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Attention deficits, Vascular Risk Factors and their contribution to Dementia Conversion

A retrospective study on MCI subjects

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Abstract

Mild cognitive impairment (MCI) is seen as a cognitive state prior to dementia, as MCI subjects are at higher risk of dementia conversion. Learning about the neuropsychological profile helps to indicate MCI subjects that will convert. The objective of this study is to see whether attentional deficits are associated with dementia conversion. Vascular risk factors (VRF) are also associated with a higher conversion rate. The second aim of this study is to see whether in our dataset MCI subjects that are diagnosed with one or more VRF have a higher risk of dementia conversion. This study uses a retrospective approach. 83 MCI patients were selected in the outpatient register. Baseline examination of attentional deficits was directly compared to follow-up measurements. No significant results were found for either attentional deficits or VRF with regard to dementia conversion. This study underlines the complexity of the relationship between risk factors and conversion. It stresses the importance of further analyzing factors that add to an increased risk of dementia conversion, in order to develop adequate intervention treatments.

Keywords: Mild Cognitive Impairment, Dementia, Conversion, Vascular Risk Factors, Neuropsychological Profile, Attention Domain

Introduction

The notion that a stage exists prior to dementia has been acknowledged for several years in the literature. In this stage subjects experience some sort of cognitive impairment within any of the cognitive domains, but without actually meeting the criteria of a dementia. The concept of this transitional stage has been of particular interest because it might signal the presence of an underlying neurodegenerative disease (Aretouli, Tsilidis & Brandt, 2013). Research has found consistent evidence claiming that subjects who are in this intermediate stage have an increased risk of developing a dementia compared to subjects with normal cognitive functioning (Lopez et al., 2012). The clinical term to describe this prior stage of dementia has however changed over the years. In 2004, Petersen was the first to propose diagnostic guidelines for the general term of Mild Cognitive Impairment (MCI). As research further progressed, the MCI group was found to be more heterogeneous than originally thought, and a great variability in both characteristics of MCI diagnosis and clinical outcome exists within this group (Petersen, 2004).

For several years the cognitive domain of memory has been considered the most important subject for the MCI group, as memory failure is often seen as the most prominent feature of dementia, especially for Alzheimer's disease (Caselli et al., 2014). Several studies have indeed found that isolated memory deficits in MCI subjects lead to a higher risk of conversion to

Alzheimer's disease (Bowen et al., 1997; Petersen, 1999; Petersen, 2001). The term amnestic-MCI (MCI-a) was proposed for MCI subjects with memory impairments. Whereas some researchers believed that all diagnosed MCI subjects share the same underlying aetiology and will eventually all develop AD, others have argued that separate subtypes of MCI exist with different underlying mechanisms and different clinical outcomes (Petersen, 2001). In their study, Lopez et al. (2003) argued for at least two subtypes of MCI; the MCI amnestic-type and the MCI multiple cognitive deficits-type, with the latter having a higher prevalence in their cohort.

Currently, there is a consensus that separate subtypes of MCI can be identified and that they differ in the risk of converting to a dementia (Lopez et al. 2003). Various studies have shown that the subtype multiple-domain MCI is considered being at higher risk for progression to dementia than the MCI subtypes with impairment in a single cognitive domain (either amnestic or non-amnestic MCI) (Alexopoulos, Grimmer, Perneczky, Domes, & Kurz, 2006; Aretouli, Okonkwo, Samek, & Brandt, 2011). Recently, it has been suggested that the concept of MCI is even more heterogeneous than assumed, and that separate MCI subtypes can be identified for different outcomes of dementia. Researchers have found evidence for the prodromal stage of other types of dementia, including PD-MCI as the stage before Parkinson disease dementia, and vascular-MCI as the stage before developing a vascular dementia (VaD) (Saito, Yamamoto, & Ihara, 2015). However, it is often seen that different types of dementia are mixed – especially Alzheimer's disease and vascular dementia - rather than that the disease is presented in a pure form. Hence, it might be that different forms of dementia – and the subtypes of MCI - share a common underlying mechanism, rather than being entirely separate and independent entities.

As the understanding of the construct of MCI changed over time, so did the focus of studies that tried to find a stable neuropsychological profile for MCI subjects. As research has shown, neuropsychological assessment is an accurate measurement tool to examine factors that can predict which MCI subjects are at higher risk for conversion into a dementia (Tierney, Yao, Kiss & McDowell, 2005; Ganguli et al., 2014) and several predictors have already been identified. Zhao et al. (2015) found that deficits in verbal episodic memory, as well as visual memory, are good predictors for conversion of amnestic MCI subjects. Others have found poor semantic memory, working memory (Wilson, Leurgans, Boyle & Bennett, 2011) and poor retrieval of information (Elias et al., 2000; Ritchie & Tuokko, 2011) to be valuable predictors of conversion. Furthermore, Aretouli et al. (2013) state that executive dysfunction can be present in the prodromal phases of not only Alzheimer's disease, but also in different types of dementia. Consequently, executive dysfunctioning might be a signal for being high at risk for developing a dementia. Different predictors have been identified, including planning/problem-solving and working memory (Brandt et al. 2009), inhibition (Clark et al., 2012) and semantic switching (Aretouli et al. 2013). Deficits in other cognitive domains have also been found to be good predictions of conversion, which were shown by poor performance on visuo-constructive and spatial tasks (Freeman et al., 2000; Garcia-Herranz, Díaz-Mardomingo & Peraita, 2015; Zhao et al., 2015), and tasks that draw upon conceptualizing and semantic knowledge (Amodeo,

Mainland, Herrmann & Shulman, 2015). Interestingly, not much research has been done on the cognitive domain of attention as being a predictor of conversion to dementia. As attention is a crucial constraint for adequate functioning in all domains, deficits within this domain might influence the performances in other cognitive domains unfavorably. This could be especially of interest because to this date it is still unknown what factors play a crucial role in the progression from MCI towards a dementia. Even though the total group of MCI subjects is indeed at higher risk to develop a dementia, many subjects remain stable over time and others even revert to a cognitive status within the norm range (Visser, Kester, Jolles & Verhey, 2006; Fisk & Rockwood, 2005; Ganguli et al., 2011). An interesting matter that increasingly receives attention within the literature is the possible role of vascular risk factors (VRF) on dementia conversion. In the first place because it is nowadays well established that VRF are associated with an increased risk of cognitive impairment and dementia (Awad, Gagnon & Messier, 2004; Biessels, Staekenborg, Brunner, Brayne & Scheltens, 2006; Kloppenborg, van den Berg, Kappelle & Biessels, 2008). Moreover VRF do not only contribute to the cognitive decline in vascular dementia, but also in Alzheimer's disease (Rius-Pérez, Tormos, Pérez, & Taléns-Visconti, 2015). Furthermore several studies have shown that specifically MCI patients recognized with VRF have a higher risk of converting into a dementia (Solfrizzi et al. 2011), and that early treatment of VRF in these subjects results in a lower risk of conversion (Saito, Yamamoto & Ihara, 2015).

VRF frequently co-occur in an individual: the clustering of these risk factors is known as the concept of Metabole Sydrome (MetS), and is diagnosed when an individual has three or more VRF combined (Exalto et al. 2015). Crichton et al. (2012) have shown in their study that MetS is associated with cognitive decline and a higher risk of dementia conversion. As MetS is associated with vascular dementia, Alzheimer's disease and in some cases with overall dementia (Panza et al. 2012), researchers have suggested that the link between MetS and dementia might be a result of neurodegenerative changes, vascular lesions or a combination of both, although the specific underlying mechanisms of the association still remain uncertain. As is apparent from the literature, it may be that VRF, or MetS, might play a crucial role in conversion to a dementia within the MCI subjects.

In order to better understand the various subtypes of MCI with regard to diagnostic purposes, clinical outcomes and intervention strategies, it is important to gain knowledge about the overall neuropsychological profile of these subjects. The aim of this study is therefore to further analyze the cognitive domain of attention with regard to MCI subjects and the risk of converting into dementia. Specifically, this study provides an answer to the question as to what extent attention deficits in MCI subjects can be seen as a valuable predictor of conversion to either Alzheimer's disease or vascular dementia. In accordance with the literature above, the second aim of this study is to investigate to what extent having VRF in MCI subjects is associated with the conversion rate of MCI subjects within our existing outpatient dataset. We will also analyze whether the relative risk of conversion increases as the number of vascular risk factors the MCI subjects is known with increases. First, we will run the analysis with all subjects that are

included in this study. Even though evidence has only been found for the influence of VRF on dementia conversion for specifically AD, VaD and mixed-type dementia, it is interesting to see whether this effect can be seen in a broader range of dementia types. The analyses are repeated, including only the subjects that converted into AD, VaD and mixed-type dementia, leaving out the subjects diagnosed with frontal dementia.

Lastly, taking into account both hypotheses described above, an interesting follow-up question arises. As VRF is associated with cognitive decline and conversion to dementia, and vascular lesions are associated with attention deficits such as processing speed (Vasquez & Zakzanis 2015), a relation between these two entities seems obvious. Therefore, in this study, we will also investigate whether a relation can be found between number of VRF and attention deficits within our outpatient database.

Methods

Participants

Participants were selected from the patient register of the Neuropsychology department of the Zuwe Hofpoort Hospital in Woerden. The register was screened for subjects that have been diagnosed with (a subtype of) MCI between 2004 and 2015. The diagnosis of MCI was given according to the guidelines described by Petersen (2004). Inclusion criteria consisted of: having a cognitive impairment in at least one of the cognitive domains (attention, memory, executive functioning, visuo-spatial processing, language and orientation), diagnosis of one of the subtypes of MCI, a structural brain image has been conducted (either a CT-scan or a MRI-scan) and having had at least one follow-up for neuropsychological testing after the baseline examination. Exclusion criteria consisted of: diagnosed with dementia at the first neuropsychological testing or presence of a known cause of cognitive impairment (such as psychiatric disorders, substance abuses or specific neurological disorders (like MS e.g.). In the available dataset we found 83 participants that met the selection criteria. Of these subjects, 23 were diagnosed with amnestic MCI (MCI-a), 22 with non-amnestic-MCI (MCI-na), 23 with multidomain-MCI (MCI-md) and 15 with Vascular Cognitive Impairment (VCI). The average age of these patients is 73.5 ± 7.7 (mean ± SD) years, with a range of 49 to 88 years. Of the participants 43 were woman (51.8%) and 40 were man (48.2%). The average follow-up period is 17.3 ± 11.9 (mean ± SD) months (range 4 – 74 months).

Neuropsychological testing

Patients were all seen at either the memory clinic or the regular neuropsychology department in the Zuwe Hofpoort Hospital. A clinical diagnosis was assigned to them after incorporating their clinical history from the patient and a heteroanamnesis, medical history, laboratory examination, psychiatric mental status, neurological examination, neuropsychological testing and neuroimaging studies. During the first neuropsychological examination a standard neuropsychological battery was carried out on all subjects, where a broad spectrum of cognitive

domains was being tested. As for the present study, the focus will be on the attention domain. Within this domain at least one test was administered, however not all subjects were given the exact same tasks due to differences in age and/or educational level. Tasks that were assessed are: Stroop Test (Ridley, Johnson & Braisted, 1978), Trail Making Test (from the Halstead–Reitan Battery, Reitan & Wolfson, 1985), Symbol Substitution (from WAIS-III) and Visual Elevator (from Test of Everyday Attention, TEA). All subjects were at least seen for one follow up in time. The neuropsychological battery that was carried out at the baseline examination was repeated at the follow up, in order to directly compare the performances on the assigned tasks. To account for a learning effect at the follow-up measurements, alternative versions of the tests were used when applicable.

Procedure

The examination consisted of an abbreviated anamnesis and neuropsychological testing. During the anamnesis patient were thoroughly questioned about any subjective experienced cognitive flaws or decline. After the anamnesis, a neuropsychological battery was administered by a trained neuropsychologist intern. The testing took no longer than one hour. All test instructions were given in the same way to the patients, according to the standardized instructions used at the department. During the assessments, the heteroanamnesis (e.g. the partner or caretaker of the patient) was taken to a separate room, after the patient had given verbal consent, where a neuropsychologist asked about the clinical history of the patient to check for any discrepancies.

Statistical analyses

This study has an explorative approach on the already existing dataset collected from 2004 until 2015 at the department of neuropsychology in the Zuwe Hofpoort Hospital. Firstly, descriptive statistics were applied to the demographic variables within the dataset. As earlier research has shown, demographic variables might be valuable predictors for people high at risk for conversion (Visser, Kester, Jolles & Verhey, 2006; Moleroa, Pino-Ramírez & Maestre, 2001; Mortamais et al., 2014). As this study uses a retrospective approach on the existing dataset, there has not yet been controlled for heterogeneity in either age or years of education. Therefore during the statistical analysis the variables age, gender and level of education will be taken as separate covariate variables. Furthermore, all analyses were repeated including the covariate follow-up period of time, as this factor varies greatly in this dataset.

Logistic Regression (Binary Logistics) is used in order to analyze whether MCI subjects with attention problems or deficits during the baseline examination have a higher risk of conversion to dementia than the MCI subjects that show no deficit in the attention domain. As not all subjects completed the same tests due to either differences in age or education, or time constraints, tests were not individually analyzed. Instead, the average performance per subject on the attention tasks that were administered to them is used as an indication of their overall functioning within the attention domain. In order to compare the performance within the

attention domain per subject, Z-scores were used. Subjects are divided in three categories based on their overall performances on attentional tasks: $Z \leq -2$ (meaning attention deficits present), $-2 \leq Z \leq -1$ (performance in attention domain is below average, thus attention problems) and $Z \geq -1$ (attention performance runs from low-average until high-average, thus no problems observed in the attention domain).

Secondly, the association between having VRF and conversion into dementia is analyzed, using a Binary Logistic regression. The medical history (lab results, medication lists etc.) of subjects is used to check whether they have one or more VRF. Binary logistics are used to analyze if having one or more VRF will add to the risk of converting into a dementia. The VRF used within this study include the six components of MetS, described by Scott et al. (2004). This includes: obesity, dyslipidemia, hypertensia, Diabetes Mellitus II, Proinflammatory state and Prothrombotic state. In order to differentiate between the number of VRF and the relative risk of conversion, a division is made between the MCI subjects, based on the amount of VRF each subject is known with. In this dataset, the maximum of VRF seen in a subject is as high as 3. Subjects are therefore placed in 4 categories (0 = no VRF, 1 = at least one of the VRF, 2 = at least two of the VRF, 3 = at least three of the VRF), and Binary Logistics are used in order to see whether a different risk exists depending on the number of VRF a subject is known with.

Lastly, the relationship between VRF and the extent to which attention deficits exist in the MCI subjects will be examined. As seen in the literature, lesions of vascular origin are often associated with attention deficits, which can be detected by neuropsychological testing. Again, Binary Regression will be used to examine the relationship between having VRF and possible deficits within the attentional domain. As the total population in this study (N=83) is too small to use the three categories of the variable attentional performances (being $Z=0$, $Z<-1$ and $Z<-2$), this variable 'attention' will be characterized dichotomous, in which MCI subjects either do or do not show attentional deficits ($Z \leq -1$ and $Z > -1$).

As described in the introduction, the analyses above will be all repeated, but only including subjects that either remained stable, or converted into: Alzheimer's disease, a dementia with a vascular origin (VaD, LBD) or a mixed-type dementia of both. The total number of MCI subjects that converted into one of the three dementia types described above is 48.

Results

Data from 83 subjects diagnosed with MCI at baseline examination were analyzed. Descriptive statistics were conducted. See table 1 below for the detailed summary of demographics, attentional deficits and VRF at baseline examination and conversion rates after follow up.

Table 1. Demographics, number of attentional deficits and VRF and Conversion rates within the data set (N=83).

	Total Data set (N=83)	*Converter (N=57)*	*Non-converter (N=26)*
Age	73.5 ± 7.7	74.1 ± 6.8	72.2 ± 9.5
Gender female/male	43/40	33/24	10/16
Education	4.5 ± 1.4	4.4 ± 1.3	4.6 ± 1.6
Follow-up period	17.3 ± 11.9	17.1 ± 10.9	17.9 ± 14.1
Attention deficits			
No attention deficits (Z ≥ -1)	27 (32.5%)	16 (28.1%)	11 (42.3%)
Attentional problems (-2≤Z≤-1)	35 (42.2%)	28 (49.1%)	7 (26.9%)
Attentional deficits (Z≤-2)	21 (25.3%)	13 (22.8%)	8 (30.8%)
Overall Z-score	0.93 ± 0.76	0.95 ± 0.72	0.88 ± 0.86
Vascular risk factors			
No VRF	32 (38.6%)	24 (42.1%)	8 (30.8%)
1 VRF	28 (33.7%)	17 (29.8%)	11 (42.3%)
2 VRF	13 (15.7%)	11 (19.3%)	2 (7.7%)
3VRF	10 (12%)	5 (8.8%)	5 (19.2%)
Conversion rate dementia	57 (68.7%)		
Alzheimer's disease	32 (56.1%)		
Vascular dementia	3 (5.3%)		
Mixed-type dementia	10 (17.5%)		
Frontal dementia	9 (15.8%)		
Subcortical dementia	3 (5.3%)		

Education= Average education using coding according to Verhage (1964). Follow up period = follow up in number of months after baseline examination. Conversion rate dementia = Number of patients and percentage that converted into dementia.

After either the first or next neuropsychological follow up, we found that 57 (68.7%) of the total population progressed into a dementia and 26 (31.3%) remained stable or revered back to normal cognitive functioning. No statistically significant differences were found between the converted and non-converted subjects in respect to age, gender or educational levels at the baseline measurement. Of the 57 MCI subjects that converted into a dementia, 32 subjects were diagnosed with Alzheimer's disease (56.1%), 3 were diagnosed with vascular dementia (5.3%), 10 with a Mixed-type dementia (17.5%), 9 of them were diagnosed with frontal dementia (either Fronto-temporal dementia or Primair Progressive dementia) (15.8%) and 3 subjects were diagnosed with subcortical dementia (Lewy Body disease or Parkinson disease dementia) (5.3%) (see table 1).

Table 2 (see below) summarizes the influences of attentional deficits and the numberof vascular risk factors on conversion to dementia, after being adjusted for age, gender and

educational differences. The first analysis concerns the effect of attentional deficits at baseline measurement on conversion rate to dementia. The Binary Regression coefficients (B), the standard error (S.E.), the odds ratio (ExpB), the confidence interval (95% C.I.) and the level of statistical significance are given for this analysis. No significant results have been found for attentional deficits Z=0 (n=27; odds ratio, .056; P= .33), Attentional problems Z<-1 (n=35; odds ratio, 2.51; 95% CI, .77 – 8.18; P=.13) and Attentional deficits Z<-2 (n=21; odds ratio, 1.14; 95% CI, .34 – 3.80; P=.83). The second hypothesis that was tested concerns the relationship between the presence of vascular risk factors and the influence on conversion rate. The results show that no statistically, no significant relation exists between the presence of VRF and a higher risk to converting into a dementia (n=83; odds ratio, -.592; 95% CI, .19 – 1.65; P=.29). Subdividing the MCI subjects in separate groups with regard to the amount of VRF they are known with, did also show no statistically significant results; VRF=0 (n=32; odds ratio, .76; P= .94), VRF=1 (n=28; odds ratio, .45; 95% CI, .13 – 1.53; P=.37), VRF=2 (n=13; odds ratio,1.36; 95% CI, .23 – 7.99; P=.73) and VRF=3 (n=10; odds ratio, .35; 95% CI, .07 – 1.74; P=.20).

Table 2. Binary Regression for the influence of Attentional deficits and Vascular Risk Factors on conversion rate to dementia. (N=83).

	B	*S.E.*	*Odds Ratio*	*95% C.I. for Odds Ratio*		*P*
No attentional deficit (Z=0)*	-2.886	2.988	.056			.334
Attentional problems (Z<-1)	.919	.603	2.508	.769	8.175	.127
Attentional deficits (Z<-2)	.133	.614	1.142	.343	3.801	.828
Overall Z-score Attention Tasks						.269
No v.s. One or more VRF**	-.592	.559	.553	.185	1.645	.289
VRF = 0 (constant)*	-.270	3.302	.763			.935
VRF = 1	-.811	.631	.445	.129	1.532	.369
VRF = 2	.310	.902	1.363	.233	7.986	.731
VRF = 3	-1.041	.814	.353	.072	1.740	.201

Binary regression adjusted for age, gender and level of education. *Attentional deficits= no attentional problems is used as reference group in this analysis. VRF= amount of Vascular Risk Factors as seen in the subjects running from 0 to 3 VRFs, where 0 VRF is used as reference group in this analysis. **No v.s. One or more VRF= 0 VRF is used as reference group in this analysis.

Table 3 (see below) summarizes the relationship between attentional deficits and the amount of vascular risk factors MCI subjects are known with after being adjusted for age, gender and educational differences. When compared to having no VRF, having one or more VRF (VRF > 1) is not statistically significant in relation to attentional deficits (odds ratio, 1.55; 95% CI, .55 – 4.39; P=.41). When the MCI subjects are subdivided in groups based on the amount of VRF they are diagnosed with, we find that attentional deficits are not significantly associated with having either zero, one, two or three VRF; VRF=0 (n=32; odds ratio, .03; P= .31), VRF=1 (n=28; odds ratio, .3.0; 95% CI, .80 – 11.32; P=.10), VRF=2 (n=13; odds ratio, .55; 95% CI, .13 – 2.26; P=.41) and VRF=3 (n=10; odds ratio, 2.0; 95% CI, .37 – 10.80; P=.42). When the analyses were repeated,

and only included the MCI subjects that did convert into a dementia, to see if the relationship between (the amount of) VRF and attentional deficits exists within the converted population, similar results were obtained for the odds ratios and the statistical significant associations.

Table 3. Binary Regression for the influence of Vascular Risk Factors on attention deficits seen in MCI subjects.

	B	*S.E.*	*Odds Ratio*	*95% C.I. for Odds Ratio*		*P*
No v.s. One or more VRF*	.439	.532	1.550	.547	4.394	.409
VRF = 0 (constant)**	-3.479	3.406	.031			.307
VRF = 1	1.102	.676	3.009	.800	11.316	.103
VRF = 2	-.597	.720	.550	.134	2.259	.407
VRF = 3	.691	.862	1.995	.369	10.800	.423
VRF overall						0.177

Binary regression adjusted for age, gender and level of education. No v.s. One or more VRF= 0 VRF is used as reference group in this analysis. **VRF= amount of Vascular Risk Factors as seen in the subjects, running from 0 to 3 VRFs, where 0 VRF is used as reference group in this analysis. Note: The variable 'Attentional deficits' has a dichotomous character, with attentional deficits as present or absent in the MCI subjects.

The analyses were repeated with only including the subjects that either remained stable or converted into Alzheimer's disease, a dementia of vascular origin (VaD, LBD) or a mixed-type of both, leaving out subjects diagnosed with frontal dementia. Table 4 summarizes the influences of attentional deficits and the number of vascular risk factors on conversion to the selected types of dementia, after being adjusted for age, gender and educational differences. No statistically significant results were found for all of the three categories; No attentional deficits Z=0 (n=24; odds ratio, .042; P= .31), Attentional problems Z<-1 (n=31; odds ratio, 2.66; 95% CI, .78 – 9.16; P=.12) and Attentional deficits Z<-2 (n=19; odds ratio, 1.24; 95% CI, .35 – 4.39; P=.74). The second hypothesis that was tested concerns the relationship between the presence of vascular risk factors and the influence on conversion rate on AD, VaD and mixed-type dementia. The results show that no statistically significant relation exists between the presence of VRF and a higher risk to converting into the selected types of dementia (n=74; odds ratio, -.526; 95% CI, .19 – 1.84; P=.27). Subdividing the MCI subjects in separate groups with regard to the number of VRF they are known with, also did not show statistically significant results; VRF=0 (n=27; odds ratio, .45; P= .81), VRF=1 (n=26; odds ratio, .48; 95% CI, .13 – 1.73; P=.26), VRF=2 (n=12; odds ratio,1.53; 95% CI, .25 – 9.17; P=.65) and VRF=3 (n=9; odds ratio, .34; 95% CI, .06 – 1.78; P=.20). The results shown here are similar to the results from the analyses where all types of dementia were included.

Table 4. Binary Regression for the influence of Attentional deficits and Vascular Risk Factors on conversion rate to dementia types AD, VaD and Mixed-Type (leaving frontal dementia out). (N=74).

	B	*S.E.*	*Odds Ratio*	*95% C.I. for Odds Ratio*		*P*
No attentional deficit (Z=0)*	-3.173	3.126	.042			.310
Attentional problems (Z<-1)	.980	.630	2.664	.775	9.160	.120
Attentional deficits (Z<-2)	.214	.646	1.239	.350	4.392	.740
Overall Z-score Attention Tasks						.266
No v.s. One or more VRF**	-.526	.580	.591	.190	1.842	.364
VRF = 0 (constant)*	-.799	3.363	.450			.812
VRF = 1	-.741	.657	.476	.132	1.726	.259
VRF = 2	.422	.915	1.525	.254	9.169	.645
VRF = 3	-1.090	.851	.336	.063	1.783	.200

Binary regression adjusted for age, gender and level of education. *Attentional deficits= no attentional problems is used as reference group in this analysis. VRF= amount of Vascular Risk Factors as seen in the subjects running from 0 to 3 VRFs, where 0 VRF is used as reference group in this analysis. **No v.s. One or more VRF= 0 VRF is used as reference group in this analysis.

The analyses where only AD, VaD and mixed-type dementia were included (thus leaving out frontal dementia), were also repeated for the relationship between attentional deficits and the amount of vascular risk. Table 5 summarizes the results of this relationship, after being adjusted for age, gender and educational differences. When compared to having no VRF, having one or more VRF (VRF > 1) is not statistically significant in relation to attentional deficits (odds ratio, 1.87; 95% CI, .61 – 5.73; P=.27). When the MCI subjects are subdivided in groups based on the number of VRF they are diagnosed with, we find that attentional deficits are not significantly associated with having either zero, two or three VRFs; VRF=0 (n=27; odds ratio, -2.94; P= .41), VRF=2 (n=12; odds ratio, .78; 95% CI, .18 – 3.47; P=.75) and VRF=3 (n=9; odds ratio, 1.66; 95% CI, .29 – 9.34; P=.57). However, we do find a trend for the subgroup of MCI subjects that are diagnosed with 1 VRF (n=26; odds ratio, .05; 95% CI, .97 – 16.85; *P=.06*).

Tabel 5. Binary Regression for the influence of Vascular Risk Factors on attention deficits seen in MCI subjects. (N=74)

	B	*S.E.*	*Odds Ratio*	*95% C.I. for Odds Ratio*		*P*
No v.s. One or more VRF*	.626	.571	1.870	.611	5.732	.272
VRF = 0 (constant)**	-2.940	3.570	.053			.410
VRF = 1	1.374	.740	3.950	.926	16.850	*.063****
VRF = 2	-.243	.759	.784	.177	3.469	.749
VRF = 3	.504	.883	1.656	.293	9.342	.568
VRF overall						0.218

Binary regression adjusted for age, gender and level of education. *No v.s. One or more VRF= 0 VRF is used as reference group in this analysis. **VRF= number of Vascular Risk Factors as seen in the subjects, running from 0 to 3 VRFs, where 0 VRF is used as reference group in this analysis. Note: The variable 'Attentional deficits' has a dichotomous character, with attentional deficits as present or absent in the MCI subjects. ***Significant result P<.05.

In a final set of analyses, not only age, gender and level of education were included as covariates to be controlled for, but also follow-up time period was included. Overall the odds ratios and statistically significant associations of all analyses followed the same pattern, and results were concluded to be essentially the same as the previous conducted analyses. However, in the analysis concerned with the relationship between amount of VRF and attentional deficits, the covariate follow-up time had an influence on one subgroup of the MCI subjects; namely the VRF=1 showed a statistically significance (n=26; odds ratio, 5.0; 95% CI, 1.07 – 23.5; *P=.04*). When adjusting not only for age, gender and educational level, but also for follow-up period, having 1 of the VRF increases the risk of having an attentional deficit by 5 times. No trend has been found for either VRF=0 and VRF=2 after controlling for follow up period of time.

Discussion

The aim of this study was to investigate the influence of attentional deficits and vascular risk factors on the conversion from MCI to dementia. Furthermore, the relation between (the number of) vascular risk factors and attentional deficits was also analyzed.

Based on the literature, we hypothesized that the MCI subjects with attentional deficits at baseline examination will show a significant higher conversion rate compared to the subjects that have performances within the norm range. After controlling for various important covariates such as age, gender and educational level - and in a second analysis follow up time – no significant results have been found. When only MCI subjects that converted into AD, VaD or mixed-type dementia were included, the results show the same pattern. One explanation for this null-finding might be that deficits in the attention domain are not crucial for converting into dementia. Other cognitive domains, such as memory and executive functioning, may play a more important role in increasing the risk of dementia conversion. Indeed a recent study has shown that decline within MCI subjects prior to AD conversion is most often seen in the memory domain, executive functioning and visuo-spatial abilities (Cloutier, Chertkowd, Kergoata, Gauthiere, & Belleville, 2015). Furthermore, it might be that instead of leading to selective attentional problems, the overall cognitive functioning of MCI subjects declines. In their study, Cloutier et al. (2015) show that overall cognitive functioning indeed is declined within MCI subjects that convert into a dementia, compared to MCI subjects that remain stable. It might be that this overall cognitive decline is of more importance than selective problems within cognitive domains. A consistent measure of overall cognitive decline is however missing in this study, and therefore there has not been controlled for overall decline within the MCI subjects. In future analyses, it is recommended to include a measure that represents overall cognitive decline.

With regard to the relation between VRF and dementia conversion, we expected that the relative risk of conversion significantly increases as the number of VRF increases. However, no significant results were found to support this relationship. Our results are different from previous findings, where VRF are associated with an increased risk of dementia conversion (Biesels et al, 2008; Blom, Emmelot-Vonk & Koek, 2013; Li et al. 2011). Biesels et al. (2008) have

found that some VRF are more strongly associated with conversion than others, where especially DM II and obesity show a consistent relationship with dementia conversion. Hassing et al. (2004) have found that comorbidity of various VRF, specifically diabetes type II and hypertension show a faster decline in cognitive functioning. Based on the current study, no specific risk factors can be pointed out that contribute to the conversion of dementia, as all VRF were treated equally and no distinction has been made between the included VRF. Following this line of research, differences between VRF in the degree to which they contribute to dementia conversion seem to exist. If this indeed is the case, a distinction between the VRF is necessary in order to analyze the contribution per VRF to dementia conversion. Based on the literature, one might argue that not only the differences between VRF influences conversion rate, but other factors play a crucial role as well. Biesels et al. (2008) for example show that interacting effects between VRF and the age of the subject influence the risk of dementia conversion. More researchers have also suggested that the association between a VRF and dementia conversion might be age-dependent (Exalto et al., 2015; Kloppenborg et al., 2008). A suggestion for a future study could therefore be to repeat the analyses from this study, while including the factor age as a moderator to analyze the relationship between VRF and dementia conversion in more detail.

As explained above, VRF are associated with vascular lesions and diseases and these are in turn associated with attentional deficits seen in neuropsychological assessments. We therefore hypothesized that MCI subjects with a greater number of VRF will also show greater deficits within the attention domain and that subjects with lesser – or no – VRF will show attention deficits to a lesser degree. Our results show no relation between VRF and attentional deficits. However, when the dataset only includes MCI subjects who converted to AD, VaD and Mixed-type dementia, we found that subjects known with one VRF have a higher chance of attentional deficits than having no VRF. No such findings were seen when 1 VRF was compared to either having 2 or 3 VRF. As described earlier, these results might have been influenced by treating all VRF equally instead of looking at the contribution to conversion of the VRF separately. Another explanation might be that only moderately affected subjects, diagnosed with just one VRF, show a decline in attentional performances, whereas this decline is less apparent in MCI subjects that are vascularly more severely affected. It is possible that the association between VRF and attentional deficits in the severely affected subjects is overruled by other underlying mechanisms and pathologies. This assumption is linked to the clustering of several VRF together, the Metabolic Syndrome (MetS). As described above, severely vascular affected subjects known with three or more vascular risk factors are diagnosed with MetS. This syndrome is associated with cognitive decline and a higher risk of dementia conversion (Crichton et al., 2012). One of the factors that is assumed to play a crucial role in this cognitive decline and dementia conversion –and is present in several VRF- is insulin abnormalities. These abnormalities are often seen in DM, obesity and proinflammatory state (Guillausseau et al., 2008; Shoelson, Lee & Goldfine, 2006). Research has also shown that insulin abnormalities play an important role in the disease pathophysiology and clinically presented symptoms in Alzheimer's disease patients (for a more elaborated reading,

see Watson & Craft, 2003). Watts et al. (2013) have found that insulin abnormalities in healthy controls are associated with a more rapid decline in cognitive functioning, whereas (early-stage) better cognitive performances were seen in AD patients with the same abnormalities. This study shows that the more vascularly affected patients show another pattern of clinical outcomes than subjects that are less or not affected. If underlying processes influence the relationship between VRF and dementia conversion for those severely affected subjects, differences in clinical outcomes seem obvious. Even though the exact contribution of insulin abnormalities to cognitive functioning remains unclear, these findings do point out that there is a notable interaction between VRF and underlying pathologies and mechanisms. Although no significant results were obtained in this study, the findings do suggest that there does not seem to be a one-to-one relationship between VRF and dementia conversion. The outcome of this study indicates that the relationship is far more complex. It furthermore stresses the importance of analyzing the relation between VRF and dementia conversion in more detail, as much still remains unclear.

One important explanation of the results described above might be the heterogeneity of our dataset with regard to MCI subtypes and dementia diagnoses after conversion. In our dataset we included all MCI subtypes. However, the heterogeneity of the several subtypes might be more important than considered. As described above, research has found evidence for separate MCI subtypes for dementia, such as PD-MCI for Parkinson disease dementia and VCI for Vascular dementia. In this dataset we did not analyze the subtypes separately, as the sample size was too small. It might well be that the hypotheses claimed in this study do not apply to all MCI subtypes, but can be found in a specific subtype, such as VCI where vascular problems are highly present (Iadecola, 2013). Further research is therefore necessary in order to analyze the relationship between attentional deficits, VRF and conversion rate in the separate subtypes of MCI. Furthermore, the majority of MCI subjects that progressed into a dementia were diagnosed with Alzheimer's disease. In one population-based study of subjects over 65 years old (Lobo et al. 2000), the prevalence of Alzheimer's disease is estimated around 53.7% (range 38.5 – 78%). Our dataset is in line with this finding: 56.1% of the MCI subjects that converted are diagnosed with AD. Lobo et al. (2000) show that around 15.8% of the dementia cases can be addressed to vascular dementia. In our dataset, the prevalence of VaD was lower; only 5.3% of the MCI subjects were diagnosed with VaD. The prevalence of other dementia types in our dataset were in line with the estimated prevalence of the total population. Even though the literature shows that vascular problems influence AD as well, the presentation of cognitive problems that are associated with the neurodegenerative process shows a different pattern compared to other types of dementia. Where vascular dementia is often associated with problems in the attentional domain, the most prominent clinical feature of (the first stage of) Alzheimer's disease is most frequently associated with memory impairments (Joubert et al. 2015). This could also explain the finding that the group of converters show less attentional deficits ($Z<-1$) at baseline examination than expected. It might be that the relationship between attentional deficits and conversion is not seen in this dataset, due to the high prevalence of AD patients. Attention deficits in this group

may be less prominently present, as deficits in other cognitive domains are more common. The relationship between attentional deficits and conversion might be more clearly present in subjects that converted into a vascular dementia or a mixed-type dementia, as attentional deficits are often present in these types of dementia. Unfortunately, we could not test this hypothesis in the present study, as limited subjects within these subgroups were included.

Several limitations of this study need to be addressed. First of all, the sample size in this study is relatively small. Except for the group that converted into Alzheimer's disease, all subgroups are too small to make any valid claims with regard to our hypotheses. Furthermore, as this is a retrospective study with an explorative approach, the subjects included in this study may not reflect the overall population. Most importantly, the conversion rate of MCI subjects to dementia in this study is notably high, reaching 68.7%. This rate is substantially higher than seen in the overall population of MCI subjects, where the estimated percentage of MCI subjects that convert into a dementia per year ranges from 5-15% (Lopez et al. 2012). Thus the sample used in this study may solely represent those MCI subjects with cognitive problems that underlie a neurodegenerative disorder, leaving out MCI subjects that no longer have cognitive complaints and remain stable or convert back to normal. Even though there has been adjusted for the time of follow-up period per subject, this factor might still have influenced the findings. The subjects in this study were selected between 2004 and 2015. Whereas some of the patients were seen several years ago, leaving room for various follow-up examinations, others were seen for the baseline examination for as short as one year ago. It might be that the patients that were seen a notably shorter time ago, and are labelled as 'stable', will convert within the next couple of years.

This study underlines the complexity of the relationship between several risk factors and dementia conversion. It stresses the importance of further analyzing what factors increase the risk of dementia conversion, in order to develop adequate intervention treatments.

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