



# Hypertension, Infection and Inflammation and their Effects on Memory and Visuospatial Skills in Ageing

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# HYPERTENSION, INFECTION AND INFLAMMATION AND THEIR EFFECTS ON MEMORY AND VISUOSPATIAL SKILLS IN AGEING

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Blood pressure has previously been associated with decline in memory over time, though the exact mechanism behind this effect is uncertain. Infections, which can lead to systemic inflammation have also been linked to some cardiovascular damage to the brain, known as microbleeds, which have themselves been linked to greater declines in cognition in old age. The present study investigates whether blood pressure, a self-reported history of infection, and an indirect measure of inflammation known as the erythrocyte sedimentation rate have any association with on episodic and semantic memory and visuospatial skills in the Betula study, a Swedish longitudinal population study. The effect of elevated blood pressure (over 140 mm Hg systolic and/or 90 mm Hg diastolic), high blood sedimentation (top 33% against bottom 33% of participants), and self-reported infection were all found to not have any significant effect on episodic memory, semantic memory or visuospatial skills. Some of the possible explanations are elaborated in the discussion.

Högt blodtryck har associerats med minnesnedsättning men den exakta mekanismen hur ett samband kan förstås är dock oklar. Infektioner har visat sig ge systematiska inflammationer och har också satts i samband med vissa kardiovaskulära förändringar i hjärnan, så kallade mikrobldningar, vilka i sig har associerats med ökad risk för kognitive nedsättning i hög ålder. Denna uppsats syftar till att undersöka om blodtryck och infektion (självrapporterad infektion samt infektion indirekt mätt genom sänkereaktion) kan relateras till episodiskt och semantisk minne samt visuospatial förmåga i Betula studien, som är en svensk longitudinell populationsbaserad studie. Resultatet visade att varken högt blodtryck (över 140 mm Hg systoliskt eller 90 mm Hg diastoliskt), hög sänkereaktion (de 33 % med högst värde jämfört med de 33 % med lägst värde) eller självrapporterad infektion hade någon signifikant effekt för episodiskt minne, semantiskt minne eller visuospatial förmåga. Några möjliga förklaringar till detta resultat utvecklas i diskussionen.

There is a wealth of literature exploring how neural health and declines in cognitive ability are influenced by cardiovascular health. Whalley, Deary, Appleton, and Starr (2004) summarise some of the main features of cognitive ageing in their study, as well as some of their neurological correlates and proposed biological mechanisms. Some of the domains that have a general age-related decline are fluid reasoning, mental speed, memory and spatial ability. They claim that the rate of cognitive ageing is influenced by factors that have a negative impact on neural health, such as hypertension. The authors also suggest that the ageing brain is vulnerable to C-reactive proteins, which are found in high concentrations in inflammatory responses and are also associated with cognitive ageing in general.

Additionally, inflammations can be caused by infections. Lowe (2001) provides an overview into the relationship between infections and inflammation, and state how infections result in increased cytokine release, and some cytokines such as interleukin 1 and 6 can promote inflammation. Cytokine release has also been related to other cardiovascular disease risk factors such as smoking and obesity. However, the article does not make a claim for a causal link between infection and cardiovascular disease, although many of the mechanisms are similar to those found in so-called 'classic risk factors' such as smoking, obesity and hypercholesterolemia, an excess level of cholesterol.

The connections between blood pressure, inflammation and infection are of particular interest in the current study, to examine if any of these factors can be predictors of cognitive decline in old age. These three proposed risk factors will be explained in more detail in the following sections.

Many different studies demonstrate an effect of blood pressure on different areas of cognition, but the results are mixed and not definitive. Kuo, Sorond, Iloputaife, Gagnon, and Milberg (2004)

studied the effects of blood pressure on healthy elderly adults. They performed various neuropsychological tests, and found that those with higher blood pressure were significantly more likely to perform within the bottom 25% of the sample in the Trail-making Part B test of executive functioning, even when controlling for potential confounders. However, they did not find any blood-pressure related changes in any of the other cognitive domains, such as verbal or visual memory, although the authors admit that the cross-sectional design of the study may have been a limitation to the validity of the study as it cannot provide evidence for a causal relationship.

One study seems to suggest that blood pressure is related to cognitive performance even in young and middle-aged adults. Elias, Elias, Robbins, and Budge (2004) investigated whether blood pressure is related to declines in visualisation skills and fluid intelligence. A longitudinal study of 20 years tested the hypothesis that states that older adults would demonstrate a greater blood pressure-related decline in visualisation and fluid intelligence tasks using the Wechsler Adult Intelligence Scale than younger adults. However this hypothesis was not confirmed, and blood pressure was related to a decline in visualisation and fluid intelligence tasks for both younger and older participants similarly. They argue for the importance of reducing blood pressure even at an early age, as the declines in cognition related to high blood pressure are not reversible.

Saxby, Harrington, McKeith, Wesnes and Ford (2003) compared a hypertensive group of older adults with a normotensive group in a battery of cognitive testing. Participants aged 70-89 with matched education, performance on MMSE and age were included in their analysis as covariates. They found that the hypertensive adults were impaired in cognition speed, executive function, episodic memory and working memory compared to their normotensive counterparts. The authors admit that the mechanism for this difference is unclear, although some suggestions of possible mechanisms are discussed later in this paper.

However, Glyn et al. (1999) concluded in their study that the associations between blood pressure and cognition were very small. In a longitudinal study of middle-aged participants, they found that the only effect was in number of errors participants made in the Short Portable Mental Status Questionnaire and the East Boston Memory Test. The authors suggest that there is no simple, linear change in cognition for those with higher or lower blood pressure, but that the relationship was a more complex one. However, a limitation in this study was the fact that it was only regarding middle-aged participants, and that this effect might not necessarily be found in an elderly population.

Whether or not high blood pressure can negatively affect cognition over time is a complex topic and has gathered several seemingly conflicting conclusions. High blood pressure has previously been linked with impairments in higher cognitive functions, as in seen in Tzourio, Dufouil, Ducimetière, and Alperovitch (1999), who demonstrated that in a population of participants aged 59-71 that there was an association with high blood pressure and decline in cognitive performance over 4 years for untreated hypertension, though treatment for hypertension reduced this risk. The blood pressure was measured using a digital electronic tensiometer before testing, however, it has been found in some cases, such as White et al (2011), that a one-time measure of blood pressure is not a reliable predictor of cognitive decline, although 24-hour blood pressure monitoring does have such an association.

Jennings et al. (1998) point to some studies that suggest that hypertensives (those with hypertension) have a diminished regional cerebral blood flow response during memory tasks. In another study, using MRI assessments, Jennings et al. (2005) determined that memory performance for those with hypertension was associated with a blunted regional cerebral blood flow response, predominantly in the parietal cortex, with responses that potentially compensate for this blunted response occurring in the midbrain. Jennings and colleagues conducted their study to identify if cognitive tasks that involved consistent regional cerebral blood flow would be different for those with high blood pressure owing to compromised vasodilatory capacity

associated with high blood pressure. They performed two tasks, but of most interest to the current study is the auditory free recall task in which participants were instructed to remember and repeat nouns played at a rate of one per second, up to a maximum of twelve nouns. This was compared to repetition of a single word, and using a PET scanner they found that while performance was similar, those with hypertension had significantly different region cerebral blood flow patterns than the controls. Hypertensives had decreased responsivity to increased task difficulty.

Inflammation and infection are two other areas of interest to the present study. They are both commonly linked to cardiovascular health, and it is this connection that is the motivation for the present study. Yaffe et al. (2004) note how inflammation can be a marker of the high risk for negative effects related to cardiovascular health. The study itself focused on metabolic syndrome, a clustering of disorders including abdominal obesity and hypertension, and how this interacts with high levels of inflammation. Using the Mini Mental State Exam (MMSE) to measure cognition with measures of inflammation, defined as an elevated level of C-reactive protein and interleukin 6, the authors performed a 5 year longitudinal study. Its goal was to study the effect of both metabolic syndrome (measured by the National Cholesterol Education Program guidelines) and inflammation on cognition. They found that there was a statistically significant interaction between inflammation and metabolic syndrome. Those with metabolic syndrome and inflammation were significantly more likely to experience cognitive impairments compared to those without inflammation, however it should be noted that the MMSE is a very short test designed to screen for cognitive decline and is not recommended as a clinical diagnostic tool (Tombaugh & McIntyre., 1992).

Klipper et al. (2013) investigated whether a person's erythrocyte sedimentation rate (ESR), a marker of inflammation, is associated with increase in brain volume after stroke, and whether this is also associated with cognitive decline. Both hippocampal volume increase and a decline in cognition were associated with ESR, and therefore it is reasoned that the increase in the ESR might be associated with decline in cognition. The erythrocyte sedimentation rate will be used in the current study to measure inflammation.

However, while some of these studies found results that would suggest that inflammation can affect cognition in ageing, Phillips et al. (2011) demonstrate an association in the reverse direction, where lower cognitive ability can lead to risks of poor cardiovascular health. They found that participants with poor cognitive ability in early adulthood had a higher risk of inflammation in midlife than those with normal to high cognitive ability. This will be controlled for in the current study by using education as a covariate, although this is only a rough indication of early cognitive ability.

There have been several cardiovascular diseases that studied to assess their effect on cognition, some of which could potentially be linked with blood pressure, infection or inflammation. Cerebral microbleeds are small brain haemorrhages which Martinez-Ramirez, Greenberg, and Viswantathan (2014) claim are likely to be caused by structural faults of small vessels in the brain, and linked by some authors in the following paragraphs to cognitive decline. Werring et al. (2004) studied the effects of microbleeds on various cognitive processes, and by using a T2-weighted MRI they managed to produce a high detection of microbleeds in participants. Using a battery of tests, such as verbal and visual memory, naming, processing speed, attention and others, a group of participants with high levels of microbleeds were compared to a control group. Their results demonstrate that there was executive dysfunction in 60% of the microbleed group and only 30% of control participants. Those with executive dysfunction had more microbleeds in frontal region, highlighting the possible association with microbleeds in that area and executive dysfunction. Martinez-Ramirez claim that this distribution of microbleeds and correlation to cognitive domains affected could be evidence of direct damage of microbleeds on tissue as the pathogenic mechanism.

Risk factors for cardiovascular disease have also been found to be risk factors for microbleeds. Goos et al. (2010) studied microbleeds in patients in a memory clinic. Microbleed patients had more progression of white matter hyperintensity in MRI scans, which have been associated with cognitive deficits. The microbleed patients were found to have more progression of small vessel diseases, and also were more likely to have hypertension. The authors suggest that through management of vascular risk factors, memory clinic patients may reduce further microbleeds and consequently slow cognitive decline.

Inflammation has also been linked to cognitive declines that are not specifically related to normal cognitive ageing. Ahles and Saykin (2007) investigated the role of inflammation and chemotherapy-related cognitive decline. They say that inflammation may promote oxidative stress and mediate DNA damage that triggers a release of cytokine. This in turn leads to more oxidative stress and creates a cycle of cytokine release. Howcroft et al. (2013) also explored this concept, and made some suggestions about the role of the inflammatory cytokine TNF, which was believed to be implicated with cell death for dopamine dependent cells, and could possibly be linked to Parkinson's disease. It seems that inflammation and cytokines can have a relatively clear effect on cognition in these specific situations, and it motivates this study to investigate whether inflammation can have a role in the normal cognitive ageing as well.

Reducing inflammation has also been demonstrated to have an effect at slowing cognitive decline. Cotman, Berchtold, and Christie (2007) suggests a system through which exercise can reduce cognitive decline, by reducing inflammation in the brain of elderly participants. Subsequently, there is a growth of grey and white matter, and this is reasoned to allow cognitive decline to be slowed in participants in an exercise program compared to controls.

The purpose of the current study was to investigate whether an elevated blood pressure, infection and inflammation may be correlated with long-term decline in episodic and semantic memory, as well as a performance in a block design task for visuospatial ability. While blood pressure already has been shown to be associated with cognitive impairments in some studies, but definitely not all, as presented in the introduction, the effect of inflammation and infection has not been so widely investigated. Blood pressure in this study will be measured while the participants are lying down. Additionally, the study will use a self-report of infection within the five years prior to the study, and a blood sedimentation score (ESR), an indirect measure of inflammation.

The first hypothesis in the present study is that participants with elevated blood pressure in the baseline test wave (T2 of the Betula study) will perform worse overall on all memory tasks and the block design task. The second is that there will be an interaction effect in which these elevated blood pressure participants will decline more in all of the cognitive tasks over time than the non-hypertensive individuals. The third hypothesis is that those participants with the highest sedimentation rate will perform worse overall in all tasks than those with the lowest ESR, and the fourth is that they will decline more over time. The fifth hypothesis is that those with who had an infection five years prior to the baseline will perform worse overall on all tasks than those who did not, and the sixth is that they will decline more over time than those without infections.

## Method

The data for this study were drawn from the Betula cohort study. The Betula study is a prospective population-based study that started in 1988 at Umeå University with the aim to assess how health and memory functions change from adulthood to old age, to identify risk factors and preclinical signs of dementia (Nilsson et al., 1997; 2004). It has currently run for six time periods from 1988 to 2010 where data were taken every five years. The Betula study was approved by the regional board of the ethics committee in Umeå, Sweden, and the participants were free to leave the study at any time.

The sample was randomly drawn from the population registry for Umeå, Sweden, a city that contained approximately 89000 in 1988, the year in which the first data were collected. The study collects data from participants aged 25-80, in five year intervals (e.g. 25, 30, 35 years old, etc.) and divides each of these into separate age groups. There are 100 people in each of the age group, totalling 1000 participants at the first time point. After the first time point, further tests were performed every five years on the same participants.

The measures from the Betula study that are of interest to the current study are cognitive measures such as episodic memory, semantic memory and visuospatial ability. Episodic memory tasks involved recall tasks such as the cued recall of nouns task, semantic memory was assessed by tasks such as word fluency tasks, and visuospatial ability was measured by performance in the block design task. Additionally, the Betula study also contained health related information, such as different measures of blood pressure, questionnaires related to medical history, which included a question regarding infection, as well as a measure of blood sedimentation, which is an indirect marker for inflammation.

### *Participants*

In the present study, only the participants present in the first cohort (Sample 1, S1) which started in 1988, will be considered for data analysis as they have the highest number of completed test waves. Furthermore, only data from the second time point (known henceforth as the baseline) and beyond will be considered since some questions relating to the current research question were revised or included for the first time at the second test occasion. An example of this is the question regarding infection, which was revised in the second wave to only include whether the participant had an infection during the last five years (e.g. in-between the test occasions), rather than the first wave which asked about whether the participant had ever had an infection before. Moreover, only participants aged 55 and above at the baseline were included.

Participants from the initial 1000 were excluded if they were younger than 55 at the baseline ( $n=300$ ), and if they had no information relating to education from the baseline ( $n=98$ ). Of these remaining participants, only participants that completed all the test waves were included. Those that were excluded for not completing all test waves were assessed for exclusion independently for semantic memory, episodic memory and block design. That is to say that if a participant is missing data for one semantic memory task, they are not excluded from episodic memory analyses automatically, for example. This leads to different numbers of participants for each analysis, as seen in Table 1.

Table 1. *Descriptive statistics for baseline characteristics for participants present in the semantic memory task ( $n=198$ ), episodic memory task ( $n=187$ ) and the block design task ( $n=183$ ).*

	Semantic Memory		Episodic Memory		Block Design	
Participants, n	198		187		183	
Age, mean, SD	61.24	6.22	60.80	5.86	60.79	5.84
Sex, female %	44.95		44.92		44.81	
Years of Education, SD	10.28	3.75	10.33	3.72	10.34	3.75

### *Group Assignment*

Assignment of blood pressure group (elevated or normal) was determined by assigning all participants with a systolic blood pressure of over 140 mm Hg, or diastolic blood pressure of over 90mm Hg to the elevated group, as suggested by Pickering et al. (2005), who define hypertension in this manner in their paper regarding recommendations for blood pressure measurement. That is to say that one who has either elevated systolic or diastolic blood

pressure would be assigned to the elevated blood pressure group (n = 68), and participants not meeting this criteria were assigned to the normal blood pressure group (n = 121). Assignment of high sediment (n = 57) or low sediment group (n = 60) was done differently and was age-controlled. For each age group, the participants who were in the highest 33<sup>rd</sup> percentile for sedimentation were assigned into the high sediment group. The lowest 33<sup>rd</sup> percentile for each age group were assigned to the low sedimentation group. This is to control for any differences in sedimentation that might occur due to age alone, documented by Böttiger and Svedberg (1967). As such, these participants were age matched and age was not used as a covariate for this analysis. The same was not done in the hypertension group due to the nonlinear patterns of age-related changes in blood pressure, particularly systolic blood pressure (Franklin et al, 1997). Those who reported having an infection (n = 58) in the last 5 years at the baseline (i.e. between T1 and T2) were assigned to the infection group, but only if they did not report any further infections at any later time points. Those that did not have an infection 5 years prior to baseline, and also throughout the experiment, were assigned to the no infection group (n = 33).

Table 2. *Descriptive statistics for baseline characteristics for participants in the hypertensive group (n=68) and the non-hypertensive group (n=121).*

	Hypertensive	Non-hypertensive
Participants, n	68	121
Age, mean, SD	62.28* (5.76)	60.04* (5.76)
Sex, female %	50%	42%
Years of Education, SD	9.92 (3.58)	10.51 (3.78)

\*Significance at  $p < .01$

Table 3. *Descriptive statistics for baseline characteristics for participants in the high sedimentation group (n=57) and the low sedimentation group (n=60).*

	High Sedimentation	Low Sedimentation
Participants, n	57	60
Age, mean, SD	60.26 (5.38)	60.83 (5.14)
Sex, female %	33%*	70%*
Years of Education, SD	9.99 (3.81)	10.59 (3.88)

\* Significance at  $p < .01$

Table 4. *Descriptive statistics for baseline characteristics for participants in the previous infection group (n=58) and the non-infection group (n=33).*

	Infection	No Infection
Participants, n	58	33
Age, mean, SD	61.03 (5.98)	61.21 (6.85)
Sex, female %	52%	61%
Years of Education, SD	10.10 (3.92)	10.67 (3.43)



## *Materials*

Several different tests were used to measure the three cognitive domains that will be included in the present study.

### *Cognitive Tests*

#### *Measurement of Semantic Memory*

Semantic memory was measured by four individual measures; three verbal fluency tasks and one vocabulary task. During the verbal fluency tasks the participants were asked to generate as many words as possible during one minute, with the following restrictions: a) generate words with the initial letter A (but not names); b) words beginning with the letter M and containing five letters (but not names); and c) professions beginning with the letter B. The test-retest reliability of verbal fluency tasks has been demonstrated to be high ( $r=.94$ ) in a study by Harrison, Buxton, Husain and Wise (2000). The vocabulary test was a modified version of the SRB Swedish word comprehension test (Dureman & Sälde, 1959). Participants were required to match 30 target words to synonyms. Participants were scored on how many synonyms they could correctly match up in a seven minute time period. The Z-scores for each test were averaged to create an average Z-Score for semantic memory, improving reliability.

#### *Measurement of Episodic Memory*

Episodic memory was measured with the following memory tasks: The standardised Z-Scores for each episodic memory test were averaged for greater reliability.

##### *Free recall of sentences*

The participants were shown 16 written sentences, for eight seconds each. The sentences were also read aloud by the experimenter. This was followed by free recall of as many sentences as possible and participants were scored based upon the number of correct remembered sentences.

##### *Free recall of actions*

Participants were presented with 16 written sentences in the same way as the free recall of sentences task. The sentences contained objects and also actions for the participants to act out. Participants were then asked to recall as many of the sentences as possible and are scored based upon the number of correct sentences.

##### *Cued recall of nouns*

The participants were instructed to recall as many nouns as possible from the free recall tasks described above (for both sentences and actions). Eight semantic categories were presented as cues for recollection. The participant has three minutes to recall as many nouns as possible from the lists, and is scored based upon the number of correctly recalled nouns. The validity of similar tests has been demonstrated by Youn, Park, Jung and Lee (2011), where the authors state that it has good validity and correlates with memory measures.

##### *Working memory/divided attention*

This task is divided into four parts. In all four, there is a list containing 12 nouns which are read aloud by the experimenter. Participants are then instructed to recall as many as possible immediately afterwards for task 1. In task 2, there is a sorting task to be completed during the study phase, where participants are asked to sort cards into piles at a rate of one every 2 seconds, the same rate at which the experimenter reads the words. In task 3 this occurs during the retrieval phase, where the participants are asked to recall the words. In task 4 this occurs at both the study phase and the retrieval phase. The number of correctly recalled words from all phases are added together.

### *Measurement of visuospatial ability*

The block design task was a task where participants had to arrange red and white blocks in a manner that formed the same pattern as one that was presented to them within 60 – 120 seconds per pattern. The time period was dependent on the number of cubes. Points were given to participants dependent on the difficulty and time taken to solve the task. This task is reported to have good ecological validity as a measure of everyday spatial ability (Groth-Marnat & Teal, 2000).

### *Covariates*

Sex, age, and years of education were included in the analysis to control for any confounding effects that might interfere with the results of the analysis.

Education is a very important covariate as it is associated with overall level of cognitive ability (Whalley et al., 2004). Low educational attainment was also identified as a risk factor for Alzheimer's disease and mild cognitive impairments in an epidemiological study (Sattler, Toro, Schönknecht & Schröder, 2012). The effect of age on memory and visuospatial skills is well-documented, such as in Whalley et al. (2004) where declines are generally seen from middle age into old age. There are also differences in performance of these tasks between sexes. There is a difference in episodic memory favouring women (Herlitz, Nilsson, & Bäckman 1997), as well as a difference in visuospatial ability favouring men (Weiss et al., 2003). Additionally, there is a difference in semantic memory processing between sexes in terms of brain activation patterns (Baxter et al., 2003).

### *Design*

Decline in cognitive performance will be calculated for all participants who completed all experiments at all time points. For each age cohort, the 33% of eligible participants who demonstrated the highest sedimentation rate, an indirect measure of inflammation were compared to the 33% of participants with the lowest sedimentation rate. The cognitive scores for the composite episodic memory, semantic memory and block design were compared at the second time point and every additional time point until the fifth time point. The above-normal blood pressure group will be compared to those non-elevated blood pressure in the same tests. Additionally, those with infections within the last 5 years from the first time point were compared to those who did not over the remaining time points.

### *Statistical Calculations*

All measures of semantic memory had z-transformations applied to them to produce standardised z-scores. The mean of the semantic memory z-scores was calculated and used whenever semantic memory was analysed. The same was done with episodic memory. The block design scores were also standardised into z-scores. The rank function was used to rank participants from each age group by sedimentation rate, and participants in the 33<sup>rd</sup> highest percentile for sedimentation and those in the lowest 33<sup>rd</sup> were divided to create two separate groups, known henceforth as the high sedimentation group and the low sedimentation group. This extreme-group comparison was motivated by Preacher (2015), who states that extreme-group comparisons may be best suited for pilot studies, where the goal is to detect trends that show promise to motivate further investigation. Due to some of the limitations of the extreme group comparison, such as poorer reliability, it was not used for blood pressure as this has been studied many times previously and a more reliable method was preferred. SPSS 23 was also used to calculate which participants were in the elevated blood pressure and normal blood pressure groups.

Differences between the different groups previously specified, as well as the main effect of time and the interaction effect will be calculated in SPSS 23 using a repeated measures ANCOVA test, with the covariates being age, years of education and sex.

Participants that were excluded due to missing data were excluded on a case-by-case basis depending on the measure being analysed. This leads to different numbers of participants for most individual analysis. Participants missing education data are excluded as this are used as a covariate for all analyses. All significance values quoted below take the covariates (sex, age, education) into consideration. Each of the three groupings (by blood pressure, history of infection and by sedimentation rate) and each of the cognitive measures (episodic memory, semantic memory and visuospatial ability) had separate repeated measured ANCOVA tests performed upon them, to create nine separate analyses. The repeated measures ANCOVA measures the scores on each test starting from the baseline.

## Results

### Blood Pressure

Participants were divided into a normal or an elevated blood pressure group based upon their values at the baseline. This is to assess the long-term effects of high blood pressure on each of the measures, rather than just the blood pressure at the time of each test.

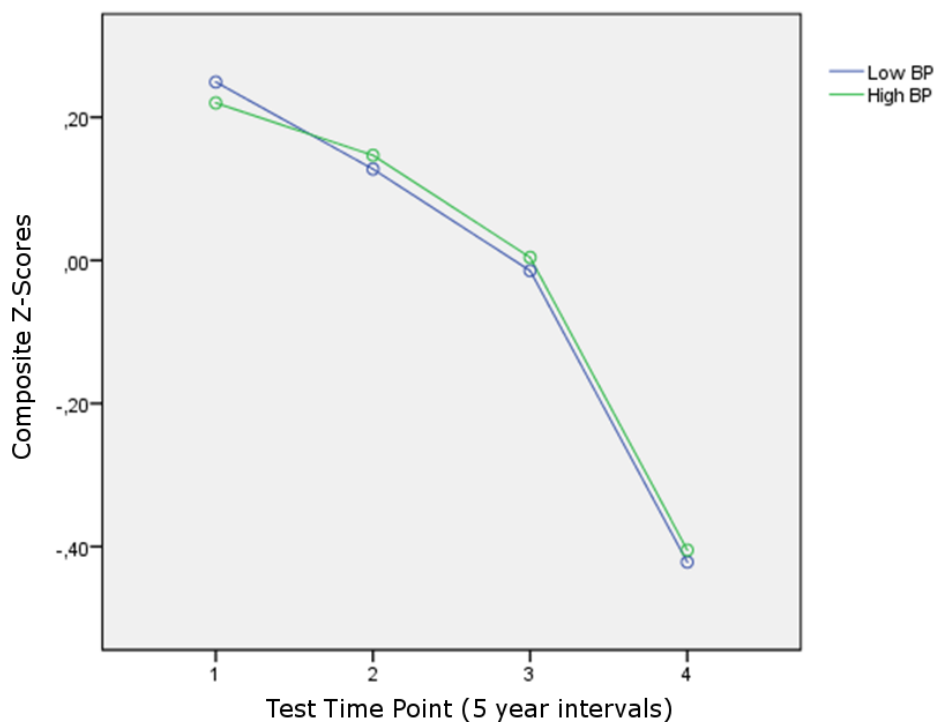


Figure 1. Change in episodic memory over time for high and low blood pressure groups

For episodic memory, those deemed to have high blood pressure ( $n = 92$ ) did not significantly differ in their performance in episodic memory compared to the low blood pressure group ( $n=94$ ),  $F(1, 181) = 0.009$ ,  $p = .925$ , so no main effect of group was found. There was also not a significant interaction effect between blood pressure group and time,  $F(3, 179) = .301$ ,  $p = .825$ . This means that the effect of time had the same pattern of effect on both groups. There was a significant main effect of time,  $F(3, 179) = 5.259$ ,  $p < .005$ , indicating that both groups' performance over time was significantly reduced. Results from Mauchly's Test of Sphericity was significant,  $p < .01$ , indicating a departure from sphericity, so statistics corrected by SPSS were used to counteract this effect. This is true of all but one of the following tests (which will be noted separately).

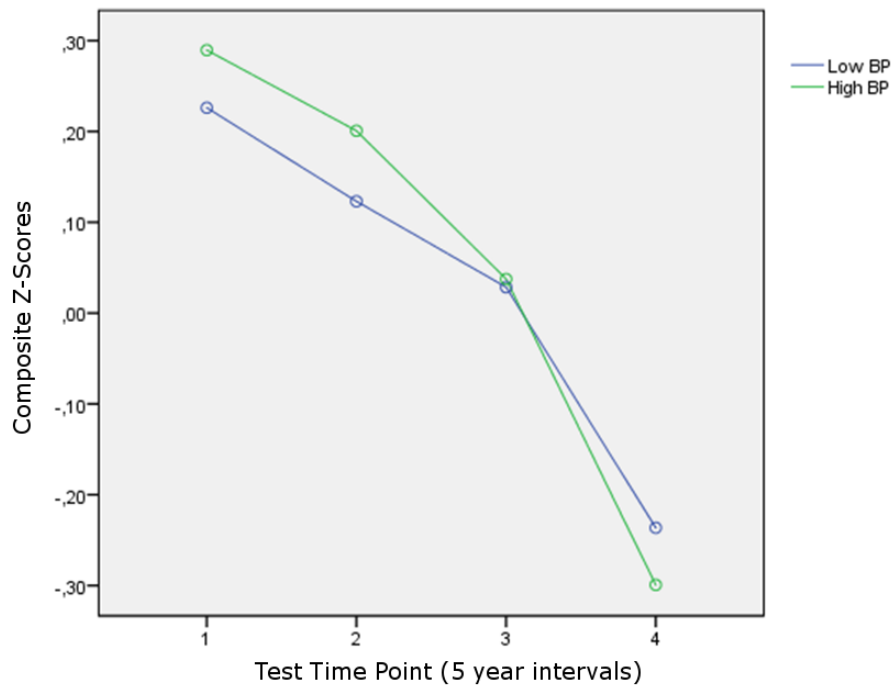


Figure 2. Change in semantic memory over time for high and low blood pressure groups

For semantic memory, there was also no significant main effect of blood pressure group,  $F(1,192) = .054, p = .816$ , and no interaction effect of group and time,  $F(3, 190) = 1.319, p = .270$ . For semantic memory, there was a non-significant main effect of time,  $F(3, 190) = 2.598, p = .054$ .

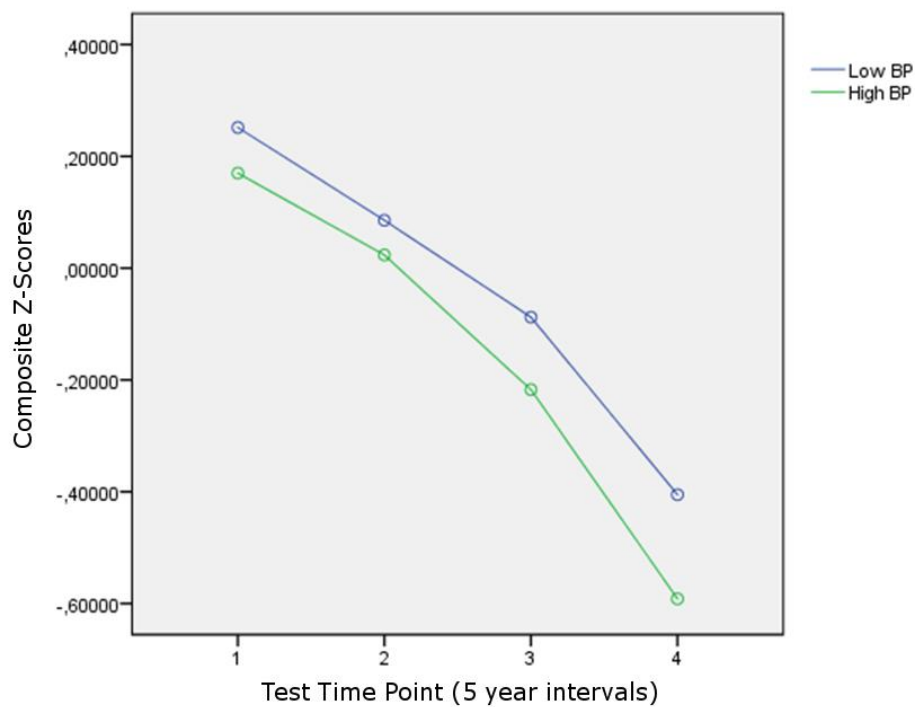


Figure 3. Change in visuospatial ability over time for high and low blood pressure groups

For the block design test, no significant main effects or interactions were found at all. There was no main effect for group,  $F(1,177) = 1.609, p = .206$ , no interaction,  $F(3, 175) = .616, p = .605$  and no main effect of time  $F(3, 179) = .367, p = .777$ .

#### *Sediment Level*

The second method of dividing the participants was by blood sedimentation scores. The highest and lowest 33% of participants at the baseline were compared for performance in memory tasks and the block design task.

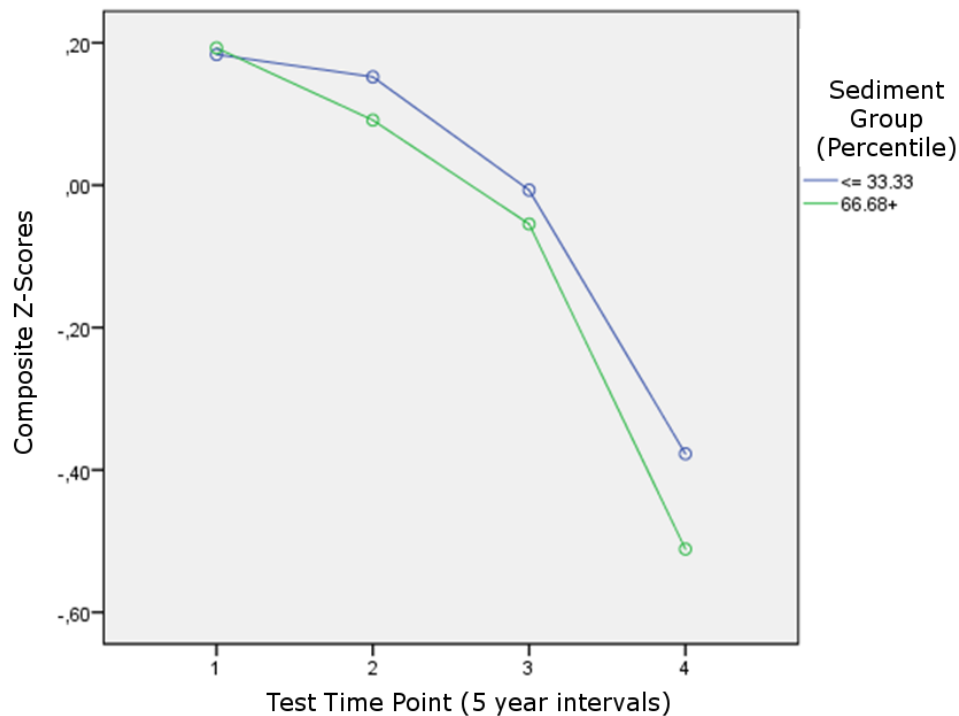


Figure 4. Change in episodic memory over time for high and low sedimentation groups

There was no main effect for sediment group on episodic memory task performance,  $F(1,108) = 0.404, p = .526$  and no interaction between group and time,  $F(3, 108) = 0.595, p = .620$ . There was a main effect of time,  $F(3, 108) = 4.442, p < .01$ , implying that performance on episodic memory tests declined over time.

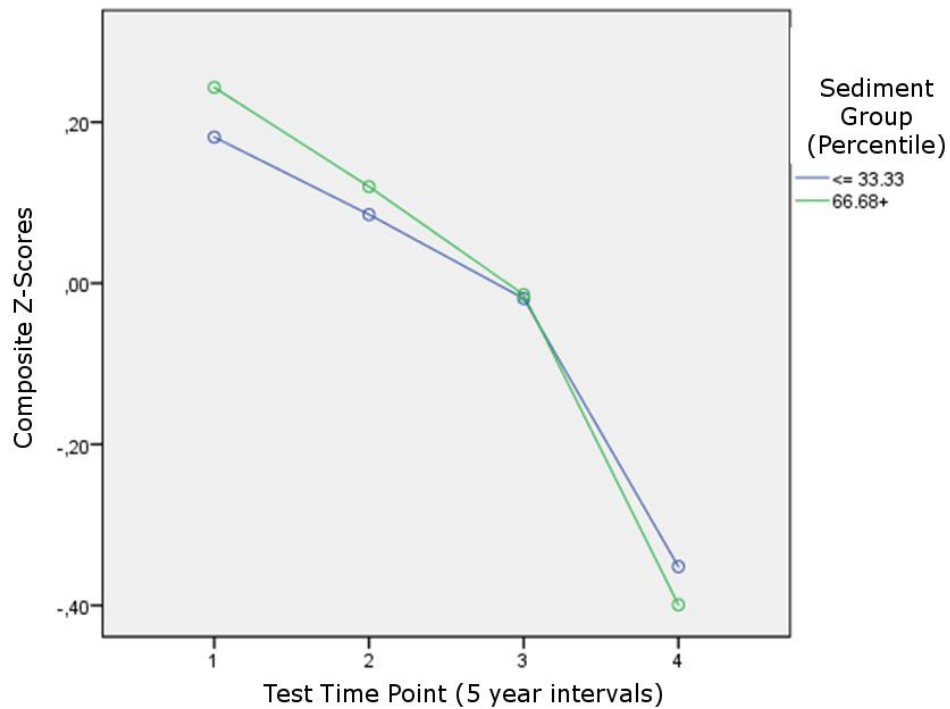


Figure 5. Change in semantic memory over time for high and low sedimentation groups

Again, there was no significant effect of sediment group,  $F(1,116) = 0.061, p = .805$ , nor an interaction,  $F(3, 114) = 0.398, p = .755$ . There was a significant main effect of time,  $F(3, 114) = 2.781, p < .05$ , where scores on the semantic memory test decreased over time.

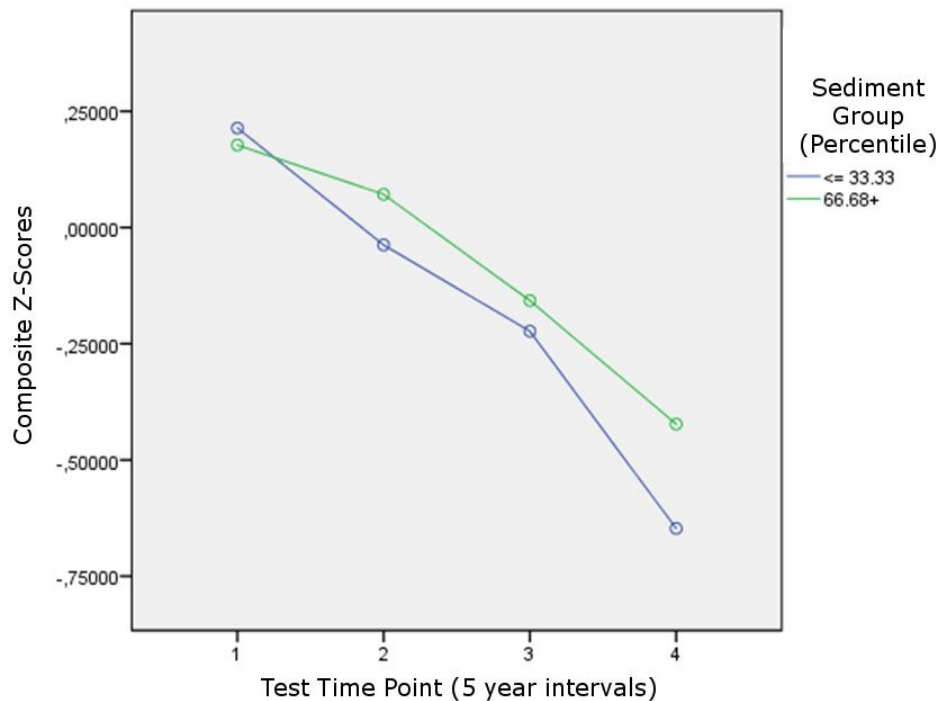


Figure 6. Change in visuospatial skills over time for high and low sedimentation groups

No significant results were found for the block design task with regards to the main effect of sediment group,  $F(1,108) = 0.601, p = .440$ , nor any interaction with group and time,  $F(3, 106) =$

1.282,  $p = .285$ . There was also no significant difference in scores over time,  $F(3, 106) = 1.048$ ,  $p = .374$ . This test did not have a significant effect on Mauchly's test of sphericity and as such was not corrected by SPSS.

### Infection

The final grouping involved separating individuals who reported an infection in a self-report questionnaire. Those who reported an infection in the five years prior to the baseline were divided into the infection reporting group, and those who did not into the no infection group. Additionally, participants were excluded if they reported infection at any later time point.

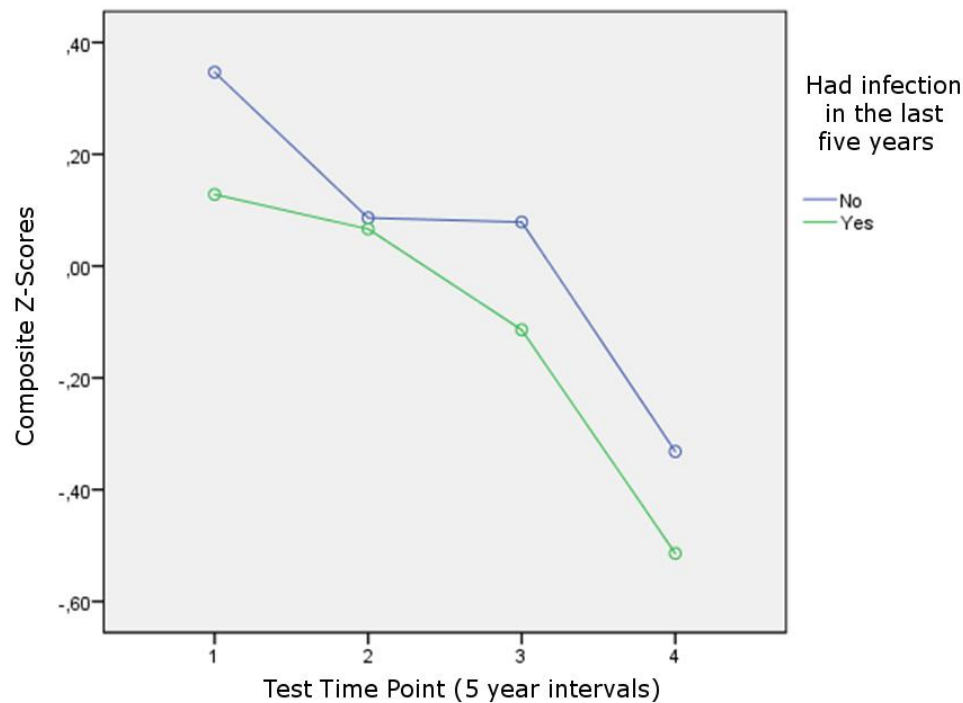


Figure 7. Change in episodic memory over time for those with and without infections

There was no significant main effect of group,  $F(1,77) = 1.908$ ,  $p = .171$ , between those with a history of infection ( $n=51$ ) and those without ( $n=31$ ). There was also no interaction effect between time and infection,  $F(1,77) = 1.908$ ,  $p = .171$ . There was a non-significant main effect of time,  $F(3, 75) = 2.654$ ,  $p = .055$ , although this is very close to significance.

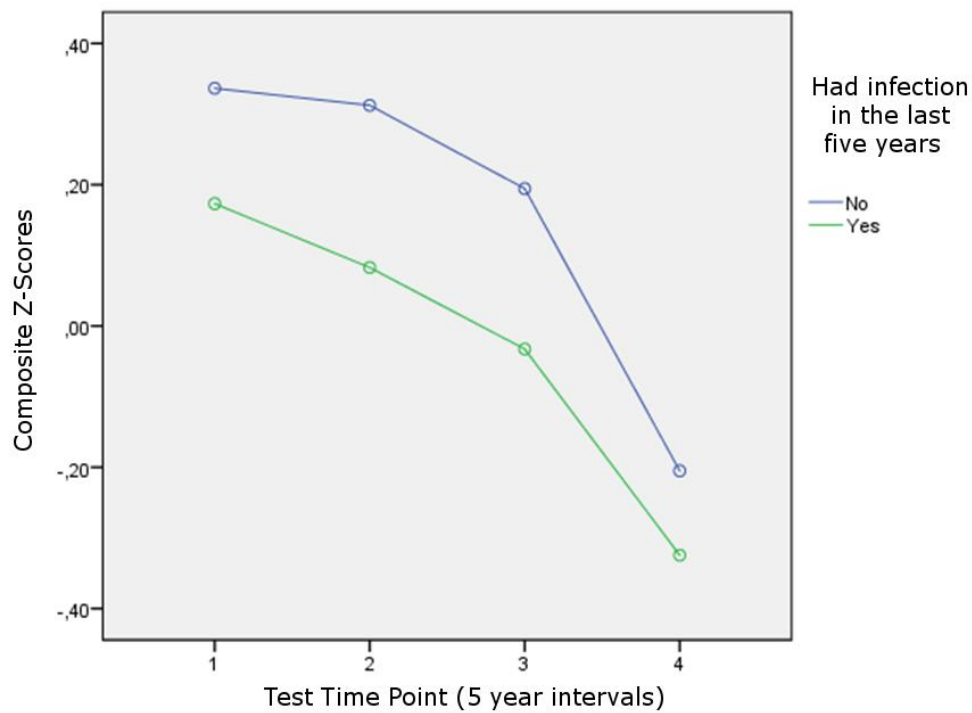


Figure 8. Change in semantic memory over time for those with and without infections

There was no significant main effect of infection group on semantic memory,  $F(3, 79) = 0.488, p = .691$ , and no interaction of time and infection,  $F(3, 79) = 0.488, p = .691$ . There was a main effect of time on semantic memory, suggesting that semantic memory performance decreases over time,  $F(3, 79) = 3.926, p < .05$ .

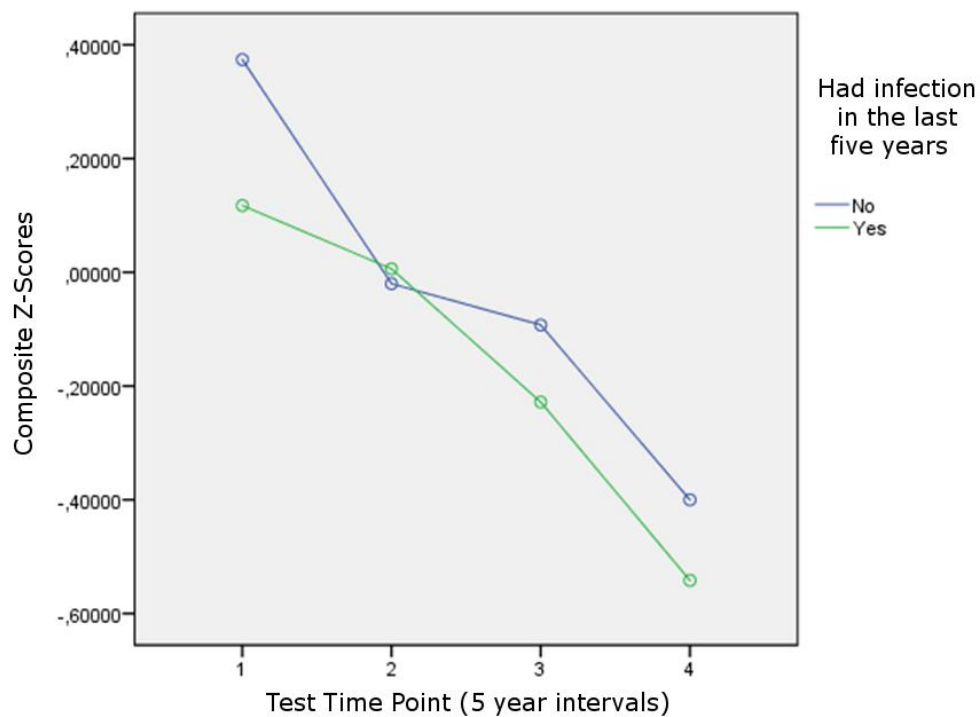


Figure 9. Change in visuospatial skills over time for those with and without infections



There were no significant main effects of infection group on block design task performance,  $F(1, 75) = 0.707$ ,  $p = 0.403$  nor an interaction with time,  $F(3, 73) = 1.450$ ,  $p = 0.235$ . There was also no main effect of time on block design performance,  $F(3, 73) = 0.618$ ,  $p = 0.606$ .

### Discussion

This study was designed to investigate the relationship between blood pressure, blood sedimentation and history of infection with changes in semantic memory, episodic memory and in the visuospatial task performance over a time period of fifteen years. The hypotheses were that each of the grouping variables would negatively impact scores in these tests, as well as to accelerate decline over time in an interaction effect. None of these hypotheses were supported by the results from the analyses.

No significant main effect of any of the grouping variables were shown to have an effect on any of the cognitive tests, nor were there any interaction effects. The analyses demonstrate that performance on cognitive tests of episodic memory, semantic memory and visuospatial skills were not dependent on any of the grouping variables of blood pressure, sedimentation or infection, after controlling for the covariates of age, sex and education. The results largely indicated that there was a general decline in semantic and episodic memory over time, but not in visuospatial skills, which were not deemed to be statistically significant.

The results from this study are largely in line with the conclusion drawn by White et al. (2011), where they state that a single measure of blood pressure is not sufficient to predict decline in participants. If a 24-hour measure had been included in the Betula study, it may have provided more accurate results owing to less noisy data by reducing error in the blood pressure grouping.

In the present study, the criteria for high blood pressure, high sedimentation rate and history of infection groupings also have their own limitations. Each of them was only based on one time point and therefore may not be representative of a more long-term view of each of the measures. As an example, one might have some short term reason for having an elevated blood pressure at the baseline and therefore have a higher blood pressure than it would be if averaged across the whole year. Additionally, some participants might have increased blood pressure while being tested due to the 'white-coat effect', which might complicate any calculations if it not controlled for, as in this study. This effect can be demonstrated by Stergiou, Zourbaki, Skeva and Mountokalakis (1998), who report significant differences between blood pressure taken at the participants' homes and an ambulatory blood pressure measurement. This again largely supports White et al. (2011), where only a 24-hour blood pressure measurement could be used as a predictor of decline in cognitive skills in later life. This was a confounding variable that the current study could not control for.

The covariates used in this study were often deemed to have a significant effect on the results of the cognitive test performance, specifically age and education. Generally, those with a higher level of educational attainment performed better on all tasks than those with a lower level of educational attainment. This could be interpreted in two ways: firstly that those with a higher level of educational attainment become better at the cognitive skills measured in this study and also retain this ability over time, and retain these skills as they age, or secondly those who have better cognitive skills are more likely to pursue higher education. Both of these interpretations may have some truth to them, but it is beyond the scope of this study and additional studies would be needed to explore this idea further. Additionally, age was also a strong covariate and often yielded significant effects. This generally supports the idea that the performance in these skills declines with age, as was demonstrated by Whalley et al. (2004) and Saxby et al. (2003) for example.

Given the strength of education as a covariate, the grouping variables of this study (blood pressure, sedimentation and infection) seem to be much less important on determining the future outcomes on memory and visuospatial ability than education. It is possible that the

covariates largely explain the differences seen in the graphs between groups, and not the grouping variables themselves, especially considering the cognitive reserves hypothesis (Sattler et al., 2012).

There are limitations to this conclusion. The most important limitations are the relatively crude measurements of infection (self-report question), and blood pressure. A much more rigorous biological study would be needed to more accurately record infections, and the importance of a 24-hour measure of blood pressure has already been discussed earlier in the paper. Sedimentation group assignment also relied on extreme-groups comparison, which reduced the reliability of the measure compared to a median split.

Although this experiment controlled for education, age and sex, there may be more factors that could influence the results of this study. Socio-economic status may be accountable for individual differences in both blood pressure and memory performance, but this was not measured by the Betula study, which preferred to control for this through education. While there may be a strong link between education and economic status, it would have seemed more reasonable to include it in its own right with a combination of measures of income, expenditure and savings. Sustained economic hardship especially has previously been demonstrated to have a negative effect on cognition (Lynch, Kaplan & Shema, 1997), for example. It is possible, if unlikely, that controlling for this variable may have contributed to the study finding a significant relationship between the grouping variables and cognition over time, if the grouping variables are strongly associated with socioeconomic status.

Additionally, exercise may be a factor that could affect both memory and blood pressure quite feasibly. In Muscari et al (2010), 120 healthy adults aged 65-74 were tested in an experiment in which half received a twelve-month endurance exercise training program, to test the hypothesis that this exercise program would prevent a reduction in scores in the Mini Mental State Examination over time. The control group scores declined significantly, and were also significantly different to the scores of the experimental group, who did not decline as much as the controls. The experimental group were also 2.74 times more likely to remain at a normal cognitive level than the controls. If a standardised measure of exercise were to be recorded and included, it would have been beneficial to include in this study, as the confounding variable of exercise may have contributed to the non-significance of this study regarding blood pressure, infection and inflammation and their relationship to cognitive ability over time.

Another limitation is the sample size, which is especially salient in the infection analyses due to the exclusion criteria. While the graphs appeared to show some downward trends, some of the analyses failed to even provide significant results that cognitive performance decreases over time, which is a well-documented effect, for example in Whalley et al. (2004). The small sample may have contributed to the non-significance of some of the analyses, especially in the infection group analyses due to strict exclusion criteria. Other types of grouping could be applied to the infection grouping too, such as a median split, which would have resulted in larger groups.

Because of the present study, as well as the literature it was based upon, it does not seem that blood pressure is a reliable method of predicting future cognitive decline, and the same can be said for infection and inflammation. While this study did not provide any support for its hypotheses, it does not necessarily rule out that these factors have an impact on cognition. Detailed biological studies might be able to provide a clearer picture of the effects of certain biological processes that are related to blood pressure, infection and inflammation that the Betula study is simply unable to provide, such as the role of cytokines. Literature such as Lowe (2004), who show the relationships between cardiovascular risk factors such as hypertension and other factors such as inflammation, and many other authors who demonstrate at least some association with blood pressure and cognitive ability provides at least some promise to this idea, but it seems that a much more rigorous study would be needed to be able to truly assess these ideas.

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