PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (http://bmjopen.bmj.com/site/about/resources/checklist.pdf) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Incidental Findings on Brain MRI of Cognitively Normal First-Degree Descendants of Alzheimer's Disease Patients: a cross-sectional analysis from the ALFA (Alzheimer and Families) project</th>
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<tr>
<td>AUTHORS</td>
<td>Brugulat, Anna; Rojas, Santiago; Bargalló, Nuria; Conesa, Gerardo; Minguillon, Carolina; Fauria, Karine; Gramunt, Nina; Molinuevo, José; Gispert, Juan</td>
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VERSION 1 - REVIEW

<table>
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<tr>
<th>REVIEWER</th>
<th>Frederik Barkhof</th>
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<td></td>
<td>UCL, London, UK</td>
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<td>I work with the 2 of the authors on another dementia project</td>
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<td>REVIEW RETURNED</td>
<td>26-Jul-2016</td>
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GENERAL COMMENTS

This work reports so-called incidental findings (IF) form the baseline scans of elderly subjects participating in the ALFA study addressing preclinical findings of Alzheimer's disease

Unlike various other papers, the others have included some "normal" aging findings in the definition, which inflates the figures relative to other reports - mostly due to inclusion of WML. In effect, this paper defines what is deviant from successful aging (something we all strive for). Suggest updating the terminology in the paper to reflect this goal better

For WML, I agree that a Fazekas score >1 is not good news (see LADIS papers), but one could argue that Fazekas=0 would be even better than Fazekas=1. In fact, for other findings the cut-off for abnormal is more stringent (e.g. any microbleed).

The ethical disclosure section should be improved. In our institution, and also in the Rotterdam scan study, a list of IFs with presumed low relevance is accepted by the IRB with findings that will NOT be reported to participants due to unknown benefit. It seems that in this study ALL findings seem to have been disclosed. What is the benefit of knowing you have a DVA or a single MB? How was the disclosures of such minimal findings perceived by participants?

The authors stress the use of high quality 3T (and the image appear good quality in the Figures), yet their prevalence of MBs is unexpectedly low certainly given the risk factor for dementia; is there a technical explanation?

The GCA scale is very crude and the interpretation of abnormality (atrophy abnormal for age) vague. this should be clarified or omitted
Finally, I would be intrigued to see whether the major research question of the ALFA study has an impact on IF; did subjects with a positive family history have more IF, especially WML and atrophy?

**REVIEWER**  
Boutet, Claire  
University Hospital of Saint-Etienne, France

**REVIEW RETURNED**  
27-Jul-2016

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| Incidental findings on brain magnetic resonance imaging in the elderly: the PROOF study.  
Boutet C, Vassal F, Celle S et al.  
Brain Imaging Behav. 2016 Feb |
| Prevalence, Clinical Management, and Natural Course of Incidental Findings on Brain MR Images: The Population-based Rotterdam Scan Study.  
Bos D, Poels MM, Adams HH, et al.  
Radiology. 2016 Jun 23 |
| The authors might consider citing both. |

**REVIEWER**  
Vernooij, Meike  
Erasmus MC  
the Netherlands

**REVIEW RETURNED**  
13-Oct-2016

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low”. The current body of literature in this field has rapidly increased and I think the authors should address this in more detail. Personally, I think that the prevalence of incidental findings on brain MRI is not that low (see also the recent publication by Bos et al. from the Rotterdam Study in Radiology (2016)). Please carefully rewrite this section and properly cite all relevant literature.

- Overall, I think the introduction is too long and should be more to-the-point. As stated above – there is currently quite some data on the prevalence of IF on brain MRI, and I feel the authors should focus more on the additive value of their specific paper – especially the fact that these are first-degree descendants of AD patients. If anything, what would the authors expect to find more in these persons compared to persons without parents with AD?

3. Methods:
- After reading the Results-section I am somewhat confused. Apparently not all participants are descendants of patients with AD? This should be very clear.
- Were all IFs rated by the same neuroradiologist?
- If I understand correctly, all IFs were reported back to the participants? Also IFs that are known to be clinically irrelevant (such as arachnoid cysts) or findings of which the clinical relevance remains unclear? How were for example WMHs reported to the participants? What did you tell them? Who was the clinical consultant? Was this an MD?
- Which findings were referred for follow-up? This section really needs to be more detailed.
- Please provide confidence intervals for the prevalence estimates.
- What was exactly determined with the Pearson correlation coefficient? The relation between age and any IF? Or specific IFs?

4. Results
- In the first paragraph I assume that the authors mean that the person with the metallic device was NOT scanned. The sentence currently reads as if the person was scanned, but an artefact appeared on the scan. Please clarify. I assume that prior to scanning all persons were asked about metal implants etc.
- The authors present that vascular abnormalities were present in 10.8% of participants. I suggest that the authors present the percentages of the specific vascular abnormalities as percentage of the total population (This also holds for the other abnormalities). These numbers give a better feeling for the overall prevalence.

5. Discussion:
- The huge differences in IF between the current study and previous studies may be largely explained by the fact that WMHs and brain atrophy were also counted as IF. One could question whether global brain atrophy should be counted as IF, given that this is also largely
part of the aging process.
- The discussion could be more concise.
- The authors should specifically state the limitations of their study.
- Please rewrite the conclusion into a 1-2 sentence statement.

Additional comment: Please carefully revise the paper on the written English.

REVIEWER
K. R. Anandh
IIT Madras, Chennai, India.

REVIEW RETURNED
15-Oct-2016

GENERAL COMMENTS
Comments to the authors

Manuscript title: Incidental Findings on Brain MRI of Cognitively Normal First-Degree Descendants of Alzheimer’s Disease Patients
Manuscript Id: bmjopen-2016-013215

In this paper, the authors have investigated the presence of MRI incidental findings in the normal population of first-degree descendants of Alzheimer subjects using statistical tests. This is an interesting area of research. However, the paper needs revision as it lacks the need for this study. More literature is to be added. Following are some of my specific comments to improve the quality of the paper.

In the introduction section, the authors shall add more information about the importance of IF in the early diagnosis of AD. Few state-of-art papers are to be cited in this section. How IF becomes a key indicator or bio maker for AD diagnosis? Mention about the image processing methodologies that are applied in this context from the literature. For example, the pre-processing, segmentation or about significant image based signatures etc. This might add value to the paper.

Why specifically IF for AD diagnosis? There are many reports on the shape changes of brain structures that are clearly visible in MRI. The authors need to justify the dependence/use of IF for AD diagnosis. I suggest the authors to cite the following papers in the context of shape changes of brain structures.

This would enable the readers to understand the need for this study and how the results are better than the reported works.
I don’t find any role of image processing techniques in this work other than the use of MRI?

RESPONSE TO COMMENTS FROM REVIEWER 1:
Reviewer Name
Frederik Barkhof
Institution and Country
UCL, London, UK
Please state any competing interests or state ‘None declared’:
I work with the 2 of the authors on another dementia project

Comments 1&2:
This work reports so-called incidental findings (IF) form the baseline scans of elderly subjects participating in the ALFA study addressing preclinical findings of Alzheimer's disease.
Unlike various other papers, the others have included some "normal" aging findings in the definition, which inflates the figures relative to other reports - mostly due to inclusion of WML. In effect, this paper defines what is deviant from successful aging (something we all strive for). Suggest updating the terminology in the paper to reflect this goal better.
For WML, I agree that a Fazekas score >1 is not good news (see LADIS papers), but one could argue that Fazekas=0 would be even better than Fazekas=1. In fact, for other findings the cut-off for abnormal is more stringent (e.g. any microbleed).
Response:
We thank the reviewer for his valuable comments. We report Fazekas > 1 as a “finding” according to a reference manual authored by the reviewer [1] that reports a score of 1 to be considered “normal” in the elderly, whereas a score of 2 is thought to be abnormal in subjects under the age of 75 (the maximum age in our population). This same criterion has been used in other works reporting incidental findings [2]. Certainly, there is an unavoidable degree of arbitrariness on the definition of what constitutes an abnormality, but the definition of “successful aging” is subject to a similar level of ambiguity (cfr. [3]). Throughout the paper, we introduce this criterion and clearly identify that this is the reason why our figures are increased with respect previous papers. This criterion does not extend to other findings which are also more prevalent with aging but constitute an injury per se, such as microbleeds. We have now extended the methods and discussion sections regarding this this point and referenced the LADIS papers [4-5].

References:

Comment 3:
The ethical disclosure section should be improved. In our institution, and also in the Rotterdam scan study, a list of IFs with presumed low relevance is accepted by the IRB with findings that will NOT be reported to participants due to unknown benefit. It seems that in this study ALL findings seem to have been disclosed. What is the benefit of knowing you have a DVA or a single MB? How was the disclosures of such minimal findings perceived by participants?
Response:
The criterion used in the ALFA study was to provide with the neuroradiological report to all participants, even in the majority of cases where it did not have any clinical consequence, as a benefit for future reference. Then, a trained physician commented the findings to the participants in order to provide clear context about the clinical relevance of the findings.
We agree with the reviewer that there is little benefit in knowing one has a single MB or DVA. Nonetheless, there is no inconvenience either if properly explained to the study participant. Indeed, this holds true for many other findings. In such a way, there is also no benefit in knowing that one has a calcified meningioma in the parietal bone since usually they do not grow or an isolated cavernoma that are usually asymptomatic during lifetime. Establishing this distinction is not simple and, in any case, it could be considered that one would be trying to avoid a non-existent problem.
Please note that, of course, all participants were informed in advance and agreed in the informed consent form that they would be informed of any finding before MRI realization. Actually, they perceived this practice as an indirect benefit of their participation in our research. We did not find any case in which the communication of this information caused any inconvenience. Participants thanked the information and felt positive about the feedback.

Comment 4:
The authors stress the use of high quality 3T (and the image appear good quality in the Figures), yet their prevalence of MBs is unexpectedly low certainly given the risk factor for dementia; is there a technical explanation?
Response:
The low prevalence of MB may be due to the relatively young age of our sample, the stringent inclusion criteria of the ALFA project including a very sensitive cognitive and clinical evaluation. Indeed, recruited volunteers presented with low cardiovascular risk factors (BMI, Smoking status, Dyslipidemia, Diabetes and Hypertension) (see Molinuevo et al., 2016).

Comment 5:
The GCA scale is very crude and the interpretation of abnormality (atrophy abnormal for age) vague. this should be clarified or omitted
Response:
Following this reviewer suggestion, we have now clarified that we followed the neuroradiologist assessment for reporting abnormal atrophy for age (page 9):
“Brain volume loss was considered as IF by the radiologist when greater than that expected by age.”

Comment 6:
Finally, I would be intrigued to see whether the major research question of the ALFA study has an impact on IF; did subjects with a positive family history have more IF, especially WML and atrophy?
Response:
We appreciate this reviewer’s comment and have accordingly performed the suggested analyses that are now shown in Table 4 and in the results and discussion sections (page 12 and page 15,
respectively): E.g. see discussion on page 15: 
“Unexpectedly, individuals without a family history of AD showed a greater prevalence of abnormal brain atrophies for their age. However, this difference was driven by atrophies in the frontal lobe and, therefore, it cannot be attributable to early AD pathology. In regions known to be affected by AD, such as the temporal and parietal cortices, no differences in atrophy prevalence were found between participants with and without familiar history of AD.”

RESPONSE TO COMMENTS FROM REVIEWER 2
Reviewer Name
Boutet
Institution and Country
University Hospital of Saint-Etienne, France
Please state any competing interests or state ‘None declared’: None declared

This is a fine manuscript that adds meaningfully to the data on incidence of structural abnormalities detected on brain MRI at 3 T. The authors report more IF findings than others in the past, but in general the data are consistent.

Comment 1: 
P7, ligne 35: how the authors did select the 608 participants invited to take part in this study? 
Response: Following this reviewer’s suggestion, we have now added the following information (page 7): “All ALFA cohort participants were enquired about their parental history of AD at baseline and categorized as family history positive (FH+) if they had at least one of their parents that had been diagnosed with AD before the age of 75. FH+ and FH- matched by sex and age groups were invited to participate in the present study (NCT02198586) which resulted in the inclusion of 608 individuals of the ALFA parent cohort that had no contraindications to brain MRI. Recruitment initiated in April 2014 and finished in June 2015.”

Comment 2:
P9, ligne 11: the categories “cysts” and “other” miss in the method part, whereas they appear in the results part 
Response: We thank this reviewer for pointing out this missing categories that we have now added (in bold below) in our revised version of the manuscript (page 9): “IF were categorised as WMH, vascular abnormalities (including lacunar infarcts, microhaemorrhages, aneurysms, cavernous malformations and malformations of venous development), cysts, neoplasias and others, including brain volume loss, and their prevalence calculated.”

Comment 3:
Consider that incidental findings requiring follow-up evaluation could be detailed 
Response: Following this reviewer’s suggestion, we have now added the following information on our revised version (page 8): “An independent clinical consultant reviewed those that contained IF and clinically relevant IF (e.g. tumours, vascular abnormalities, WMH with comorbidities, cysts, chiari malformations, syringomyelia, ventriculomegaly suspicious of normal pressure hydrocephalus and encephalomalacia) were personally informed and participants referred for follow-up by the appropriate specialist (n=90/155).”
More recent papers of incidental findings on European population have been published:
Incidental findings on brain magnetic resonance imaging in the elderly: the PROOF study.
Boutet C, Vassal F, Celle S et al.
Brain Imaging Behav. 2016 Feb
Prevalence, Clinical Management, and Natural Course of Incidental Findings on Brain MR Images: The Population-based Rotterdam Scan Study.
Bos D, Poels MM, Adams HH, et al.
Radiology. 2016 Jun 23
The authors might consider citing both.
Response:
Following this reviewer’s suggestion we have added these very recent references to the present version of the manuscript. Please note that these appear in the Introduction and Discussion sections.

RESPONSE TO COMMENTS FROM REVIEWER 3
Reviewer Name
K. R. Anandh
Institution and Country
IIT Madras, Chennai-India.
Please state any competing interests or state ‘None declared’: None Declared.

The authors present an interesting report on the prevalence of incidental findings on brain MRI in a cognitively healthy cohort of first-degree descendants of AD patients. Although potentially interesting there are several issues that need to be fully addressed:

Comment 1:
Abstract:
I suggest that the authors report all percentages with one decimal.
Response:
Following this reviewer’s appreciation, percentages are now reported with one decimal in the abstract and throughout the manuscript.

Comment 2:
2. Introduction:
- I do not understand the statement of the authors in the first paragraph w.r.t. that the prevalence of “these findings is necessarily low”. The current body of literature in this field has rapidly increased and I think the authors should address this in more detail. Personally, I think that the prevalence of incidental findings on brain MRI is not that low (see also the recent publication by Bos et al. from the Rotterdam Study in Radiology (2016)). Please carefully rewrite this section and properly cite all relevant literature.
Response:
We appreciate this reviewer’s comment and have added the relevant literature suggested (page 5). Furthermore, we have deleted the statement “Although the prevalence of these findings is necessarily low” which leaves the section as follows (page 5):
“...In these scans, it is not unusual to detect incidental findings (IF), unexpected abnormalities of potential clinical significance and unrelated to the purpose of the study. Estimating the chance of discovering IF is important to help clinicians and researchers to adequately inform individuals and manage these situations...”
- Overall, I think the introduction is too long and should be more to-the-point. As stated above - there is currently quite some data on the prevalence of IF on brain MRI, and I feel the authors should focus more on the additive value of their specific paper - especially the fact that these are first-degree descendants of AD patients. If anything, what would the authors expect to find more in these persons compared to persons without parents with AD?
Response:
According to the reviewer’s suggestion, we have now analysed the impact of parental family history on the prevalence of IF (included on Table 4 and page 12 [results] and 15 [Discussion] of the manuscript).

Comment 3:
3. Methods:
- After reading the Results-section I am somewhat confused. Apparently not all participants are descendants of patients with AD? This should be very clear.
Response:
We agree with this reviewer the original version manuscript was confusing with regards to family history of AD. We have categorised study participants as positive or negative family history depending on whether or not they had a mother and/or father that had been diagnosed with AD before the age of 75. This has now been clarified in our revised version (methods section, page 7) and, as mentioned in the previous comment, we have now analysed the impact of parental family history on the prevalence of IF (included on Table 4 and page 12 [results] and 15 [Discussion] of the manuscript).

- Were all IFs rated by the same neuroradiologist?
Response:
All scans were indeed rated by the same neuroradiologist thus maximizing the homogeneity of the readings and reports. We have now added this information (in bold below) on page 8: “Scans were evaluated by the same trained neuroradiologist within the following week from MRI acquisition.”

- If I understand correctly, all IFs were reported back to the participants? Also IFs that are known to be clinically irrelevant (such as arachnoid cysts) or findings of which the clinical relevance remains unclear? How were for example WMHs reported to the participants? What did you tell them? Who was the clinical consultant? Was this an MD?
Response:
Participants received the neuroradiological report of the MRI in the same way that if MRI has been performed by any other reason different to their participation in the study. Clinically irrelevant findings such as arachnoid cyst are also reported in MRIs carried out for example to evaluate chronic headache. Our criterion was that not reporting a finding makes no sense even if their clinical relevance is uncertain. In the future, the patient may be prescribed another MRI for their clinical management and the previous information of MRI may become relevant. One example of this, a trigeminal neuralgia could be related with the bleeding of al a cavernous malformation in the brain stem. However if it is know that this malformation exist before the neuralgia and no changes of it has been observed an alternative cause for the neuralgia should be considered. WMHs were reported in the same way that they are reported in the current clinical practice and their relevance was explained accordingly by a trained MD. These participants were interrogated about the vascular risk factors and the improvement of their control was recommended if it was applicable. The clinical consultant in charge to report the findings was Santiago Rojas that is an MD and a PhD. He also derived the participants for further evaluation by specialist if it was necessary.

- Which findings were referred for follow-up? This section really needs to be more detailed.
Response:
Following this reviewer’s suggestion, we have now added the following information on our revised version (page 8):

"An independent clinical consultant reviewed those that contained IF and clinically relevant IF (e.g. tumours, vascular abnormalities, WMH with comorbidities, cysts, chiari malformations, syringomyelia, ventriculomegaly suspicious of normal pressure hydrocephalus and encephalomalacia) were personally informed and participants referred for follow-up by the appropriate specialist (n=90/155)."

- Please provide confidence intervals for the prevalence estimates.
Response:
Following this reviewer’s suggestion we have now added confidence intervals for the prevalence estimates in Tables 2, 3, new Table 4 and throughout the text.

- What was exactly determined with the Pearson correlation coefficient? The relation between age and any IF? Or specific IFs?
Response:
With the Pearson correlation coefficient we assessed the effect of age in the most prevalent incidental findings. We have added this information in the Methods section.

Comment 4:
4. Results
- In the first paragraph I assume that the authors mean that the person with the metallic device was NOT scanned. The sentence currently reads as if the person was scanned, but an artefact appeared on the scan. Please clarify. I assume that prior to scanning all persons were asked about metal implants etc.
Response:
We agree with re reviewer that this sentence needed clarification. We confirm that all participants were asked about metal implants and other devices incompatible with MR scanning. The specific case the reviewer refers to that was stated as “metallic device” in our original manuscript were in fact MRI-compatible metallic earrings. We have now specified it (in bold below) in the Results section page 10:

“608 ALFA parent cohort participants were invited to take part in the present brain MRI study. Of these, 595 volunteers agreed to undergo brain MRI and 575 provided valid MRI images. Reasons that prevented MRI acquisition were claustrophobia (n=16), physical size or shape that precluded from lying in the scanner (n=3), and an imaging artefact caused by irremovable MRI-compatible metallic earrings (n=1)."

- The authors present that vascular abnormalities were present in 10.8% of participants. I suggest that the authors present the percentages of the specific vascular abnormalities as percentage of the total population (This also holds for the other abnormalities). These numbers give a better feeling for the overall prevalence.
Response:
This has now been addressed throughout.

- How were persons handled who had more than one of the same IFs? E.g. two meningiomas?
Response:
Participants were handled in the same way than those who had only one. Handling of these participants was done according to current clinical practice and the corresponding accepted guidelines in our country. Clinical management of the findings depends on the characteristics of the finding more than the number. For example, a single meningioma in the middle fossa is more clinically relevant than two meningiomas in the parietal bone due to the risk of affectation of II, III, IV,VI cranial nerves, carotid artery and cavernous sinus. In a similar way two meningiomas showing signs of calcification are less relevant that a single one without it.
Probably there is only one case in which the number is relevant; this is the occurrence of cavernomatous malformations. Multiple malformations are suggestive of familial cerebral cavernomatosis and the study of other members of the same family may be indicated.

- I am somewhat confused by the last paragraph of the results. The title of the manuscript implies that this is a study in persons from parents with AD. Now, in this section results are being provided for those persons with and without a parental history of AD? How many of the 575 persons did not have a parental history of AD? If there are also persons without a parental history of AD this should be made very clear from the beginning - e.g. also in the abstract.
Response:
According to the reviewer's comment we have now clarified this throughout the manuscript. Specifically, 325 participants were categorised as positive family history (had a mother and/or father that had been diagnosed with AD before the age of 75) and 210 as negative. The title of the manuscript has remained the same since we are indeed still studying the impact of family history in IF (as compared to a group of individuals without AD family history).

- How many persons were referred for further evaluation? With what findings? This is crucial information which needs to be addressed (also in the Discussion).
Response:
As mentioned before, clinically relevant IF were personally informed and referred for follow up by the appropriate specialist. This resulted in 90 out of 155 IF. This has now been specified on page 8: “An independent clinical consultant reviewed those that contained IF and clinically relevant IF (e.g. tumours, vascular abnormalities, WMH with comorbidities, cysts, chiari malformations, syringomyelia, ventriculomegaly suspicious of normal pressure hydrocephalus and encephalomalacia) were personally informed and participants referred for follow-up by the appropriate specialist (n=90/155).”

Comment 5:
5. Discussion:
- The huge differences in IF between the current study and previous studies may be largely explained by the fact that WMHs and brain atrophy were also counted as IF. One could question whether global brain atrophy should be counted as IF, given that this is also largely part of the aging process.
Response:
We agree with the reviewer that the definition of what constitutes a finding has a strong impact on the prevalence estimates of IFs. Regarding global atrophy, it was only categorised as a finding in those cases where the atrophy was abnormal given the age of the volunteer according to the neuroradiologist criterion.

Comment 6:
- The discussion could be more concise.
Following this reviewer's appreciation, we have revised the discussion section of the manuscript, which we believe improves its clarity.

Comment 7:
- The authors should specifically state the limitations of their study.
Response:
This has been added to the end of discussion in the revised version (pages 16-17). “The strict recruitment criteria in the ALFA study may underlie the main limitation of the present study in that the results reported here may not reflect the prevalence of IF in the general population. A greater percentage of our volunteers were first-degree descendants of AD patients than what would be expected from the general population. Therefore, our prevalence estimates should not be regarded from an epidemiological perspective, but are of interest for design of AD prevention trials. Another limitation is the operationalization of family history status as enrichment criteria for these trials. Ideally,
family history should be supported by clinical records that might be difficult to access. In our cohort, 53% of the cases with positive family history were backed up by confirmed medical records. On top of this, there is a certain arbitrariness in establishing a cut-off value in the age of AD onset in the index case to determine a positive family history status and selecting different threshold values may impact the observed prevalence estimates. In the ALFA cohort, this threshold is fixed at <75 years based on previous literature supporting that the age of AD onset in the index case needs to be limited as dementia occurring at a very old age is less likely to have a strong genetic component. This 75 year-old limit has been used by us and other studies that combine multiple susceptibility loci into a global genetic risk score to improve the prediction of individuals at risk of suffering AD.

Comment 8:
- Please rewrite the conclusion into a 1-2 sentence statement.
Response:
Following this reviewer’s appreciation, we have rewritten the conclusion on both the abstract and the discussion section of the manuscript.

Comment 9:
Additional comment: Please carefully revise the paper on the written English.
Response:
We appreciate this reviewer’s comment and following his suggestion, the English has been revised throughout the manuscript.

RESPONSE TO COMMENTS FROM REVIEWER 4
Reviewer Name
Bos
Institution and Country
Erasmus MC the Netherlands
Please state any competing interests or state ‘None declared’:
None declared

Comment 1:
In this paper, the authors have investigated the presence of MRI incidental findings in the normal population of first-degree descendants of Alzheimer subjects using statistical tests. This is an interesting area of research. However, the paper needs revision as it lacks the need for this study. More literature is to be added. Following are some of my specific comments to improve the quality of the paper.
Following this reviewer’s suggestion, we have introduced the rationale of our study more concisely, and we have added additional recent literature on the topic (Table 4 and throughout the manuscript).

In the introduction section, the authors shall add more information about the importance of IF in the early diagnosis of AD. Few state-of-art papers are to be cited in this section. How IF becomes a key indicator or bio maker for AD diagnosis? Mention about the image processing methodologies that are applied in this context from the literature. For example, the pre-processing, segmentation or about significant image based signatures etc. This might add value to the paper.
We did not intend to investigate IF as an indicator or biomarker of AD or their impact on imaging processing methodologies. We aimed to assess whether familiar history of AD had an impact on the prevalence of IFs. Familiar history is a common enrichment strategy for AD prevention trials and our study may therefore help in providing guidance for the management of volunteers in this context.
Regarding processing methodologies in the ALFA study, scans identified with space-occupying lesions (i.e. neoplasias) or anatomical alterations (i.e. chias) were excluded from subsequent
processing. Therefore, the impact of the IF on the processing pipelines exceeds the interest of this work.

Why specifically IF for AD diagnosis? There are many reports on the shape changes of brain structures that are clearly visible in MRI. The authors need to justify the dependence/use of IF for AD diagnosis. I suggest the authors to cite the following papers in the context of shape changes of brain structures.


This would enable the readers to understand the need for this study and how the results are better than the reported works.

I don’t find any role of image processing techniques in this work other than the use of MRI?

Response:

We did not try to investigate the relation of IF with AD. In fact, subjects of the cohort are all cognitively healthy, so there is no way we could conduct this kind of analysis. We believe that the practical totality of the findings here reported are unrelated to Alzheimer’s. Excluding the cerebral atrophy and, perhaps WMH, the other findings have no association with AD pathology. We thank the reviewer for the excellent papers suggested that are very interesting but we believe that they present slight relation with the main aim of our study.

VERSION 2 – REVIEW

REVIEWER
Frederik Barkhof
UCL, London, UK
I work with the 2 of the authors on another dementia project

REVIEW RETURNED
25-Dec-2016

GENERAL COMMENTS
I still disagree to disclose irrelevant findings to avoid anxiety

REVIEWER
Vernooij, Meike
Erasmus MC
the Netherlands

REVIEW RETURNED
28-Dec-2016

GENERAL COMMENTS
Although in the response to reviewers there seems to be a mix-up of
my review with that of one of the other reviewers (not sure if this is due to the system or if the authors accidentally did this - the comments of reviewer 4 Bos are actually displayed under reviewer 3), the authors have been very responsive to my comments. I have only some questions:
- I am still surprised by the fact that all IFs are reported to the participants. Just out of curiosity; do the authors get many questions with regard to the non-clinically relevant findings (e.g. WML, AC's)? It would be interesting to investigate the psychological impact of knowing these findings on the quality of life of these participants.
- The authors write about the prevalence of brain atrophy (e.g. in the abstract: Additionally, brain atrophy was significantly more prevalent in participants without parental history of AD). It is important to stress that this pertains to brain atrophy that is more than what is expected based on age only.
- Following my previous comment, it is quite interesting that the prevalence of brain atrophy was higher in the participants with a negative parental history of AD. Yet, as the authors state in the discussion, this was driven by atrophy in the frontal lobe, which is unlikely to represent AD pathology.

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**REVIEWER**

Dr. K. R. Anandh  
IIT Madras, Chennai, India.

**REVIEW RETURNED**

26-Dec-2016

**GENERAL COMMENTS**

The authors have addressed some of my suggestions. However, I would like to suggest authors to bring out and present the major and salient insights of this paper in the conclusion section. Also, they can list the major limitations of this study and this would pave way for future research.

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**VERSION 2 – AUTHOR RESPONSE**

Comment #1: I still disagree to disclose irrelevant findings to avoid anxiety  
Response: We understand the reviewer’s argument and agree that this is an important matter of debate. Therefore, we have introduced a new paragraph (2nd paragraph, page 17) in the discussion reflecting the views in current reference reports. In summary, we think that the debate is still open, that there is variability on the way that different centres address the disclosure of findings and that more research in the prevalence of IF and the impact of disclosing them is needed. In our case, an MD disclosed the findings to the participants and offered a help line in case they had further questions. Out of the 65 individuals that were contacted for non-clinically relevant findings, none of them called back. In addition, please note that our policy to disclose the findings was explicitly stated in the study Informed Consent and, therefore, participants knew and agreed in advance to this procedure. These considerations have now been introduced in the paper (Methods, page 8 and Discussion page 17-18).

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**RESPONSE TO COMMENTS FROM REVIEWER 2:**

Reviewer Name  
K. R. Anandh
In conclusion, we describe here that brain MRI scans of healthy middle-aged subjects show a relatively high prevalence of IF (27.0%) even after excluding individuals with subtle cognitive alterations. As a whole, positive correlation between the prevalence of IF and increasing age was found and, within specific IF categories, relevant WMH, lacunes and brain volume loss prevalence significantly increased with age. Jointly, no significant differences between genders in the general prevalence of IF were found. However, brain volume loss were more frequent in men and neoplasias were more prevalent in women.

The main limitation of this study is the particular recruitment criteria in the ALFA project which argues against the generalisation of our data in the general population. In addition, the difficulty to establish a cut-off value in the age of AD onset in the index case may have an impact on whether IFs are more prevalent in first degree relatives of AD patients. Nevertheless, it is worth mentioning that most of our participants are first-degree descendants of AD patients and, therefore, the results presented here are of special relevance for novel imaging studies in the context of AD prevention in cognitively healthy middle-aged subjects.

RESPONSE TO COMMENTS FROM REVIEWER 3:
Bos
Institution and Country
Erasmus MC
the Netherlands
Please state any competing interests or state ‘None declared’:
None declared

Although in the response to reviewers there seems to be a mix-up of my review with that of one of the other reviewers (not sure if this is due to the system or if the authors accidentally did this - the comments of reviewer 4 Bos are actually displayed under reviewer 3), the authors have been very responsive to my comments.

I have only some questions:

Comment #1:
I am still surprised by the fact that all IFs are reported to the participants. Just out of curiosity; do the authors get many questions with regard to the non-clinically relevant findings (e.g. WML, AC’s)? It would be interesting to investigate the psychological impact of knowing these findings on the quality of life of these participants.
Response:
We understand that this is still an open-debate and have specifically addressed this topic in an
additional paragraph in the discussion (please see response to comment #1 for reviewer #1).

Finally, we agree with the reviewer that it would be interesting to investigate the psychological impact of knowing these findings on the quality of life of these participants. In fact, these subjects form part of the ALFA cohort and, as such, are being invited to further participate in additional studies sponsored by us. We will consider performing such study.

Comment #2:
The authors write about the prevalence of brain atrophy (e.g. in the abstract: Additionally, brain atrophy was significantly more prevalent in participants without parental history of AD). It is important to stress that this pertains to brain atrophy that is more than what is expected based on age only.
Response:
We thank the reviewer for this suggestion. We have added the specific information on the abstract of our revised version (page 2):
“...A positive correlation between increasing age and the presence of IF was found. Additionally, brain atrophy greater than that expected by age was significantly more prevalent in participants without parental history of AD”

Comment #3:
Following my previous comment, it is quite interesting that the prevalence of brain atrophy was higher in the participants with a negative parental history of AD. Yet, as the authors state in the discussion, this was driven by atrophy in the frontal lobe, which is unlikely to represent AD pathology.
Response:
We agree that this unexpected finding is interesting and that its aetiology is intriguing. One potential explanation might arise from the stringent inclusion criteria of the ALFA project (Molinuevo et al., 2016) which may have excluded individuals with sub-clinical cognitive deficits and, hence, greater atrophy patterns as expected for their age.

Incidental findings on brain MRI of cognitively normal first-degree descendants of patients with Alzheimer's disease: a cross-sectional analysis from the ALFA (Alzheimer and Families) project

Anna Bruguñol-Serrat, Santiago Rojas, Nuria Bargalló, Gerardo Conesa, Carolina Minguillón, Karine Fauria, Nina Gramunt, José Luis Molinuevo and Juan Domingo Gispert

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