: “Bold rows are practices located in the Dutch ‘Bible Belt’, a predominantly orthodox Protestant region”.

- Table 6: What are the reference categories for the OR in table 6?
We used the following reference categories for the OR in table 6:
- Protestantism: not being a Protestant
- Catholicism: not being a Catholic
- Islam: not being a Muslim
- Increasing age: 30 years or younger
- Above average income: below average or average income
- Higher education: low education
- East region: West Region
- Limited proficiency in Dutch: excellent proficiency in Dutch
- First generation: second generation
We added a footnote with the reference categories.

3. Discussion
- It would be worthwhile to mention recent non-invasive diagnostic tests.

We thank the referee for this remark and mention the recent developments of non-invasive prenatal testing in the Netherlands. We added in the discussion: “Finally, a remark on recent developments in prenatal anomaly screening. Since April 2014, the non-invasive prenatal test (NIPT) is implemented in the Dutch prenatal anomaly screening in a nationwide study context [45]. The NIPT is offered after a positive result of the CT and before a diagnostic test such as an amniocentesis. Only women who are at high risk, e.g. have a child with Down’s syndrome in a previous pregnancy, can choose to have the NIPT without a CT; women who are 36 years or older must first have a CT. Therefore, understanding the determinants of the CT uptake takes on new importance. With the implementation of the NIPT, prenatal anomaly screening has now four steps: 1) CT, 2) follow up positive CT results with the NIPT, 3) follow up positive NIPT result with diagnostic tests which carry an associated 0.5% risk of miscarriage, and 4) when a positive finding is confirmed, to terminate the pregnancy before 24 weeks’ gestation or prepare for having a child with an anomaly.”

Finally, we changed the affiliation of one of the co-authors.

References:


45. http://niptconsortium.nl/

We very much appreciate the work the reviewer has conducted to further improve our paper; many of the observations indicate that our text was confusing and these comments were helpful to tighten the text.

We hope that our paper can now be accepted for publication in your journal.

Yours sincerely,