Aspirin moderates the association between cardiovascular risk, brain white matter hyperintensity total lesion volume and processing speed in normal ageing

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ABSTRACT

Objectives

Cardiovascular risk is associated with cognitive decline and this effect is attributed to brain pathology including white matter hyperintensity (WMH) burden. Low dose aspirin is frequently recommended for reducing vascular events. We aimed to investigate the effect of taking aspirin on the association between cardiovascular risk, WMH burden and cognitive function.

Study design

The study sample was drawn from 318 dementia free adults aged 67-71 years. Brain Magnetic Resonance Imaging (MRI) scans were acquired from 239 participants.

Main outcome measures

WMH total lesion volumes (TLV) were extracted using the automated lesion segmentation algorithm. We measured cardiovascular risk by calculating ASSIGN score. Cognitive ability was measured using a processing speed test. We developed structural equation models to test our hypothesis.

Results

Taking aspirin was reported by 68 participants (47.1% male, mean age=68.8 years). The demographic measures did not differ significantly by aspirin use. In aspirin users, there was a strong negative association between WMH TLV and cognition ($\beta = -0.43$, p-value < 0.001) while in non-users of aspirin, the only significant predictor of poorer cognition was cardiovascular risk ($\beta = -0.17$, p-value $=0.001$).

Conclusions

Aspirin use moderates the negative effect of WMH burden on cognition. Considering WMH burden in addition to cardiovascular risk could improve the prediction of cognitive decline in older adults with aspirin use.

Keywords: Aspirin; Cardiovascular risk; Brain white matter hyperintensity; Cognition; Older adults

1. INTRODUCTION

1.1.Background

Low dose aspirin reduces the frequency of adverse vascular events in those at increased risk of occlusive cardiovascular disease (CVD). People who benefit include those: with a history of myocardial infarction, ischaemic stroke, unstable or stable angina, peripheral arterial disease, or atrial fibrillation (1). The pathophysiology of CVD risk contributes to cognitive decline through multiple pathways that include cerebral hypo-perfusion, hypoxia, hippocampal atrophy, emboli, or infarcts (2, 3). However, the value of aspirin use in prevention of cognitive impairment remains uncertain since results relating to the influence of taking aspirin on cognitive function are inconsistent (4-6).

Brain Magnetic Resonance Imaging (MRI) detected white matter hyperintensities (WMH) provide a biomarker of cardiovascular and cerebrovascular disease and are a ubiquitous imaging finding in older adults (7, 8). The relationship between WMH and cognitive decline is well-documented (9, 10), making WMH a potential factor in the pathway through which aspirin could affect cognition in older people. Few studies examine a possible association between aspirin use and MRI markers of cerebrovascular disease (11, 12). Although one study reported that there was no clinically significant effect of long-term aspirin use on WMH volume in women (13), the study was carried out in older women over 75y and did not examine the effect of aspirin on dementia-related pathology or on cognition.

Among all cognitive domains, information processing speed seems to be more affected by WMH burden due to injury or disease and ageing (14, 15). The Rotterdam Scan study showed a significant association between white matter lesion progression and reduced information processing speed (16). Similarly in a non-demented elderly population the increased periventricular WMH volume was associated with reduced cognitive speed, but not with memory (17). The Digit Symbol (DS) test is a widely-used and standardized

psychometric test with high re-test reliability that evaluates the performance of cognitive processes including visual analysis, focused attention, response selection and motor operations fluently under time pressure (18). Because of its psychometric properties, the DS test was adopted as the measure of information processing speed for this research.

1.2.Aims

Against this background, we aim to (i) assess the relationship between CVD risk factors, WMH total lesion volume (TLV) and processing speed measured by DS test, and (ii) investigate the effect of aspirin use on possible associations observed here.

2. METHODS

2.1.Study design and participants

Participants were volunteers recruited to a longitudinal observational study of people born in 1936, the Aberdeen 1936 Birth Cohort (ABC1936). The mental ability of all participants was estimated using a cognitive test (The Moray House Test, MHT) at age 11±0.5y as part of Scottish Mental Survey of 1947 (SMS 47). With the approval of the NHS Local Research Ethics Committee (reference 03/0151- abc1936), 498 survivors of SMS 47 aged between 63y to 67y were recruited into ABC1936 though 1999-2002. Full details of ABC1936 are described elsewhere (19). For this study purpose we used data from wave three of ABC1936 controlling for childhood factors. Cognitive performance, general health parameters and MRI brain exams were completed satisfactorily at age 68y as part of the third assessment and have been used in this study. A fellow chart summarising how the sample was recruited for the ABC1936 study is shown in Fig. 1.

2.2.Aspirin use and cardiovascular risk score

Participants were asked about their current medications at the baseline and all waves of examination. Aspirin use was based on self-reported aspirin administration. CVD risk was measured using the ASSIGN score. ASSIGN was developed in the Scottish Heart Health

Extended Cohort, aiming to target social gradients in predicting cardiovascular outcome (20). We used age, sex, adulthood socioeconomic status (SES), family history of coronary heart disease or stroke, history of diabetes and rheumatoid arthritis, number of cigarettes smoked daily, systolic blood pressure, total cholesterol and HDL cholesterol to calculate ASSIGN (Version 1.5.1, http://www.assign-score.com/estimate-the-risk/). Scottish Index of Multiple Deprivation (SIMD) obtained through participants' postcode was used as an estimate of adult SES and was considered as a CVD risk factor in ASSIGN calculation.

2.3.Brain MRI scans and image analysis

Brain MRI exams were obtained using a 1.5 T (NVi GE system, Milwaukee, WI) scanner with T2 axial (TR/TE 4,900/81.4, slice thickness 5 mm, space 1.2 mm), fluid attenuation inversion recovery axial (FLAIR) (TR/TE 9,002/1.33, TI 2,200, slice thickness 5mm, space 1.2mm) and 3D T1-weighted (TR/TE 20/6ms, flip angle 35°, slice thickness 1.6 mm, matrix 256 × 192, in-plane resolution 1 × 1mm) sequences (21).

White matter total lesion volume (WMH TLV) was obtained using the Lesion Growth Algorithm provided by the open-source Lesion Segmentation Toolbox (https://www.applied-statistics.de/lst.html). This fully-automated lesion segmentation algorithm separates brain tissue classes (white matter, grey matter, cerebrospinal fluid) using a T1 image, then utilises the FLAIR image to detect and classify hyperintense (bright) voxels, providing a lesion prediction map, total lesion number, and TLV. Further information about this segmentation approach can be found elsewhere (22).

2.4.Cognition and education

Processing speed was measured using the Digit Symbol (DS) test (18). DS scores were transformed to an IQ-type score (mean =100, standard deviation = 15).The highest educational qualification attained was coded from "none" as 1, lower and higher leaving certificate coded 2 and 3, Scottish vocational certificate coded 4; ordinary grades coded 5;

Higher / Advanced level were coded 6; undergraduate and postgraduate degrees coded 7 and 8 respectively, up to "professional or higher degree" levels coded as 9 (19).

2.5. Statistical analyses

The distribution of data was explored visually and by skewness test. The two groups were compared using Chi-Square test for categorical variables, the Mann-Whitney U tests for not normally distributed outcomes and the Independent-Sample t test for normally distributed outcomes.

Structural Equation Models (SEMs) were developed with WMH TLV, ASSIGN and the standardised DS score. ASSIGN was assumed to have a direct and an indirect effect on cognition. The indirect effect of ASSIGN on cognition was hypothesised to be through its effects on WMH TLV. We also hypothesised that WMH TLV would have a direct effect on cognitive function. We adjusted SEMs for the confounding effect of age, gender, childhood IQ and education on late life cognition. The goodness of fit was assessed according to the combined value of Comparative Fit Index (CFI) ≥ 0.95 and Root Mean Square Error of Approximation (RMSEA) ≤ 0.06 as an acceptable fit of the model to the data (23). All analyses were carried out using IBM SPSS v24 and p value <0.05 was considered as significant.

3. RESULTS

3.1. Characteristics

The study sample was drawn from 318 dementia free adults aged 67-71y (Table 1). The demographic measures did not differ significantly by aspirin use. Aspirin users were more likely to be taking anti-hypertensive medication and statins, and to have a history of cardio- and cerebrovascular events and diabetes. No significant difference was observed between groups by DS, ASSIGN or WMH TLV.

3.2. SEMs results; ASSIGN, WMH, cognition and the moderating effect of aspirin

Fig.2 shows a brain MRI scan of a subject with WMH (A) and same slice with lesion map overlaid (B).

Results of the SEM for all participants and for aspirin vs no aspirin group are shown in Fig.3 and Fig.4 These models are adjusted for confounders including age, gender, childhood IQ, and education (Fig.3).

In all participants (Fig. 3), ASSIGN was associated with poorer cognition (β= -0.17, p-value <0.001). In addition, we found a direct independent negative effect of WMH TLV on cognition (β= -0.12, p-value =0.038). The negative effect of ASSIGN on cognition was not mediated through WMH TLV (β = 0.04, p-value= 0.478). Model fit indices (CFI =0.98 RMSEA =0.03) indicated a very good fit of the model to the data.

We then performed a multiple group comparison to control for these relationships in aspirin use (Fig.4a and 4b). For simplicity confounders are not shown here. Among those who do not report aspirin use there is a significant association between ASSIGN and cognition (β= -0.17, p-value =0.001) and the association betweenWMH TLV and cognition was not significant. Among aspirin users, WMH TLV significantly affected cognitive function with β = -0.43, p-value <0.001, the effect of ASSIGN on cognition is not significant. We controlled the model for factors that are different between aspirin use and no use, taking anti-hypertensive medication and statins, and a history of cardio- and cerebrovascular events, and it did not change the results. Differences in the standardised regression weights in models of aspirin use and non-use were assessed by examining the critical ratio of estimated parameters. The effect of WMH TLV on cognition is significantly stronger among aspirin users (Z score = -3.053, p-value=0.002).

As seen in table 1, 50.7 % of aspirin use group had a history of cardio- and cerebrovascular events. We developed a similar path diagram for the association of ASSIGN, WMH and DS score and performed a multiple group comparison for the presence and absence of history of cardio- and cerebrovascular events. In those with no history of events, ASSIGN was significantly associated with poorer cognitive function (β= -0.21, p-value <0.001) but in existence of a history of event, WMH was the only significant predictor of cognitive decline (β= -0.52, p-value <0.001). These results were comparable to our hypothesized model for aspirin.

4. DISCUSSION

4.1. Interpretation of results

This study shows that aspirin use exacerbates the negative effect of WMH burden on information processing speed. This may be because aspirin treatment and brain lesion burden share a common cause, such as a history of stroke or myocardial infarction that are not included in ASSIGN. Our results show that the underlying mechanism for cognitive decline, with a focus on information processing speed, could be different in older adults with aspirin consumption.

Low dose aspirin conveys substantial benefit for secondary prevention of recurrent events in patients who have suffered cardio- and cerebrovascular events such as MI or stroke (24), but the existing evidence cannot support an advantage of aspirin use in the prevention or treatment of age-related cognitive decline.

In preliminary analyses in ABC1936 of an association between CVD risk factors and brain lesions associated with cerebrovascular disease we observed significant links between CVD risk and WML's (21, 25). In this analysis using more informative statistical models than previously available, we do not find an association between ASSIGN and WMH TLV. This

may be due to ASSIGN not incorporating diastolic BP, which has been shown to influence the severity of WMH burden (25). It may also be the case that measures of cardiovascular risk taken in mid-life are more reflective of WMH burden in late-life (26), whereas here we measured cardiovascular risk in older adults.

There are alternate plausible explanations for the association between ASSIGN and cognitive function already suggested in several studies. These alternatives, for example, include a role for brain microvascular changes following hyperglycaemia, enhanced amyloid β degradation following insulin resistance in diabetic patients (27), the effect of hypertension on vascular structure of the brain (28) and inflammation associated with smoking (29). Future studies could clarify the association of ASSIGN and poorer information processing we found here.

Many studies have evaluated the effect of taking aspirin on cognitive function or dementia but the effect of aspirin on the biomarker of subclinical cerebrovascular health has only been investigated in a small number of studies with inconsistent results (12, 13). There has been increasing interest to explore this relationship. Holcomb et al reported no significant association between chronic aspirin use and WMH volume in women. Their study consisted of a large sample (n=1193) of older adults, however, only including women participants with the average age of 77 years at MRI examination (13). The ongoing ASPREE-NEURO study aims to investigate the effect of aspirin on cerebral micro-bleeds and WMH but is yet to report (30).

The results of our SEM analyses reveal a negative association of WMH volume and cognition among aspirin users. Our results might represent related bases for taking aspirin and brain lesion burden that are not included in ASSIGN such as a history of stroke or myocardial infarction. As the comparison of the path diagram in people with and without history of cardio- and cerebrovascular events showed similar results to our model. This could be further

investigated in a larger sample by comparing aspirin usage in people with and without a history of cardio and cerebrovascular events. It also demonstrates that underlying pathways towards cognitive decline could be different in older adults' aspirin users.

These results show that inclusion of WMH volume in addition to the CVD risks built in ASSIGN score could improve the prediction of cognitive decline in older adults who take aspirin. For example, it may be beneficial to include categories of WMH burden (mild, moderate, and severe). However, as volumetric analysis of WMH burden is a relatively recent method and the pathogenesis of WMH remains unclear, further research is required to determine appropriate thresholds of WMH burden to create mild/moderate/severe categories.

4.2. Strength and weakness

To our knowledge, this is the first study to evaluate the effect of WMH volume on cognition, whilst simultaneously examining the moderating effect of taking aspirin on this association. This study benefits from availability of a life course model considering wide ranges of covariates and predictors for cognitive function and WMH burden. Uniquely, we were able to account for childhood IQ as strong predictor of cognitive ability in late life. We were also able to account for composite cardiovascular risk using ASSIGN score which is relevant to the population studied.

Self-reported medications and disorders might introduce recall bias. However, the participants included in this study were dementia free which would attenuate the likelihood of misclassification or under/over-estimation of the self-reported variables and the results. Cross sectional analysis of WMH is insufficient to explain the causal relationship for the difference between aspirin users and non-users observed in this study. There are other potential confounders that could influence the association reported in this study which were not included in our model such as exercise and diastolic blood pressure. ASSIGN score used to

estimate cardiovascular risk factor in this study is not representing current cardiovascular disease which could be potential confounders in our model.

4.3.Future research

Future studies should take into account of changes in prescribing perhaps captured through routinely recorded pharmacy prescribing information to adequately account for effect of aspirin and other cardiovascular related medications on this relationship. Longitudinal MRI data analysis could potentially enable researchers to examine whether effects of taking aspirin on the brain are causal after controlling for the effects of potential confounders.

5. CONCLUSION

Aspirin use moderates the negative effect of WMH volume on cognition. This probably represents the same case made for taking aspirin and brain lesion burden such as history of cardiovascular events that are not included in ASSIGN score. The underlying pathways towards cognitive decline may differ among older aspirin users.

Contribution

Mina Khezrian contributed to the Investigation, Methodology, Formal analysis and Writing-original draft.

Jennifer M.J. Waymont contributed to Investigation, Software, Formal analysis, Writing-reviewing and editing.

Phyo K. Myint contributed to Conceptualisation, Supervision, Writing-reviewing and editing.

Christopher J. McNeil contributed to Conceptualisation, Supervision, Writing-reviewing and editing.

Lawrence J. Whalley contributed to Conceptualisation, Supervision, Writing-reviewing and editing.

Roger Staff contributed to Conceptualisation, Formal analysis, Methodology, Writing-reviewing and editing.

Alison D. Murray contributed to Conceptualisation, Supervision, Writing-reviewing and editing.

Conflict of interest

The author declares no conflict of interest.

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Statement of Ethics

Approval for this study was obtained from the NHS Grampian Local Research Ethics Committee with reference 03/0151(abc1936).

Data Statement

The data that support the findings of this study are available from the authors upon reasonable request.

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Table 1. Participants' characteristics. (The two groups were compared using Chi-Square test, Mann-Whitney or Independent-Sample t test where appropriate).

Characteristics	**No aspirin n= 250**	**Aspirin use n=68**	**P-value**
Demographic			
No of male (%)	118(47.2)	32(47.1)	0.547
Childhood IQ	101.9(13.1)	102. (14.7)	0.814
Age Mean [y](SD)	68.7(0.8)	68.8(0.7)	0.187
Education Mean(SD)	3.3(2.2)	3.4(2.3)	0.658
Body Mass Index Mean(SD)	27.2(4.6)	27.4(4.1)	0.361
Medications			
Statins yes (%)	36(14.4)	41(60.3)	<0.001
No of anti-hypertensive, yes (%)	88(35.2)	47(69.1)	<0.001
Cardiovascular risk			
No of smoking None (%)	116(47.9)	31(45.5)	0.054
No of smoking Ex (%)	88(36.4)	33(48.5)	
No of smoking Current (%)	38(15.7)	4(5.9)	
Systolic BP	137.9(16.8)	135.0(17.8)	0.229
Diastolic BP	78.2(8.7)	76.1(9.8)	0.083
HDL cholesterol	1.5(0.3)	1.4(0.4)	0.381
Total cholesterol	5.7(0.9)	5.4(1.0)	0.031
Diabetes yes (%)	20(8.1)	12(17.2)	0.038
Family history of CVD yes (%)	179(74.2)	50(76.9)	0.748
SIMD	15.1(12.4)	14.7(11.7)	0.853
ASSIGN score	28.9(11.8)	29.6(13.3)	0.642
Cardio- & cerebrovascular event yes (%)	15(6.1)	34(50.7)	<0.001
Cognitive ability tests, Mean(SD)			
Standardised Digit Symbol	100.4(14.8)	98.4(15.8)	0.575
Total lesion volume (ml) (n=190:49)	4.1(5.5)	5.2(8.4)	0.267

CVD; cardiovascular disease, SIMD; Scottish Index of Multiple Deprivation

Figures

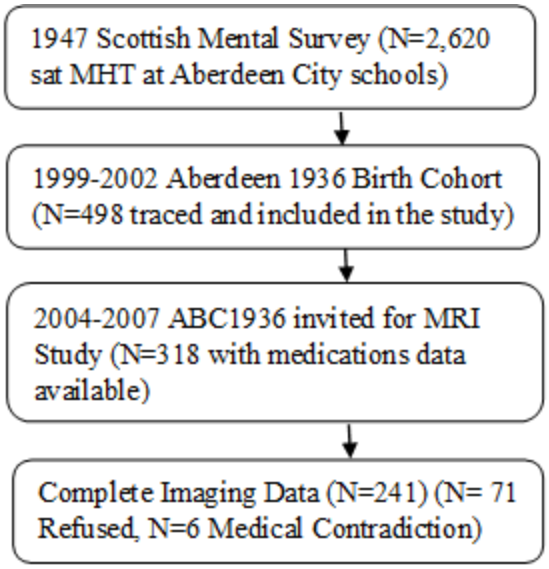

Fig. 1. Fellow chart summarising how the sample was recruited for the ABC1936 study.

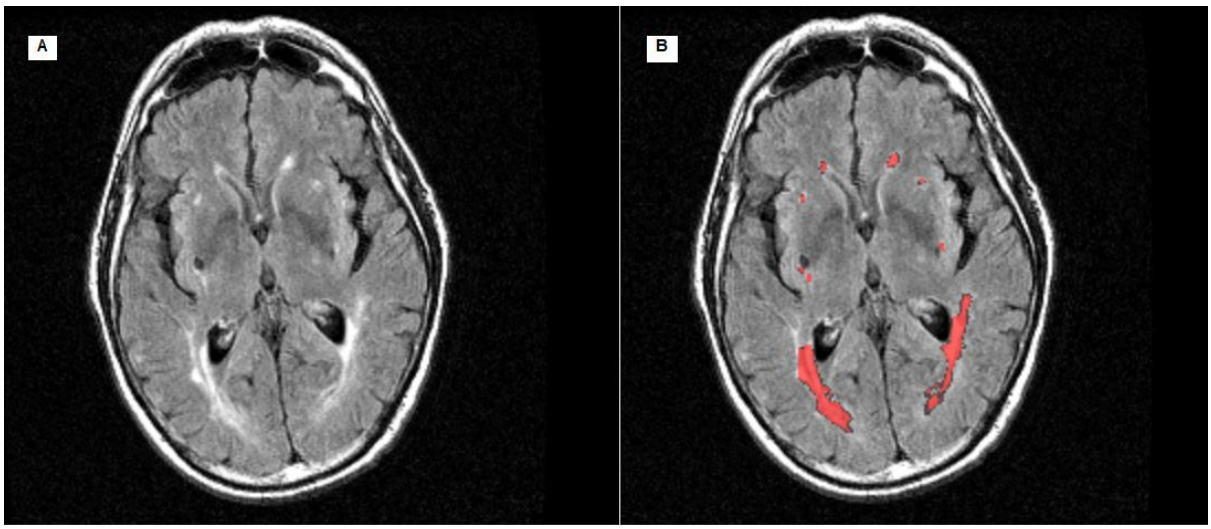

Fig. 2. Brain MRI scan of a subject shows white matter hyperintensity burden in fluid attenuation inversion recovery axial (FLAIR). (A) 3D T1-weighted MR image with white matter lesions and (B) automated segmentation of the white matter hyperintensity burden (in red) obtained using Lesion Growth Algorithm.

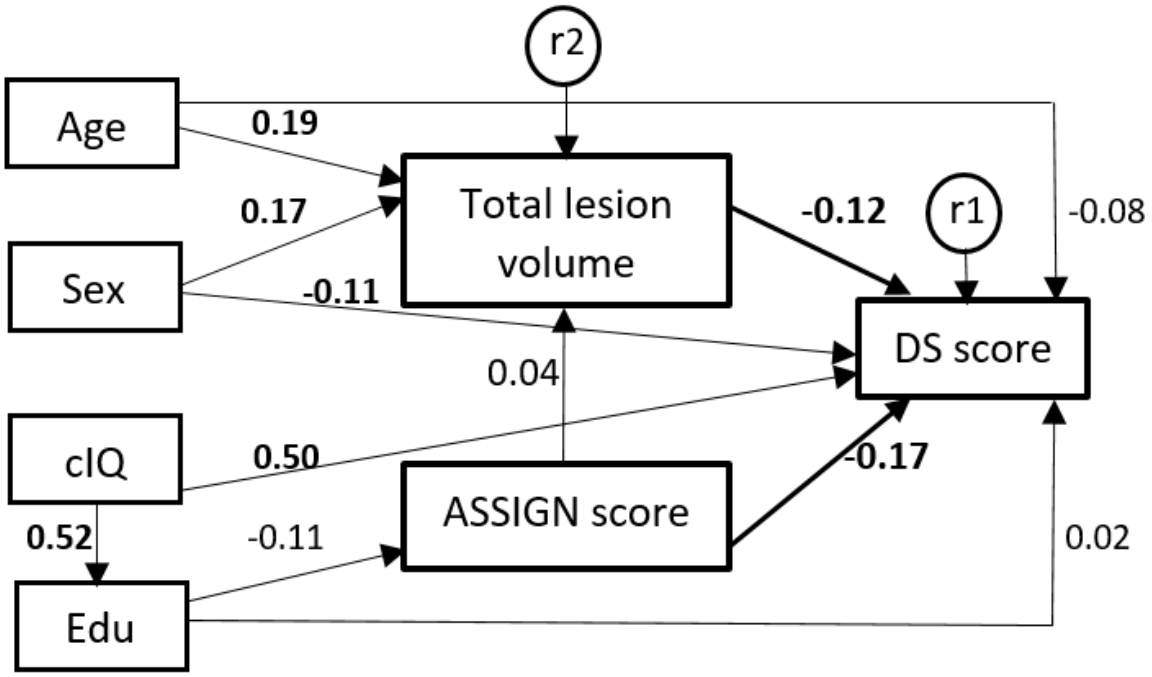

Fig. 3. Path diagram of overall hypothesised model (n=241), bold standardised regression weights represents in the diagram are statistically significant (p< 0.05). r1 and r2 are residuals. cIQ; childhood IQ, Edu; Education.

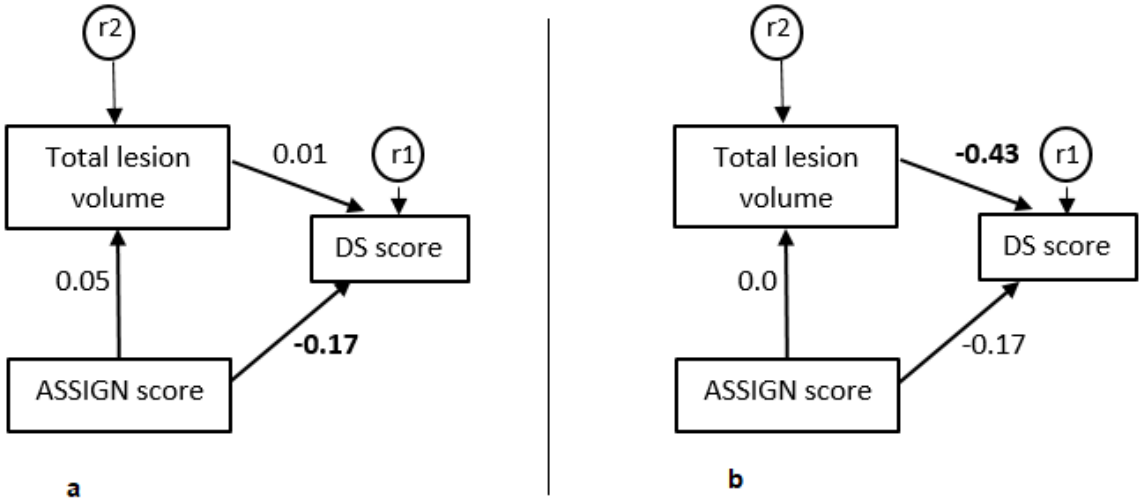

Fig. 4. Path diagrams for multiple group comparison between (a) no aspirin use (n=190) and (b) aspirin use (n=49) in the overall hypothesised model, confounders are not shown for simplicity, bold standardised regression weights represents in the diagram are statistically significant (p< 0.05). r1 and r2 are residuals.