# Associations between Childhood Abuse, Reductions of White Matter Integrity of the Corpus Callosum and White-Matter Hyperintensities, and the Role of Tobacco and Alcohol Use.

## A meta-analysis and cross-sectional study

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## Abstract

**Objective.** Childhood Abuse (CA) is a devastating experience early in life, which can have major consequences and increases the risk of psychiatric disorders in adulthood. It is suggested that CA counteracts a normal development of the Corpus Callosum (CC), which in turn could reflect an impaired integrity of White Matter (WM). It might be that long-term neurobiological alterations of WM integrity and volume, caused by CA, eventually reflect in the onset of White-Matter Hyperintensities (WMH) later in life, but literature about this relationship is lacking. WMH are of major concern because they can cause a range of negative consequences and even increase the risk of death. Yet, the etiology and causes of WMH are not completely understood. The present study aims to investigate the effect of CA on WM integrity within the CC and the onset of WMH later in life, and to investigate other risk factors of WMH (tobacco and alcohol use). **Methods**. Study 1 presents a meta-analysis ($N$ = 16) concerning WM impairments within the CC among individuals with a history of CA. Study 2 presents a cross-sectional study where WMH volumes of individuals with manifest arterial disease ($N$ = 679) are compared upon a history of CA, smoking status and alcohol intake. **Results.** CA strongly associates with WM impairments within the CC (Study 1). Only currently smoking significantly increases WMH volumes (Study 2). **Conclusions.** CA is strongly associated with reductions of WM integrity and volume, but not with WMH. For the onset of WMH, other factors emerged more important, such as increasing age, physical health (manifest arterial disease) and life-style factors (currently smoking). Further research should investigate the possible moderating influence of tobacco and alcohol use (and other unhealthy life-style factors) on the associations between CA and reductions of WM integrity, and CA and WMH.

# General Introduction

Childhood Abuse (CA) is a devastating experience early in life, which can have major consequences and has been shown to increase the risk and severity of a number of psychiatric disorders in adulthood. For example, it is found that CA associates with depression, post-traumatic stress disorder (PTSD), substance abuse, anxiety and personality disorders (Brietzke et al., 2012).

Moreover, CA has frequently been associated with long-term neurobiological alterations of the brain (Jackowski, de Araújo, de Lacerda, de Jesus Mari & Kaufman, 2009; McCrory, de Brito & Viding, 2012). These alterations are broadly varying, such as reductions of hippocampal volume (Bremner et al., 1997; Stein, Koverola, Hanna, Torchia & McClarty, 1997), amygdala volume (Ahmed-Leitao, Spies, van den Heuvel & Seedat, 2016; Weniger, Lange, Sachsse & Irle, 2008), and gray matter volume of the prefrontal cortex (Gorka, Hanson, Radtke & Hariri, 2014). Structural and functional abnormalities caused by CA are found to attribute to cognitive and psychological impairments and divergent types of psychopathology, which often become manifest during adolescence or early adulthood (Brietzke et al., 2012; Jackowski et al., 2009; McCrory et al., 2012; Teicher & Samson, 2016).

Furthermore, when children and adolescents are abused, reduced integrity of White Matter (WM) and volume of the Corpus Callosum (CC) have consistently been reported (Galinowski et al., 2015; Teicher et al., 2003; Teicher & Samson, 2016). The CC consists of more than 200 million WM tracts and is the largest WM structure in the human brain. Because it coordinates cortical activity across the right and left hemisphere, the CC is crucial for inter-hemispheric integration and communication (de Bellis et al., 1999; Franco et al., 2008). Moreover, human cognitive development depends upon the microstructural integrity of WM, therefore reductions of WM integrity and CC volume caused by CA can cause a number of negative consequences (Franco et al., 2008).

The development of the CC reflects a permanent adjustment and fine-tuning of WM tracts, consisting of myelination, redirection, and selective pruning, which is necessary for WM to become integrated (Rinne-Albers et al., 2016). At an early stage, the brain generates more axons in the CC than at maturity, and certain axons will be selected while others are discarded (Kalat, 2009, P. 411; Mori, Oishi & Faria, 2009). These integration processes most dramatically occur in childhood and adolescence, and the CC is particularly vulnerable to environmental influences at this stage. Early-life stress has therefore frequently been associated with reductions of WM integrity within the CC (McCrory et al., 2012; Paul et al., 2008; Rinne-Albers et al., 2016; Teicher et al., 2003; Teicher, Samson, Anderson & Ohashi, 2016).

The integrity of WM can also been affected during adulthood, as exemplified by White-Matter Hyperintensities (WMH). WMH primarily reflect ischemic vascular impairments and correspond to demyelination, loss of axons or nerve fibres, proliferation of glial cells, and finally cavitation and infarction (Assareh, Mather, Schofield, Kwok & Sachdev, 2011; Beyer, Young, Kuchibhatla & Krishnan, 2009; Wang, Leonards, Sterzer & Ebinger, 2014). WMH are regarded as typical signs of underlying small vessel disease and often located within affected vessels. It is presumed that WMH are induced by chronic hypo-perfusion of WM and disruption of the blood-brain barrier, leading to chronic leakage of plasma into WM (Debette & Markus, 2010; Shi & Wardlaw, 2016). The majority of research differentiates between WMH occurring in periventricular- and deep-white matter of subcortical brain regions (Beyer et al., 2009).

WMH are associated with functional, cognitive (especially in attention and executive functioning) and psychological impairments, such as gait and balance abnormalities, urinary problems (including incontinence) and physical disability (Assareh et al., 2011; O'Brien, 2014), dementia (Ferreira et al., 2017), depression and schizophrenia (Beyer et al., 2009; Wang et al., 2014), and Parkinson's disease (Assareh et al., 2011). WMH almost triple the risk of stroke, double the risk of dementia and increase the risk of death (Shi & Wardlaw, 2016). The etiology and causes of WMH are not completely understood; therefore investigation about the risk factors of WMH is of major importance (Assareh et al., 2011; van der Veen et al., 2015).

It might be that tobacco and alcohol use are risk factors for the onset of WMH. Reductions of WM integrity have frequently been found in alcoholics and nicotine dependents (Papp-Peka, Tong, Kril, de la Monte & Sutherland, 2016; Pfefferbaum et al., 2000; Pfefferbaum & Sullivan, 2005; Zhang et al., 2011), and Rostrup and colleagues (2012) even found an association between self-reported alcohol and tobacco consumption and the occurrence of WMH.

The literature above indicates an important association between CA and reductions of WM integrity and CC volume, which can result in a number of negative consequences. The literature also indicates that WMH are associated with negative consequences. It might be that long-term neurobiological alterations of WM integrity and volume, as caused by CA, eventually reflect in the onset of WMH later in life, but (to my knowledge) literature about this relationship is lacking. Therefore, the present study aims to investigate the effect of CA on different forms of WM abnormalities; reduced integrity and volume of WM within the CC and the onset of WMH. Moreover, the present study aims to investigate if tobacco and alcohol use are risk factors for the onset of WMH. To do this, a meta-analysis (study 1) of literature concerning WM volume and integrity within the CC among individuals with a history of CA, and a cross-sectional study (study 2) in which WMH volumes of participants are compared upon a history of CA, smoking status and alcohol intake, are conducted.

# Study 1

A meta-analysis of literature concerning reductions of WM integrity within the CC and volume of the CC, among individuals with a history of CA is conducted. Although the developmental consequences of CA are reflected in many brain regions, it was decided to concentrate on the CC because this is the major, and most identifiable, WM fibre bundle of the brain, and controls the important function of inter-hemispheric integration and communication (de Bellis et al., 1999; Franco et al., 2008).

For measuring volumetric reductions of the CC, T1-weighted Magnetic Resonance (MR) images are used. For measuring reductions of WM integrity, Diffusion Tensor Imaging (DTI) is used, which is a form of MRI that allows for measuring the diffusivity of water molecules within WM tracts, and is more sensitive to structural brain abnormalities than MRI (Paul et al., 2008). DTI can measure the pattern (rate, magnitude and direction) of water diffusivity, which is called anisotropic, and subsequently the myelin density or integrity of WM. When axons or their myelin layers are impaired, water molecules cannot as easily diffuse, which results in decreased water diffusivity. The DTI parameter mostly used is called Fractional Anisotropy (FA). An increase in FA suggests a better-developed WM integrity, while a decrease in FA suggests an impaired WM integrity, or possible tissue damage (Zalsman et al., 2016).

It is hypothesized that a history of CA causes significant reductions of WM integrity within the CC and volume of the CC.

## Methods

### Search strategy

A systematic literature search was conducted using the PubMed database, covering all periods and was based on two key components: There should be a) made use of DTI measures of WM integrity within the CC, or MRI measures of the CC volume, and b) investigated childhood adversity, trauma or abuse. The following terms and text words were used: “corpus callosum” or "white matter" in combination with "childhood neglect" or "childhood stress" or "childhood maltreatment" or "maternal deprivation" or "childhood trauma" or "childhood adversity", and terms related to the type of measure: “DTI” or “MRI”. Studies were selected first by screening titles and abstracts. If a study appeared relevant, the full text was reviewed to identify whether it fulfilled the inclusion criteria (for details about the inclusion criteria, see below).

Second, a snowballing strategy was used to find more relevant papers. The requirement that negative experiences must have occurred during childhood was adjusted to negative experiences during the lifespan, because it was expected that the consequences were

comparable to a certain extent.

Therefore, in the third and last step, a systematic literature search was conducted using the PubMed database with different terms and text words, covering all periods, and was based on the components: there should be a) made use of DTI measures of the CC, and b) investigated some type of trauma. The following terms and text words were used: “corpus callosum” in combination with "events" or "stress", and the term related to the type of measure: “DTI”. Studies were selected by screening titles, methods and results. See Fig. 1 for a flow chart of the systematic literature search.

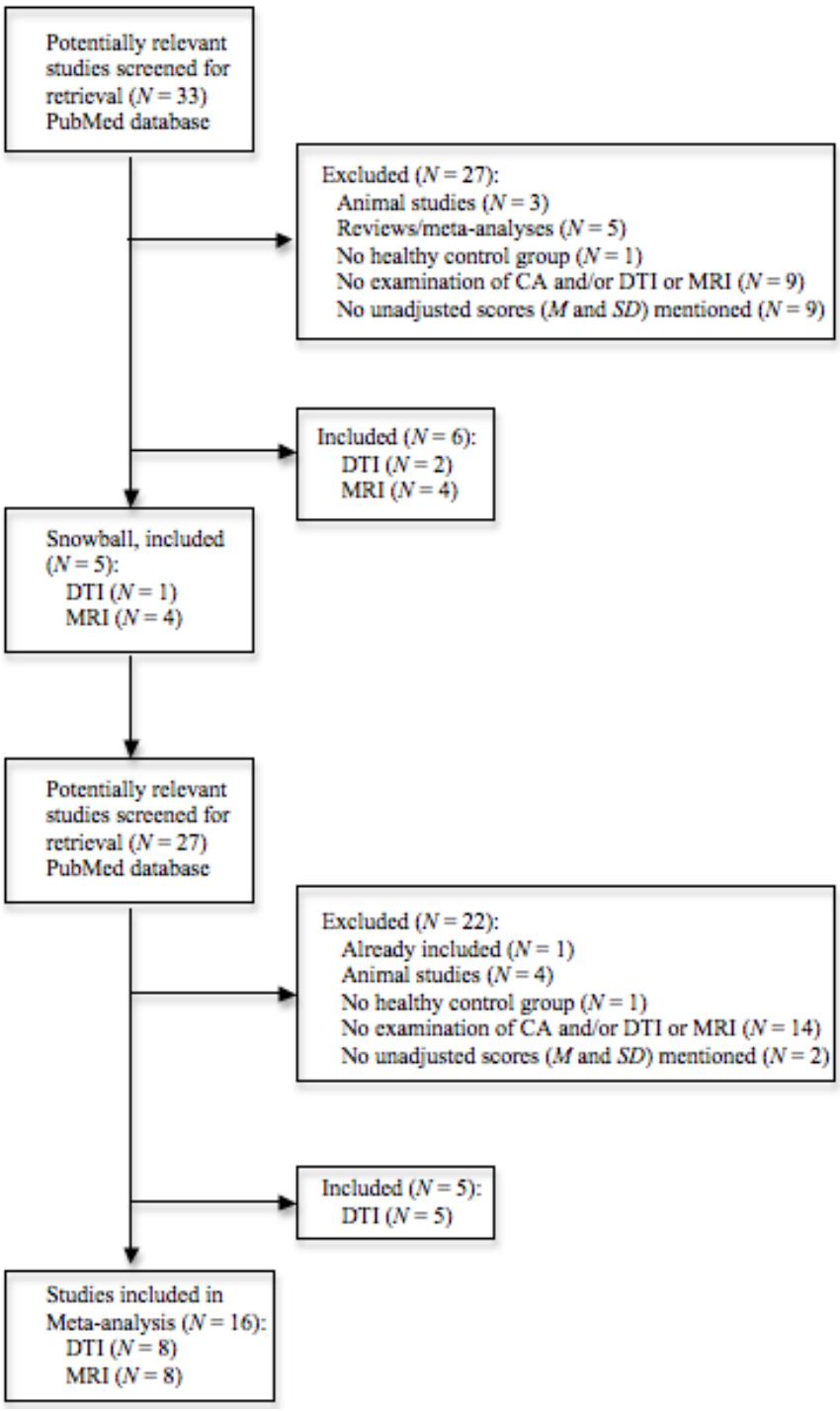


**Fig. 1**. Flow chart of studies identified during the systematic literature search

Inclusion criteria

For step 1, studies were included when they met the criteria: 1) participants were human, 2) the aim was to investigate negative childhood events, 3) WM within the CC or CC volume was measured, 4) there was no overlap between participants of the included studies, 5) the sample included a healthy control group, and 6) an equal number of DTI and MRI studies was reached. Furthermore, no reviews or meta-analyses were included. For step 3, criterion 2) the aim was to investigate negative childhood events, was adjusted in 2) the aim was to investigate some type of trauma. Other criteria remained equal.

Statistical analysis

Demographic variables were measured using SPSS Statistics (IBM SPSS Statistics 2013, version 22.0). Mean values (*M*) and standard deviations (*SD*) for WM integrity and CC volume were extracted from the studies, for participants with and without trauma. Using the "meta" package (version 4.3-0) in R (version 3.2.1; www.r-project.org/), standardized mean differences (SMDs) were modelled with the restricted maximum-likelihood estimator for tau squared, using random effects in the function "metacont." Heterogeneity was assessed with $I^2$. Metaregression and subgroup analyses were run for the moderators: gender and age. To examine publication bias, forest plots were modelled. Overall correlations were estimated.

**Results**

Descriptives

Table 1 presents the study characteristics and main findings of the 16 included studies. All studies were published in English and mentioned *M*s and *SD*s.

The first search identified 33 studies. After exclusion of studies that did not met the inclusion criteria (see Fig. 1), 6 were included in the meta-analysis. All 6 evaluated differences in WM integrity within the CC, or CC volume between participants with a history of CA and controls (Bücker et al., 2014; Huang et al., 2012; Lu et al., 2013; Ritchie et al., 2012; Spies et al., 2016; Teicher et al., 2004).

Second, the inspection from 1 reviews' reference list (Daniels et al., 2013) yielded 5 studies that met the inclusion criteria, and were included to the meta-analysis. All 5 evaluated differences in WM integrity within the CC, or CC volume between participants with a history of CA and controls (snowballing; de Bellis et al., 1999; de Bellis et al., 2002; Jackowski et al., 2008; Kitayama et al., 2007; Mehta et al., 2009).

The last search identified 27 studies in PubMed. Based on measurement type, 5 studies were included in the meta-analysis. 1 evaluated differences in WM integrity within the CC between participants with a history of CA and controls, and 4 evaluated these differences between PTSD patients (e.g. traffic accidents, war traumas) and healthy controls (Hu et al., 2016; Paul et al., 2008; Saar-Ashkenazy et al., 2016; Sorg et al., 2014; Sun et al., 2015).

**Table 1.** *An overview of the included studies*

| Method | Author | Population | *N* | Age (*M*) Experimental / Control | Region of the CC assessed | Measure of CA or PTSD | Sig.? | Increase or decrease when trauma |
|---|---|---|---|---|---|---|---|---|
| DTI: FA | | | | | | | | |
| | Hu *et al.* (2016) | MVA survivors with and without PTSD | 34 | 42,2 / 38,6 | Splenium (Forceps Minor) | - PDI<br>- CAPS<br>- SCID for DSM-IV-TR | *Sig.* | Decrease in mean FA |
| | Huang *et al.* (2012) | Adolescents exposed to CA and controls | 32 | 15,9 / 16,0 | Splenium (Forceps Major) | Childhood Adversity Interview | *Sig.* | Decrease in mean FA |
| | Jackowski *et al.* (2008) | Adolescents exposed to CA and controls | 32 | 10,6 / 10,6 | Splenium | History of protective services intervention for indication of child maltreatment | *N. Sig.* | Decrease in mean FA |
| | Lu *et al.* (2013) | Healthy adults with and without a history of CA | 42 | 21,1 / 21,8 | Genu & Body of the CC | CTQ | *Sig.* | Decrease in mean FA |
| | Paul *et al.* (2008) | Healthy adults with and without a history of CA | 116 | 41,0 / 38,1 | Splenium | Self-developed questionnaire based on Child Abuse and Trauma Scale | *N. Sig.* | Decrease in mean FA |
| | Saar-Ashkenazy *et al.* (2016) | PTSD patients recruited from the trauma-center at Soroka University Medical Center and controls | 30 | 37,0 / 31,1 | Total CC | - Structured psychiatric interview<br>- CAPS | *N. Sig.* | Decrease in mean FA |
| | Sorg *et al.* (2014) | Veterans with mild traumatic brain injury + PTSD and controls | 32 | 28,9 / 32,9 | Splenium | PCL-M | *N. Sig.* | No difference in mean FA |
| | Sun *et al.* (2015) | MVA survivors with and without PTSD | 29 | 40,2 / 36,3 | Genu | - Structured psychiatric interview<br>- ASDI<br>- CAPS | *Sig.* | Decrease in mean FA |
| MRI | | | | | | | | |
| | Bücker *et al*. (2014) | Borderline patients with and without a history of CA | 53 | 22,1 / 23,5 | Total CC area | CTQ | *Sig.* | Decrease in mean volume |
| | De Bellis *et al*. (1999) | Adolescents exposed to CA and controls | 105 | 12,2 / 12,0 | Total CC area | Trauma interview developed by DeBellis (1997) | *Sig.* | Decrease in mean volume |

**Table 1.** *Continued*

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| De Bellis *et al*. (2002) | Adolescents exposed to CA and controls | 94 | 11,5 / 11,6 | Total CC area | Trauma interview developed by DeBellis (1997) | *Sig.* | Decrease in mean volume |
| Kitayama *et al*. (2007) | Females with CA related PTSD and controls | 18 | 37,8 / 36,8 | Total CC area | CAPS | *N. Sig.* | Increase in mean volume |
| Mehta *et al*. (2009) | Romanian adoptees and non-adopted UK children | 25 | 16,2 / 16,0 | Total CC area | Severe deprivation during early years of life | *N. Sig.* | Decrease in mean volume |
| Ritchie *et al*. (2012) | Elderly individuals with and without a history of CA | 427 | 70,6 / 72,1 | Total CC area | CAQ | *N. Sig.* | Increase in mean volume |
| Spies *et al*. (2016) | HIV-positive females with and without a history of CA | 62 | 34,9 / 31,1 | Total CC area | CTQ- SF | *Sig.* | Decrease in mean volume |
| Teicher *et al*. (2004) | Adolescents exposed to CA and controls | 143 | 12,9 / 11,9 | Total CC area | Structured psychiatric interview | *Sig.* | Decrease in mean volume |

MVA: Motor vehicle accidents. PTSD: Post-Traumatic Stress Disorder. PDI: Peri-traumatic Distress Inventory. CAPS: Clinician-Administered PTSD Scale. SCID: Structured Clinical Interview for DSM Disorders. CTQ: Childhood Trauma Questionnaire. PCL-M: PTSD checklist-Military version. ASDI: Acute stress disorder inventory. CAQ: Childhood Adversity Questionnaire. CTQ-SF: Childhood Trauma Questionnaire-Short Form.

Integrity of WM within the CC (DTI) was assessed in 8 studies (50%). In 4 DTI studies (50%) and 8 MRI studies (100%), experimental groups consisted of participants with a history of CA. A decrease in mean FA was reported in 7 DTI studies (87.5%), and 1 reported no difference. A decrease in mean CC volume was reported in 6 MRI studies (75%), and 2 reported an increase.

Meta analysis WM integrity and CC volume

For WM integrity, 138 participants were included in the experimental group, and 209 in the control group. In all studies combined, a history of CA or current PTSD was associated with significant reductions of WM integrity within the CC ($Z$ = -3.17, $p$ = .002). The random effects model showed a SMD in WM integrity between CA/PTSD and control subjects of -1.05 (95% confidence interval [CI] -1.69, -0.40). Heterogeneity between studies was considerable, with $I^2$ of 82.1% ($p$ < .0001). For CC volume, 514 participants were included in the experimental group, and 413 in the control group. In all studies combined, a history of CA was associated with a significantly smaller CC volume ($Z$ = -3.43, $p$ < .001). The random

effects model showed a SMD in CC volume between CA and control subjects of -0.49 (95% confidence interval [CI] -0.76, -0.21). Heterogeneity between studies was considerable, with $I^2$ of 72.1% ($p < .001$).

Meta-regression analysis on gender and age within the WM integrity studies revealed a significant effect for age ($Z = 4.05$, $p < .0001$). The estimated model coefficient for age control versus age experimental was 0.07 ($SE = .02$, [CI] 0.03, 0.10). Meta-regression analysis on gender and age within the CC volume studies also revealed a significant effect for age ($Z = 4.66$, $p < .0001$). The estimated model coefficient for age control versus age experimental was 0.01 ($SE = .00$, [CI] 0.01 to 0.02). No differences of gender were found in both meta-regressions. Fig. 2 presents the forest plots of DTI (upper) and MRI studies (lower).

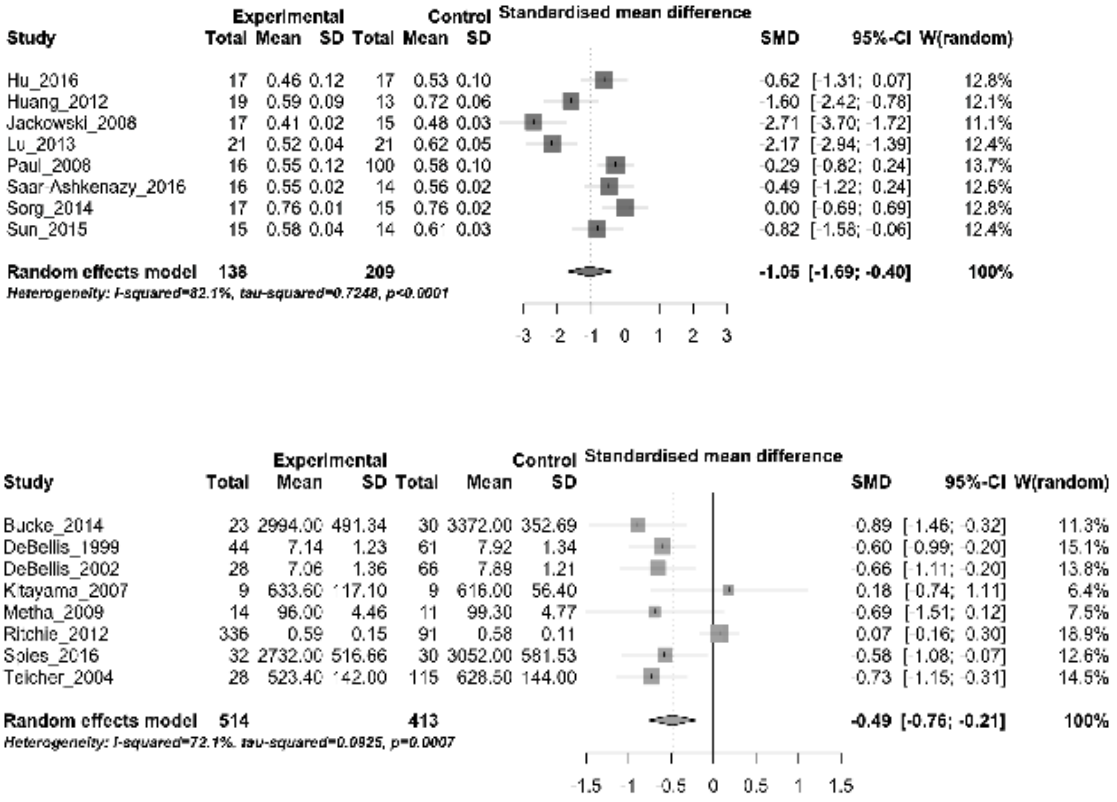


**Fig. 2**. Forest plots of standardized mean differences, 95% CI and W(random) of the included DTI studies (upper) and MRI studies (lower)

As seen in Fig. 2, there was a higher range between SMDs within the DTI studies than within the MRI studies, which was also reflected in the I-squared that showed significant heterogeneity among the studies. The lowest SMDs were found when experimental groups consisted of participants with a history of CA. Table 2 presents the SMDs organized by type of measure and experimental group.

**Table 2**. *Standardized mean differences, 95% CI and W(random) of the included DTI and MRI studies, organized by type of experimental group*

| | SMD | 95%-CI % | *W* (random) |
|---|---|---|---|
| DTI (FA): WM integrity within CC | | | |
| History of CA | | | |
| Huang et al. (2012) | -1.60 | [-2.42, -0.78] | 12.1 |
| Jackowski et al. (2008) | -2.71 | [-3.70, -1.72] | 11.1 |
| Lu et al. (2013) | -2.17 | [-2.94, -1.39] | 12.4 |
| Paul et al. (2008) | -0.29 | [-0.82, 0.24] | 13.7 |
| Current PTSD | | | |
| Hu et al. (2016) | -0.62 | [-1.31, 0.07] | 12.8 |
| Saar-Ashkenazy et al. (2016) | -0.49 | [-1.22, 0.24] | 12.6 |
| Sorg et al. (2014) | 0.00 | [-0.69, 0.69] | 12.8 |
| Sun et al. (2015) | -0.82 | [-1.58, -0.06] | 12.4 |
| MRI: CC volume | | | |
| History of CA | | | |
| Bucker et al (2014) | -0.89 | [-1.46, -0.32] | 11.3 |
| De Bellis et al. (1999) | -0.60 | [-0.99, -0.20] | 15.1 |
| De Bellis et al. (2002) | -0.66 | [-1.11, -0.20] | 13.8 |
| Kitayama et al. (2007) | 0.18 | [-0.74, 1.11] | 6.4 |
| Metha et al. (2009) | -0.69 | [-1.51, 0.12] | 7.5 |
| Ritchie et al. (2012) | 0.07 | [-0.16, 0.30] | 18.9 |
| Spies et al. (2016) | -0.58 | [-1.08, -0.07] | 12.6 |
| Teicher et al. (2004) | -0.73 | [-1.15, -0.31] | 14.5 |

SMD: Standardized mean difference. 95% CI: 95% Confidence interval. *W*(random): Weight of individual studies (in random effects model).

## Conclusion

A history of CA was highly associated with reductions of WM integrity and volume within the CC, therefore the hypothesis was confirmed. Although not all participants were individuals with and without a history of CA, overall SMDs were lower when experimental groups consisted of participants with a history of CA, than when experimental groups consisted of PTSD patients. A strong association between age and WM integrity was found.

# Study 2

A cross-sectional study is conducted in which WMH volumes of participants are compared upon a history of CA, and the potential risk factors tobacco and alcohol use are investigated. It might be that long-term alterations of WM integrity and volume, as caused by CA, eventually reflect in the onset of WMH later in life. Because WMH are more common in individuals aged 60 and older with manifest arterial disease (Beyer et al., 2009; Ferreira et al., 2017; Geerlings et al., 2010), investigation about the risk factors of WMH among this specific population could provide more insight.

Age and arterial disease are far from being the only risk factors for the onset of WMH (Rostrup et al., 2012). Tobacco and alcohol use are also found to affect WM integrity, or to contribute to the onset of WMH (Pfefferbaum & Sullivan, 2005; Rostrup et al., 2012; Zhang et al., 2011).

It is hypothesized that a history of CA is significantly related to the onset of WMH later in life for individuals with manifest arterial disease, and that tobacco and alcohol use further increase the risk of WMH.

## Methods

### Study population

Data was used from the Second Manifestations of ARTerial disease; memory, depression, and aging (SMART-Medea) study. The SMART infrastructure was initiated at the Vascular Centre of the University Medical Center Utrecht (UMCU) in September 1996. In short, the aim was to provide a broad investigation about the prevalence, detection and effectiveness of treatment and prospective incidence of cardiovascular events and risk factors in patients with manifest arterial disease, and to study their quality of life (Simons, Algra, van de Laak, Grobbee & van der Graaf, 1999).

In the SMART-Magnetic Resonance (SMART-MR) study, 1309 participants, aged 18 to 79, were newly referred to the UMCU. MRI investigation of brain changes was added to the baseline examination and patients filled out questionnaires on a history and symptoms of cardiovascular disease, and risk factors such as smoking, alcohol consumption and medical history (For more information, see: Geerlings, Appelman, Vincken & Mali, 2009).

As a follow-up, the prospective SMART-Medea study aimed to investigate how brain changes were associated with psychosocial vulnerability and stress factors. Between April 2006 and May 2009, 754 participants were reassessed by measurements of stress factors and depression, including MRI of the brain, neuropsychological testing, physical examination, blood and urine sampling, medical history and a depression interview (For more information, see: Gerritsen et al., 2011). The ethics committee of the UMCU approved the SMART,

SMART-MR, and SMART-Medea study, and written informed consent was obtained from all participants (Geerlings et al., 2009; Gerritsen et al., 2011; Simons et al., 1999).

Brain Segmentation

The MR investigations were performed on a 1.5-Tesla wholebody system (Gyroscan ACSNT, Philips Medical Systems, Best, the Netherlands). Brain volumes were calculated with a probabilistic segmentation technique, and results of the segmentation analysis were visually checked for the presence of infarcts and adapted if necessary to make a distinction between WMH and infarct volumes. Total intracranial volume (ICV) was calculated by summing up grey and white matter, WMH and cerebrospinal fluid volumes obtained with automated segmentation (Gerritsen et al., 2011). Total volume of WMH was corrected by ICV, and added as a proportion of ICV.

Covariates

The following variables were considered as covariates, because these significantly changed the relationship between WMH (outcome) and CA (independent variable) in a preliminary linear regression analysis: age, sex and Body Mass Index (BMI) score ($R^2$ change = 24.7%, $p < .001$). Smoking status (current, former, never) and alcohol intake (less than 1 drink/week, 1 to 10 drinks/week, 11 to 20 drinks/week, more than 20 drinks/week) were considered as covariates because these variables were found to predict WMH in previous research (Rostrup et al., 2012).

Statistical analysis

First, the main effect of CA was estimated on WMH volume (corrected by ICV), in a linear regression model. Second, the covariates age, sex, BMI, smoking status and alcohol intake were added to the model. Dummy variables were made for smoking status (with “never smoked” as reference), and alcohol intake (with “1 to 10 drinks/week” as reference). Third, an analysis of covariance (ANCOVA) was used to explore which groups of participants (differentiated on CA, smoking status and alcohol intake) were most affected by WMH. All analyses were conducted in SPSS Statistics (IBM SPSS Statistics 2013, version 22.0).

## Results

Descriptives

Due to missing data ($N = 75$), regression analyses were conducted with a population of 679 participants. Table 3 presents the characteristics of the SMART-Medea study population.

**Table 3.** *Characteristics of the SMART-Medea study population*

| | Total sample |
|---|---|
| *N* (% male) | 754 (82.1%) |
| Age, years | |
| Mean (S.D.) | 61.57 (9.40) |
| Range | 31 – 83 |
| Smoking status | |
| Current | 165 |
| Former | 461 |
| Never | 120 |
| Alcohol intake (drinks per week) | |
| < 1 drink | 224 |
| 1-10 drinks | 295 |
| 11-20 drinks | 139 |
| > 20 drinks | 84 |
| Body mass index | |
| Mean (S.D.) | 27.35 (3.81) |
| Range | 17.80 – 44.80 |
| Childhood abuse (0-4) | |
| No events | 590 |
| One event or more | 149 |
| White-matter hyperintensities, ml | |
| Mean (S.D.) | 2.20 (1.21) |
| Range | 1.67 – 5.58 |

Missing data occurred in the following variables: white-matter hyperintensities ($N = 63$), childhood abuse ($N = 15$), body mass index ($N = 7$), smoking status ($N = 8$), and alcohol intake per week ($N = 12$).

Multiple regression analyses

Multiple regression analysis was conducted to test relationships between WMH and CA and the covariates age, sex, BMI, smoking status and alcohol intake. In the first model, the direct association between CA and WMH was examined, which was not significant ($F(1, 677) = .43$, $p = .511$). The second model, in which the covariates age, sex and BMI were added, was highly significant ($F(4, 674) = 55.35$, $p < .001$), and changed the association between WMH and CA by 24.7%. Age had the strongest relationship with WMH ($p < .001$). In the third model, smoking status (never vs. current and former) was added, and changed the association between WMH and the covariates with 0.05% ($F(6, 672) = 37.77$, $p = .111$). Only current smoking status was significantly related to WMH ($p = .043$), while former smoking status was not ($p = .079$). Alcohol intake (1 to 10 drinks/week vs. less than 1 drink/week, 11 to 20 drinks/week and more than 20 drinks/week) was added in the fourth model, and did not change the association between WMH and the covariates ($p = .985$). No significant relationships were found. See Table 4 for an overview of the regression coefficients from each model. Overall, 25.3% of the variation in WMH was explained by the model ($F(11, 667) = 20.50$, $p < .001$).

**Table 4**. *Associations between the volume of white-matter hyperintensities, childhood abuse and confounders*

| | *b* (*SE*$_b$) | 95% CI | *β* |
|---|---|---|---|
| Model I | | | |
| Childhood abuse | .08 (.12) | -0.15, 0.30 | .03 |
| Model II | | | |
| Age | .06 (.00) | 0.05, 0.07 | .48** |
| Sex | .22 (.10) | 0.02, 0.42 | .07* |
| BMI | -.02 (.01) | -0.04, 0.00 | -.06 |
| Model III | | | |
| Smoking status | | | |
| Reference[a] vs. current | .27 (.13) | 0.01, 0.52 | .09* |
| Reference vs. former | .20 (.11) | -0.02, 0.42 | .08 |
| Model IV | | | |
| Alcohol intake | | | |
| Reference[b] vs. less than 1 drink/week | .04 (.10) | -0.16, 0.24 | .01 |
| Reference vs. 11 to 20 drinks/week | .00 (.11) | -0.22, 0.23 | .00 |
| Reference vs. more than 20 drinks/week | -.01 (.14) | -0.28, 0.27 | .00 |

Dependent variable: Volume of white-matter hyperintensities
[a] Reference in smoking status: never smoked in life
[b] Reference in alcohol intake: 1 to 10 drinks/week
** Sig. at < .001
* Sig. at < .05

Analysis of covariance

ANCOVA was used to explore which participants were mostly affected by WMH. The differentiated groups were CA: CA+ (*N* = 149) and CA- (*N* = 590), smoking status: former (*N* = 461) and current (*N* = 165), and alcohol intake: less than 1 drink/week (*N* = 224) and 11-20 drinks/week (*N* = 139). More than 20 drinks/week was not included in the ANCOVA because the small number of participants within this group (*N* = 84). No significant differences were found between the subgroups. However, as seen in Fig. 3, WMH volumes tended to increase when participants used 11 to 20 drinks/week and had a history of CA (*M* = 2.40, *SD* = 1.25) compared to participants who did not experience CA (*M* = 2.10, *SD* = 1.21). Currently smoking further increased WMH volumes (for CA+ : *M* = 2.90, *SD* = 0.58; for CA- : *M* = 2.37, *SD* = 1.17), compared to not smoking (for CA+ : *M* = 2.33, *SD* = 1.32; for CA- : *M* = 2.01, *SD* = 1.22). Surprisingly, WMH volumes tended to increase when participants did not drink alcohol and had no history of CA (*M* = 2.28, *SD* = 1.28), while WMH volumes decreased when participants did experience CA (*M* = 1.79, *SD* = 1.25). Currently smoking further increased WMH volumes (for CA+ : *M* = 2.12, *SD* = 0.63; for CA- : *M* = 2.58, *SD* = 1.23), compared to not smoking (for CA+ : *M* = 1.64, *SD* = 1.42; for CA- : *M* = 2.18, *SD* = 1.28).

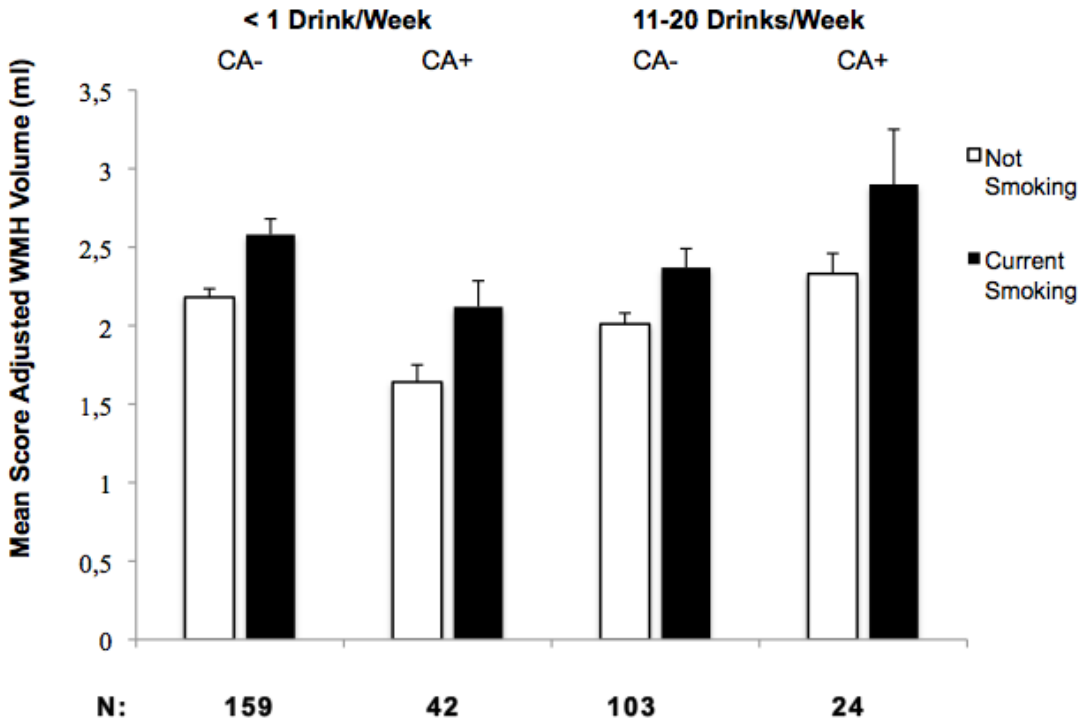


**Fig. 3.** Association of childhood abuse (CA), smoking status, alcohol intake per week and mean volumes of white matter hyperintensities (WMH), adjusted for intracranial volume

## Conclusion

No direct association was found between CA and WMH, therefore the hypothesis that a history of CA significantly relates to the onset of WMH later in life, was not confirmed. Among the risk factors, only currently smoking was significantly related to WMH, therefore the hypothesis that tobacco and alcohol use further increase the risk of WMH, was only partially confirmed. Yet, age was highly associating to the onset of WMH. Comparison of subgroups revealed that there were only small, not significant differences in WMH volumes, associated with CA, smoking status and alcohol intake.

## General Conclusion and Discussion

In the present study it was investigated if CA associated to different forms of WM abnormalities; reduced integrity and volume of WM early in life, and increases of WMH volume later in life. It was also examined if tobacco and alcohol use further increased the risk of WMH.

In Study 1 it was found that CA strongly related to reductions of WM integrity within the CC and volume of the CC, therefore the first hypothesis was confirmed. Not all participants were individuals with and without a history of CA, but standardized mean differences were lower for participants with a history of CA than for PTSD patients. Although incidentally revealed, these findings might indicate that traumatic experiences occurring early in life have more negative consequences for WM integrity and volume than traumatic experiences later in life. Sorg and colleagues (2014) concluded that the traumatic experiences of PTSD itself did not affect WM integrity, but the loss of consciousness following a head injury accounted for reductions of WM integrity.

The literature concerning brain development already established that there are early sensitive periods in which brain structures such as the CC are particularly vulnerable to the long-term influences of CA (Teicher et al., 2003). Between ages 6 months to 3 years, the processes of myelination, redirection and selective pruning of WM tracts within the CC most dramatically occur (de Bellis et al., 1999; Brietzke et al., 2012). These processes are crucial for the development of WM integrity and the development of hemispheric integration (Rinne-Albers et al., 2016; Teicher et al., 2016). The development of CC volume might have a different specific period in which it is particularly vulnerable to the influences of CA. In a cross-sectional study it was found that CA mostly affected CC volume at age 9-10 (McCrory et al., 2012). It is suggested that the different CC regions and functions have different age-windows for vulnerability to negative experiences, which all take place in childhood or adolescence (Brietzke et al., 2012). Because early traumatic experiences had more influence on WM integrity and volume than later traumatic experiences, the present results confirmed the acceptability of age-windows for vulnerability to negative experiences during childhood and adolescence.

The neurobiological changes can be viewed as a cascade of deleterious effects that are harmful for the child. Changes in how emotional and cognitive systems mediate social interaction could afterwards explain a heightened vulnerability to psychopathology (McCrory et al., 2012). From an evolutionary perspective, stress hormones caused by early traumatic experiences might have induced a long-term adaptive response, which could protect the child to environmental threat and high levels of stress (McCrory et al., 2012; Rinne-Albers et al., 2016; Teicher et al., 2003). Paul and colleagues (2008) found that stress-induced developmental modifications of WM integrity and volume were still evident in adulthood.

However, an association between a history of CA and the onset of WMH later in life was not found in study 2. An explanation could be that WMH were not reflecting long-term modifications of WM integrity and volume caused by CA. Moreover, the onset of WMH might have been subjected to other, more considerable, features than a history of CA. For example, age and WMH were highly associated. This result confirmed the amount of previous studies, in which increasing age was also found as one of the most important risk factor for WMH. WMH are affecting more than 25% of the individuals aged 65 and older (Beyer et al., 2009; Ferreira et al., 2017; Rostrup et al., 2012). Moreover, the population of study 2 consisted of individuals with manifest arterial disease, which is another crucial risk factor for the onset of WMH (Ferreira et al., 2017; Geerlings et al., 2010). Therefore, the features age and manifest arterial disease might have out voiced a history of CA as risk factors for WMH.

Another important risk factor was found in study 2; current smoking status was significantly associated to WMH volume. Previous research frequently indicated regularly smoking as an important risk factor for multiple cardiovascular diseases, including WMH (Swan & Lessov-Schlaggar, 2007). For example, Ferreira and colleagues (2017) found an exacerbation in WMH due to smoking in their longitudinal study of individuals aged 60 to 85 with a history of hypertension. Smoking status explained 19% of the increases in WMH volume over 7 years of time.

Surprisingly, alcohol intake was not associated with increases in WMH volume in the current results. Pfefferbaum and colleagues (2000) already revealed that WMH in alcoholics have only subtle functional effects and deficits. They suggested that WMH and the resulting cognitive consequences are potentially reversible with sobriety and adequate nutrition. It could be possible that some participants in study 2 adopted a healthier lifestyle because of their condition of manifest arterial disease, which consequently reversed the negative effects of former alcohol use. Another explanation might be that smoking is a more considerable risk factor than alcohol use for the onset of WMH. Papp-Peka and colleagues (2016) estimated that more than 80% of the chronic alcoholics regularly smoke, and mentioned that a considerable proportion of the damage seen in alcohol related brain damage is due to smoking.

The current results might have indicated how important a healthy life-style is for individuals with manifest arterial disease. It is previously found that an accumulating relationship between tobacco and alcohol can result in WM degeneration (Papp-Peka et al., 2016). In the current study, the individuals most affected by WMH were those who currently smoked and had daily drinking habits. Yet, none of these subgroups significantly differed.

In conclusion, the results of the present study indicated that CA is strongly associated with reductions of WM integrity and volume, but not with WMH. For the onset of WMH, other factors emerged more important, such as increasing age, physical health (manifest arterial disease) and life-style factors (currently smoking).

Limitations and further directions

The present study did not investigate a possible moderating influence of tobacco and alcohol use. It could be that individuals with a history of CA had higher levels of psychological distress (e.g. depression) and consequently adopted unhealthier life-styles (higher tobacco and alcohol use), in order to cope with the traumatic experiences. Further research should investigate the possible moderating influence of tobacco and alcohol use (and other unhealthy life-style factors) on the associations between CA and reductions of WM integrity, and CA and WMH.

Furthermore, the data in study 2 might have been subjected to information bias. The information was based upon self-reports of (e.g.) smoking status and alcohol intake, and participants might have answered in a socially desirable way. Therefore it was not known if the data was representational for the actual tobacco and alcohol use of individuals. Moreover, it was not known if participants in study 2 adopted a healthier life-style because of their condition of manifest arterial disease. Therefore, it might be that WMH actually were related to current or former alcohol use, while this was not reflected in the present data and following results.

At last, the subgroup using the highest alcohol intake per week was excluded from the analysis of covariance because the small number of participants. Therefore it was not examined if there was a linear relationship between smoking, alcohol intake and the onset of WMH in study 2. Further research should investigate if there is a linear relationship between these risk factors and the onset of WMH for individuals with manifest arterial disease. It would also be of interest to investigate if currently smoking has more influence on the onset of WMH than alcohol use.

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