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# Cohort differences in the association of cardiovascular risk and cognitive aging

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Abstract

**Aim:** Investigate birth cohort differences in associations between cardiovascular risk and fluid cognition between age 70 and 79.

**Method:** Data were drawn from representative population-based cohort samples (H70), born 1901-02, 1906-07, and 1930, measured at ages 70, 75, and 79 on fluid cognitive measures (spatial ability and logical reasoning). The Framingham Risk Score (FRS), derived from office-based non-laboratory predictors (age, gender, systolic blood pressure, BMI, smoking, diabetes status), was used to measure cardiovascular risk. Multiple-group latent growth curve models were fitted to the data.

**Findings:** Estimates revealed small associations between the FRS and fluid cognition. These associations were slightly reduced in the 1930 cohort.

**Conclusion:** Findings suggest diminishing adverse effects of cardiovascular risk on cognitive aging in later born cohorts.

**Keywords:** Aging, cardiovascular risk, cognition, cognitive change, cohort differences

## Introduction

Cardiovascular health is thought to be one of the most important determinants of cognitive decline and dementia risk in old age (Grodstein, 2007; Qiu, Xu, & Fratiglioni, 2010). Along with increasing age, risk factors of cardiovascular diseases tend to occur simultaneously, which has motivated the development of multivariable cardiovascular risk indices with the general purpose of quantifying efficiently the overall vascular burden (D'Agostino et al., 2008; Harrison et al., 2014; Joosten et al., 2013; Luchsinger et al., 2005). One of the most commonly used of these indices is the Framingham Risk Score (FRS; Harrison et al., 2014). Several previous studies have shown that higher scores on the FRS are associated with poorer cognitive performance (Elias et al., 2004; Llewellyn et al., 2008; Unverzagt et al., 2011), and a steeper cognitive decline in old age (Joosten et al., 2013; Kaffashian et al., 2011). Other studies demonstrate substantial birth cohort differences regarding the relative prevalence of cardiovascular risk factors (e.g. Harmsen, Wilhelmsen & Jacobsson, 2009; Rosengren et al., 2009; Rosengren et al., 2000; Wilhelmsen et al., 2008; Zhi et al., 2013). Although these studies show an increase in certain factors (e.g., diabetes and overweight), the overall risk tends to decrease in later born cohorts.

Given the association between cardiovascular risk and cognitive aging, and the overall decrease in cardiovascular risk in later born cohorts, we may expect the strength of the association between cardiovascular risk and cognition to be attenuated in the later born cohorts. That is, even though the mechanisms linking cardiovascular risk and cognitive functioning have not changed at the individual level, cardiovascular risk may be of less relative importance, in comparison to other determinants, in relation to individual differences in cognitive functioning in later born cohorts as a result of the decreased prevalence.

In this study, we tested this hypothesis using data from three cohorts, born in 1901-02, 1906-07, and 1930, systematically selected from a Swedish population, and examined at ages

70, 75, and 79 with two fluid cognitive measurements (i.e. logical reasoning and spatial ability) as part of a longitudinal aging study (H70). We determined cardiovascular risk using the FRS based on non-laboratory, i.e., office-based, predictors (D'Agostino et al., 2008) and evaluated the moderating effect of birth cohorts on the associations between the FRS and level and change in the cognitive performances.

## Method

### Participants and sampling design

Data from three representative population-based birth cohorts, born in 1901-02, 1906-07, and 1930, with cognitive measurements at ages 70, 75, and 79, and measurements of cardiovascular risk at age 70, were drawn from the Gerontological and Geriatric Population studies in Gothenburg (H70; see Rinder, Roupe, Steen & Svanborg, 1975; Steen, 2002; Svanborg, 1977). The H70 is a multidisciplinary research program based on longitudinal prospective studies of population-based samples of different birth cohorts.

**Cohort 1901-02.** All 70-year old inhabitants in Gothenburg were identified using the Swedish Revenue Office Register. One thousand one hundred forty-eight, or about 30% of the population, born between July 1, 1901-June 30, 1902 on dates ending with 2, 5 or 8 where invited for participation in the H70 study. Baseline response rate was 85%, yielding a representative sample (Rinder et al., 1975). All participants were given a number from 1-5, and participants with numbers 1 and 2 were selected for psychometric testing (N=460). The participation rate in this subsample was 80% and non-mortality follow-up rates (i.e. follow-up rates of the non-deceased) were 88 % at age 75 and 72 % at age 79. All participants were invited to a medical examination, which included measurements of cardiovascular risk factors. A total of 371 participants in this cohort had measurements on the cognitive tests and the measurements of the cardiovascular risk factors at baseline age 70. Attrition rate due to mortality was 14% at age 75 and 21% at age 79 and attrition due to other reasons, such as

relocation, refusal to participate, or administrational reasons (e.g. shortage of time) was 10% at age 75 and 8% at age 79.

**Cohort 1906-07.** A second cohort was selected for participation in the study in 1976. Twelve hundred eighty-one individuals, constituting about 30% of the 70-years-old living in Gothenburg, born between July 1, 1906-June 30, 1907, were selected in the same manner as the first cohort. The baseline response rate for this cohort was 81% (Jönsson, Rosenhall, Gause-Nilsson & Steen, 1998), constituting a representative sample (Dey, Rothenberg, Sundh, Bosaeus & Steen, 2002). Participants in this cohort were given a number from 6-10, and those with numbers 6 and 7 were selected for psychometric testing (N=513). Participation rate for this subsample at age 70 was 75% and non-mortality follow-up rates 85% and 75% at ages 75 and 79, respectively. A total of 381 participants in this cohort had measurements on the cognitive tests and the cardiovascular risk factors at baseline age 70. Attrition rate due to mortality was 13% at age 75 and 13% at age 79, and attrition due to other reasons was 13% at age 75 and 5% at age 79.

**Cohort 1930.** In the year 2000, individuals born in 1930 on days 3, 6, 12, 18, 21, 24, or 30 in each month were sampled and invited to study participation (N=767). The baseline response rate for this cohort was 66%, constituting a representative sample. Assessments indicate that there were no differences between responders and non-responders (at baseline age 70 years) regarding gender, marital status, 3-year mortality rate, or inpatient psychiatric care (Sacuiu et al., 2010; Wiberg, Waern, Billstedt, Östling and Skoog, 2013). At the baseline measurements, at age 70, half of the responders were randomly selected for psychometric testing (N=254), but at the subsequent measurements at age 75 (N=768) and 79 (N=597) all responders were invited to such testing. Participation rate at age 70 for this subsample (n=254) was 90% and non-mortality follow-up rate was 88% at age 75 and 88% at age 79. For this study we only used data from participants with cardiovascular measurements at age 70

whom also had participated at the cognitive measurements at age 70 and/or at subsequent measurement occasions, giving a total of 454 participants in this cohort. Attrition rate due to mortality was 4% at age 75 and 7% at age 79. Attrition due to other reasons was 29% at age 75 and 29% at age 79.

The H70 study was approved by the Ethics Committee of University of Gothenburg, and informed consent was obtained from all participants.

**Cognitive measures**

We measured logical reasoning through a Figure Logic test (see Dureman, Eriksson, Kebbon & Österberg, 1971). In this test participants are presented geometrical figures, organized in rows with five figures per row. Participants are asked to identify which figure differs in some specific aspect from the other figures. The test consists of 30 rows of figures, with an 8 minute time limit and maximum score of 30.

We measured spatial ability through a Swedish version of the Block Design test (Dureman et al., 1971). In this test participants are asked to organize colored wooden blocks in accordance with seven different patterns presented on cards. The test has a 20 minute time limit and maximum score of 42.

These tests were administered in a similar manner for all three cohorts at the same ages, except that the Figure Logic test was omitted at ages 75 and 79 for the 1906-07 cohort. Therefore, data from the 1906-07 cohort, on the Figure Logic test, was omitted from the analyses.

To minimise bias due to floor effects on the change estimates for the cognitive measurements, produced by factors such as severe cognitive impairment or dementia, we omitted participants with a score of zero on the cognitive measures at baseline (i.e. age 70). For the same reason, we also omitted measurements at age 79 for all participants with a score

of zero on both the 75 and 79 year measures. This way the initial level of functioning and the decline for these participants could be included in the analyses but the risk of incorporating further measures from seriously demented participants decreased. Twenty-one participants were omitted from cohort 1901-02, 11 from cohort 1906-07, and 21 from cohort 1930, giving a total of 53 participants omitted from the analyses.

**Cardiovascular risk**

To assess cardiovascular risk, we used the FRS based on office-based non-laboratory predictors. This constitutes a weighted composite score measure of the risk of developing cardiovascular disease event within 10 years from the assessment (i.e. it represents a global assessment of cardiovascular risk rather than a measure of the risk for a specific type of cardiovascular disease event) (D'Agostino et al., 2008).

The non-laboratory based composite score is based on predictors that do not require laboratory analyses. The variables included are age, sex, systolic blood pressure (SBP), body mass index (BMI), current smoking status (non-smoker=0, current smoker=1), diabetes status (non-diabetic=0, diabetic=1), and use of anti-hypertensive medication (D'Agostino et al., 2008). The equations used for calculating the cardiovascular risk differ for females and males, and systolic blood pressure is weighted differently depending on use of anti-hypertensive medication (Framingham Heart Study, 2017). For females not using anti-hypertensive medication the FRS is calculated as

$$1 - 0.94833^{\exp([2.72107\times\log(Age)+0.51125\times\log(BMI)+2.81291\times\log(SBP)+0.61868\times Smoking+0.77763\times Diabetes]-26.0145)}.$$

For females using anti-hypertensive medication, the systolic blood pressure beta weight is $2.88267 \times \log(SBP)$. For males not using anti-hypertensive medication the FRS is calculated as

$$1 - 0.88431^{\exp([3.11296 \times \log(Age) + 0.79277 \times \log(BMI) + 1.85508 \times \log(SBP) + 0.70953 \times Smoking + 0.53160 \times Diabetes] - 23.9388)}$$

For males using anti-hypertensive medication, the systolic blood pressure weight is $1.92672 \times \log(SBP)$.

Blood pressure was measured using a mercury sphygmomanometer in the right arm in a seated position after a five minute rest and registered to the nearest 5 mmHg. The same measurement procedure was used across all three cohorts.

BMI was calculated as weight (kg) divided by height squared ($m^2$). Standing height was recorded to the nearest centimeter and weight to the nearest 0.1 kg. Measurements were taken in the morning with participants wearing light clothing. In order to minimize methodological differences regarding the measurements, all investigators simultaneously received the same training and instructions.

Data regarding smoking and diabetes status, as well as use of anti-hypertensive medication, was obtained through self-report during the examinations.

**Statistical analyses**

In order to evaluate the moderating effects of birth cohorts on the associations between the FRS and both level and change in cognitive performance from age 70 to 79, we used multiple groups latent growth curve models (LGCM) within structural equation modelling (SEM) (McArdle & Anderson, 1990; McArdle & Nesselroade, 2002) using the statistical program AMOS 20.0 (Arbuckle, 2011). In all models we included gender and

education as covariates and in order to reduce model complexity the effects of these covariates were assumed constant across the birth cohorts. Gender was coded as women = 0 and men = 1, and education was coded as compulsory education (i.e. 6 years or less for cohorts 1901-02 and 1906-07, 7 years or less for the 1930 cohort) = 0 and more than compulsory education = 1. We note that 6 years of education (7 years for the 1930 cohort) refers to “Folkskola”, which was the compulsory level of education for these birth cohorts. The FRS variable was grand mean centered and scaled such that the estimates would refer to change in the outcome per 10 percent increase in the cardiovascular risk.

We fitted three types of LGCM to the data from each of the two cognitive outcomes (see Figure 1). In all models we estimated average level of performance at age 70, and average linear rate of change (in years) between ages 70 and 79, as unique parameters for each of the three birth cohorts. In Model 1 we constrained all the FRS effects to zero (this model was mainly used for comparative purposes). In Model 2, we freed (i.e., estimated) the FRS effects on both the level and the change factor but we constrained these parameters as equal across the birth cohorts. In Model 3, we further released these parameter constraints across the birth cohorts such that the effects of FRS on both the level and change factor were free parameters. Occasional missing data was handled using full information maximum likelihood estimation based on the assumption of missing at random, as conventionally defined (Little & Rubin, 1987).

As noted in Figure 1, we specified the slope factor component loadings as 0, 5, and 9 in all models. The between-person differences in time intervals between the measurements were small in all birth cohorts. For the 1901-02 cohort between T1 and T2: M=5.02 years, SD=0.22, min = 4.42, max=5.95; and between T2 and T3: M=4.11 years, SD=0.24, min=3.31, max=4.90. For the 1906-07 cohort between T1 and T2: M=5.02 years, SD=0.22, min=3.98, max=5.87; and between T2 and T3: M=4.05 years, SD=0.14, min=3.32, max=4.43. For the

1930 cohort between T1 and T2: M=4.88 years, SD=0.18, min=4.40, max=5.78); and between T2 and T3: M=4.69 years, SD=0.30, min=3.38, max=5.56.

Figure 1 about here.

## Results

Sample characteristics stratified by cognitive measure, birth cohort, gender, education, and measurement occasions, are presented in Table 1 and the sample characteristics regarding the cardiovascular risk factors, stratified by cohort, are presented in Table 2. There were significant cohort differences concerning the FRS ($F_{2, 1128}$=17.50, $p$<.001), systolic blood pressure ($F_{2, 1128}$=47.15, $p$<.001), and BMI ($F_{2, 1128}$=7.29, $p$=.001). Post hoc tests (Games-Howell) indicate that the 1930 cohort had lower mean FRS and systolic blood pressure ($p$s<.001), but higher mean BMI ($p$s<.05), compared to the 1901-02 (Cohen's d=0.39, d=0.58, and d=0.22 respectively) and 1906-07 cohorts (d=0.33, d=0.60, and d=0.24 respectively). There were no significant differences between the 1901-02 and 1906-07 cohorts regarding these measures (d=0.18, d=0.03, and d=0.02 respectively). Further, there were significant cohort differences regarding smoking status ($\chi^2_{2, N=1131}$=23.51, $p$<.001, Cramer's V=.14), with a larger proportion of current smokers in the 1901-02 cohort compared to the later born cohorts. There were no significant cohort differences concerning gender distribution ($\chi^2_{2, N=1131}$=1.25, $p$=.54, Cramer's V=.03), diabetes ($\chi^2_{2, N=1131}$=5.35, $p$=.07, Cramer's V=.07) or antihypertensive medication status ($\chi^2_{2, N=1131}$=1.50, $p$=.47, Cramer's V=.04). There were significant cohort differences in educational attainment, with a larger proportion of participants with more than compulsory education in the 1930 cohort compared to earlier born cohorts ($\chi^2_{2, N=1131}$=94.86, $p$<.001, Cramer's V=.29).

Table 1 about here

Table 2 about here

Estimates from the multiple groups LGCM fitted to the spatial ability and reasoning data are shown in Tables 3 and 4, respectively. In all the presented models we constrained the variability and covariability components equal across birth cohorts, as releasing these constraints did not significantly improve the model fit (spatial ability: $\Delta\chi^2(6) = 2.26$, $p = .90$, and reasoning: $\Delta\chi^2(3) = 4.56$, $p = .21$). As indicated by the differences between Models 1 and 2, releasing constraints on the FRS effects on both the level and the change factors improved the model fit (spatial ability: $\Delta\chi^2$ (2) = 11.14, $p = 0.004$, and logical reasoning: $\Delta\chi^2$ (2) = 6.17, $p = 0.046$), indicating associations of the FRS index with both cognitive outcomes. For the spatial ability test, a 10 percent increase in cardiovascular risk was related to an average increase in decline by 0.04 points (standardized estimate= -0.01, 95% CI [-0.02, -0.002]) per year. For the reasoning test, there was a significant negative effect of FRS on baseline performance, where a 10 percent increase in cardiovascular risk was related to an average decrease in baseline performance by 0.29 points (standardized estimate= -0.10, 95% CI [-0.18, -0.01]).

As indicated by the comparisons of Models 2 and 3, including separate FRS effects, for each birth cohort, on both the level and the change factors improved the model fit when using the reasoning ability test as outcome ($\Delta\chi^2(2) = 7.72$ $p=0.021$) but not spatial ability ($\Delta\chi^2(4) = 1.31$ $p = 0.86$). For the reasoning test, there was a negative effect of FRS on baseline performance in the 1901-02 cohort, where a 10 % increase in the risk of cardiovascular disease was associated with a decrease in expected baseline performance of 0.54 points (standardized estimate= -0.18, 95% CI [-0.29, -0.08]). For the 1930 birth cohort, a

comparable estimate was a, non-significant, increase in baseline performance by 0.05 points (standardized estimate= 0.02, 95% CI [-0.10, 0.14]). The fixed effect estimates from Models 3 are plotted in Figure 1 and indicate that the relative influence of the FRS index is somewhat stronger in the 1901-02 birth cohort in comparison to the 1930 cohort, particularly on the reasoning test.

Tables 3 and 4 about here

Figure 2 about here

## Discussion

We investigated the moderating role of birth cohorts on the associations between the FRS index and levels and rates of change in fluid cognition between age 70 and 79 in a Swedish population-based sample. Our main findings indicate a relatively small association between the FRS and both level and rate of change. However, these associations were somewhat larger in the first birth cohort, providing at least a partial support for the notion of the moderating effects of birth cohorts.

A potential explanation for the relatively small effect sizes found in this study could be that the FRS index used, i.e., based on non-laboratory predictors, is not well enough suited for quantification of cardiovascular burden when assessed at age 70. This may be due to that the beta weights, as generated from the original Framingham cohort and used in the computation of the FRS, are not completely generalizable to the observed sample at this age. The FRS was developed using a sample ranging from 30 to 74 years of age at baseline, with a mean age of 49 (D'Agostino et al., 2008), which only partly overlaps with the age range in this study. Another potential explanation may relate to the non-linearity of the associations between some of the ingredients of the FRS index and cognitive performance and dementia

risk, such as blood pressure (Kennelly & Collins, 2012; Skoog et al., 1996; Thorvaldsson et al., 2012) and BMI (Sabia, Kivimaki, Shipley, Marmot, & Singh-Manoux, 2009), as the FRS is based on assumed linear associations. Also, smoking status was dichotomized (i.e., as non-smoker or current smoker) and this may constitute an over-simplification of the relationship between smoking and cognition, as some studies indicate differences in cognitive decline between former smokers and never smokers (Sabia et al., 2012; Anstey, von Sanden, Salim & O'Kearney, 2007). We note however that, although the reported effects sizes in this study seem relatively small, they are comparable to effect sizes from a recent meta-analysis (i.e., DeRight et al., 2015).

Our findings indicate that cardiovascular risk, measured by the FRS index, seems to be of less relative importance for cognitive functioning in later born cohorts. In line with previous studies (e.g. Harmsen, Wilhelmsen & Jacobsson, 2009; Rosengren et al., 2009, Zhi et al., 2013) we found that the overall cardiovascular risk load was significantly lower in the 1930 cohort compared to the two earlier born cohorts. Thus, it is therefore perhaps not surprising to find that cardiovascular risk is less influential on cognitive functioning in the later born cohorts. However, it is important to keep in mind that the FRS is a weighted aggregate score based on several risk factors. Even though the overall cardiovascular risk load has decreased over time, there has been an increase in risk factors such as BMI and diabetes prevalence (e.g. Harmsen et al., 2009; Rosengren et al., 2009). In line with this, we found that the 1930 cohort had a significantly larger average BMI compared to the earlier born cohorts, and a slightly higher diabetes prevalence (although not significant). A large body of research has indicated that diabetes and being overweight, or obese, is related to worse cognitive functioning and increased risk of developing dementia (e.g. Cheng, Huang, Deng & Wang, 2012; Gunstad, Lhotsky, Wendell, Ferrucci & Zonderman, 2010; Gustafson, Rothenberg,

Blennow, Steen & Skoog, 2003; Hassing, Dahl, Pedersen & Johansson, 2010; McCrimmon, Ryan & Frier, 2012).

Some of the strengths of our study are related to the design of the H70 that allows comparisons of cognitive performances in representative population-based samples, born 30 years apart, followed over nine years with measurements at the same chronological ages (i.e. 70, 75, and 79 years), using the same cognitive tests and physiological measures across time and cohorts. Another strength is that the birth cohorts were age-homogenous, i.e. all participants in each cohort were born at most only 12 months apart.

Several limitations should also be acknowledged, such as that we only analyzed two fluid cognitive tests in this study. This entails limitations to the types of cognitive domains we can generalize our findings to. Also, we only had three measurement waves, a detailed modelling of cohort differences in non-linear trajectory shapes would optimally require more waves of data. Yet another limitation relates to the lower baseline response rate in the 1930-cohort (66 %) compared to the 1901-02 and 1906-07 cohorts (85 % and 81 % respectively). A lower response rate is likely to be associated with a more selective sample. Further, to the extent that attrition compromises the representativeness of the cohorts, reasons for attrition may differ between the cohorts. As an example, attrition due to mortality was higher in the earlier born cohorts compared to the 1930 cohort, while attrition due to other reasons (e.g. relocation, refusal to participate) was higher in the 1930 cohort. A final limitation relates to the fact that we do not have access to data regarding cardiovascular events. Therefore we were unable to investigate whether the FRS predicts cardiovascular events equally well for the different cohorts. To the extent that the FRS works less well for later born cohorts this could attenuate the association between cardiovascular risk and cognitive functioning and decline.

In conclusion, our findings indicate that cardiovascular risk, calculated using the FRS as derived from office-based non-laboratory predictors, was negatively associated with

cognitive functioning and rate of decline from age 70 to 79. The effect sizes were small and almost non-existing in the latest born cohort.

## References

Anstey, K. J., von Sanden, C., Salim, A., & O'Kearney, R. (2007). Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies. *American journal of epidemiology*, *166*(4), 367-378. *doi: 10.1093/aje/kwm116*

Arbuckle, J. L. (2011). IBM SPSS Amos 20.0 [computer program]. *New York: IBM*.

Cheng, G., Huang, C., Deng, H., & Wang, H. (2012). Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. *Internal medicine journal*, *42*(5), 484-491. doi: 10.1111/j.1445-5994.2012.02758.x

D'Agostino, R. B., Vasan, R. S., Pencina, M. J., Wolf, P. A., Cobain, M., Massaro, J. M., & Kannel, W. B. (2008). General cardiovascular risk profile for use in primary care: the Framingham heart study. *Circulation, 117*, 743-753. doi: 10.1161/CIRCULATIONAHA.107.699579

DeRight, J., Jorgensen, R. S., & Cabral, M. J. (2015). Composite cardiovascular risk scores and neuropsychological functioning: A meta-analytic review. *Annals of Behavioral Medicine*, *49*(3), 344-357. doi 10.1007/s12160-014-9681-0

Dey, D. K., Rothenberg, E., Sundh, V., Bosaeus, I., & Steen, B. (2002). Waist circumference, Body Mass Index, and risk for stroke in older people. A 15-year longitudinal population study of 70-year-olds. *J Am Geriatr Soc, 50*, 1510-1518. doi: 10.1046/j.1532-5415.2002.50406.x

Dureman, I., Eriksson, U. B., Kebbon, L., & Österberg, E. (1971). Manual till DS-batteriet. Stockholm: Skandinaviska testförlaget.

Elias, M. F., Sullivan, L. M., D'Agostino, R. B., Elias, P. K., Beiser, A., Au, R., ... & Wolf, P. A. (2004). Framingham stroke risk profile and lowered cognitive performance. *Stroke*, *35*(2), 404-409. doi: 10.1161/01.STR.0000103141.82869.77

Framingham Heart Study (2017, May 9). Framingham risk functions. Retrieved from

https://www.framinghamheartstudy.org/risk-functions/index.php

Gunstad, J., Lhotsky, A., Wendell, C. R., Ferrucci, L., & Zonderman, A. B. (2010). Longitudinal examination of obesity and cognitive function: results from the Baltimore longitudinal study of aging. *Neuroepidemiology*, *34*(4), 222-229. doi: 10.1159/000297742

Gustafson, D., Rothenberg, E., Blennow, K., Steen, B., & Skoog, I. (2003). An 18-year follow-up of overweight and risk of Alzheimer disease. *Archives of internal medicine*, *163*(13), 1524-1528. doi:10.1001/archinte.163.13.1524

Harmsen, P., Wilhelmsen, L., & Jacobsson, A. (2009). Stroke incidence and mortality rates 1987 to 2006 related to secular trends of cardiovascular risk factors in Gothenburg, Sweden. *Stroke*, *40*(8), 2691-2697. doi: 10.1161/STROKEAHA.109.550814

Harrison, S. L., Ding, J., Tang, E. Y., Siervo, M., Robinson, L., Jagger, C., & Stephan, B. C. (2014). Cardiovascular disease risk models and longitudinal changes in cognition: A systematic review. *PloS one*, *9*(12), e114431. doi:10.1371/journal.pone.0114431

Hassing, L. B., Dahl, A. K., Pedersen, N. L., & Johansson, B. (2010). Overweight in midlife is related to lower cognitive function 30 years later: a prospective study with longitudinal assessments. *Dementia and geriatric cognitive disorders*, *29*(6), 543-552. doi: 10.1159/000314874

Joosten, H., van Eersel, M. E., Gansevoort, R. T., Bilo, H. J., Slaets, J. P., & Izaks, G. J. (2013). Cardiovascular risk profile and cognitive function in young, middle-aged, and elderly subjects. *Stroke*, *44*(6), 1543-1549. doi: 10.1161/STROKEAHA.111.000496

Jönsson, R., Rosenhall, U., Gause-Nilsson, I., & Steen, B. (1998). Auditory function in 70- and 75-year-olds of four age cohorts. A cross-sectional and time-lag study of presbyacusis. *Scand Audiol*, *27*, 81-93. doi: 10.1080/010503998420324

Kaffashian, S., Dugravot, A., Nabi, H., Batty, G. D., Brunner, E., Kivimäki, M., & Singh-

Manoux, A. (2011). Predictive utility of the Framingham general cardiovascular disease risk profile for cognitive function: evidence from the Whitehall II study. *European heart journal*, ehr133. doi:10.1093/eurheartj/ehr133

Kennelly, S., & Collins, O. (2012). Walking the cognitive "minefield" between high and low blood pressure. *Journal of Alzheimer's Disease, 32*, 609-621. doi: 10.3233/JAD-2012-120748

Little, R. J. A., & Rubin, D. B. (1987). *Statistical analysis with missing data*. New York: Wiley.

Llewellyn, D. J., Lang, I. A., Xie, J., Huppert, F. A., Melzer, D., & Langa, K. M. (2008). Framingham Stroke Risk Profile and poor cognitive function: a population-based study. *BMC neurology*, *8*(1), 1. doi**:** 10.1186/1471-2377-8-12

Luchsinger, J. A., Reitz, C., Honig, L. S., Tang, M. X., Shea, S., & Mayeux, R. (2005). Aggregation of vascular risk factors and risk of incident Alzheimer disease. *Neurology*, *65*(4), 545-551. doi:10.1212/01.wnl.0000172914.08967.dc

McArdle, J. J., & Anderson, E. (1990). Latent variable growth models for research on aging. In J. E. Birren & K. W. Schaie (Eds.), *Handbook of the Psychology of Aging* (21—44). New York: Academic Press.

McArdle, J. J., & Nesselroade, J. R. (2002). Growth curve analysis in contemporary psychological research. In J. Schinka & W. Velicer (Eds.), *Comprehensive handbook of psychology: Vol. 2. Research methods in psychology* (pp. 447-480). New York: Pergamon Press.

McCrimmon, R. J., Ryan, C. M., & Frier, B. M. (2012). Diabetes and cognitive dysfunction. *The Lancet*, *379*(9833), 2291-2299. doi:10.1016/S0140-6736(12)60360-2

Rinder, L., Roupe, S., Steen, B., & Svanborg, A. (1975). Seventy-year-old people in

Gothenburg. A population study in an industrialized Swedish city. I. General presentation of the study. *Acta Medica Scandinavica, 198*, 397-407.

Rosengren, A., Eriksson, H., Hansson, P. O., Svärdsudd, K., Wilhelmsen, L., Johansson, S., ... & Welin, L. (2009). Obesity and trends in cardiovascular risk factors over 40 years in Swedish men aged 50. *Journal of internal medicine, 266*(3), 268-276. doi: 10.1111/j.1365-2796.2009.02116.x

Rosengren, A., Eriksson, H., Larsson, B., Svärdsudd, K., Tibblin, G., Welin, L., & Wilhelmsen, L. (2000). Secular changes in cardiovascular risk factors over 30 years in Swedish men aged 50: the study of men born in 1913, 1923, 1933 and 1943. *Journal of internal medicine*, *247*(1), 111-118. doi: 10.1046/j.1365-2796.2000.00589.x

Sabia, S., Elbaz, A., Dugravot, A., Head, J., Shipley, M., Hagger-Johnson, G., ... & Singh-Manoux, A. (2012). Impact of smoking on cognitive decline in early old age: the Whitehall II cohort study. *Archives of general psychiatry*, *69*(6), 627-635. doi:10.1001/archgenpsychiatry.2011.2016

Sabia, S., Kivimaki, M., Shipley, M. J., Marmot, M. G., & Singh-Manoux, A. (2009). Body mass index over the adult life course and cognition in late midlife: the Whitehall II Cohort Study. *The American journal of clinical nutrition*, *89*(2), 601-607. doi: 10.3945/ajcn.2008.26482

Sacuiu, S., Gustafson, D., Sjögren, M., Guo, X., Östling, S., Johansson, B., & Skoog, I. (2010). Secular changes in cognitive predictors of dementia and mortality in 70-year-olds. *Neurology, 75*,779-785. doi: 10.1212/WNL.0b013e3181f0737c

Skoog, I., Nilsson, L., Persson, G., Lernfelt, B., Landahl, S., Palmertz, B., ... & Svanborg, A. (1996). 15-year longitudinal study of blood pressure and dementia. *The Lancet*, *347*, 1141-1145. doi:10.1016/S0140-6736(96)90608-X

Svanborg, A. (1977). Seventy-year-old people in Gothenburg. A population study in an

industrialized city. II. General presentation of social and medical conditions. *Acta Medica Scandinavica, 611*, (Suppl.) 3-37.

Thorvaldsson, V., Skoog, I., Hofer, S. M., Börjesson-Hanson, A., Östling, S., Sacuiu, S., & Johansson, B. (2012). Nonlinear blood pressure effects on cognition in old age: separating between-person and within-person associations. *Psychology and aging, 27*(2), 375. doi: 10.1037/a0025631

Unverzagt, F. W., McClure, L. A., Wadley, V. G., Jenny, N. S., Go, R. C., Cushman, M., ... & Howard, V. (2011). Vascular risk factors and cognitive impairment in a stroke-free cohort. *Neurology, 77*(19), 1729-1736. doi:10.1212/WNL.0b013e318236ef23

Wechsler, D. (1981). Wechsler adult intelligence scale-revised. San Antonio: The psychological association.

Wiberg, P., Waern, M., Billstedt, E., Östling, S., & Skoog, I. (2013). Secular trends in the prevalence of dementia and depression in Swedish septuagenarians 1976-2006. *Psychological Medicine, 43*, 2627-2634. doi: 10.1017/S0033291713000299

Wilhelmsen, L., Welin, L., Svärdsudd, K., Wedel, H., Eriksson, H., Hansson, P. O., & Rosengren, A. (2008). Secular changes in cardiovascular risk factors and attack rate of myocardial infarction among men aged 50 in Gothenburg, Sweden. Accurate prediction using risk models. *Journal of internal medicine, 263*(6), 636-643. doi: 10.1111/j.1365-2796.2008.01931.x

Zhi, X., Joas, E., Waern, M., Östling, S., Börjesson-Hanson, A., & Skoog, I. (2013). Prevalence of cardiovascular disorders and risk factors in two 75-year-old birth cohorts examined in 1976–1977 and 2005–2006. *Aging clinical and experimental research, 25*(4), 377-383. doi.org/10.1007/s40520-013-0058-1

## Conflict of interest

None

## Description of authors' roles

Peter Karlsson formulated the research questions, designed the study, analyzed the data, and wrote the paper. Boo Johansson formulated the research questions, designed the study, supervised data collection, and assisted in writing the paper. Ingmar Skoog supervised the H70 study and gave valuable comments on the paper. Johan Skoog supervised the collection and coding of data and gave valuable comments on the paper. Lina Rydén supervised the collection and coding of the cardiovascular data and gave valuable comments on the paper. Valgeir Thorvaldsson formulated the research questions, designed the study, supervised data collection, and assisted in writing the paper and analyzing the data.

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Table 1. Sample characteristics in the H70 study stratified by cognitive test, birth cohort, gender, education, and measurement occasions

| Cognitive test | N[a] | Gender[a] Women (%) | Education[a] Compulsory or less (%) | Measurement occasions Age 70 M (SD) | Age 75 M (SD) | Age 79 M (SD) |
|---|---|---|---|---|---|---|
| Spatial Ability | | | | | | |
| Cohort 1901 | 313 | 58.50 | 85.30 | 13.38 (6.64) | 12.87 (6.43) | 11.73 (7.28) |
| Cohort 1906 | 381 | 55.90 | 82.20 | 15.95 (6.91) | 14.61 (6.84) | 11.59 (7.45) |
| Cohort 1930 | 437 | 59.70 | 57.40 | 19.89 (6.82) | 17.23 (6.98) | 15.80 (6.86) |
| Total | 1131 | 58.10 | 73.50 | 16.45 (7.21) | 15.02 (7.00) | 13.26 (7.44) |
| Logical Reasoning[b] | | | | | | |
| Cohort 1901 | 371 | 58.20 | 85.70 | 12.61 (4.60) | 12.57 (5.15) | 12.41 (4.93) |
| Cohort 1930 | 454 | 58.60 | 58.60 | 16.82 (4.51) | 14.87 (5.13) | 14.66 (5.36) |
| Total | 825 | 58.40 | 70.80 | 14.17 (5.00) | 13.85 (5.26) | 13.76 (5.31) |

Note. [a] Data refers to baseline measurement at age 70. [b] Data for cohort 1906 on the Logical Reasoning test was not collected at ages 75 and 79 and therefore omitted from the present analyses.

Table 2. Baseline (age 70) descriptives for the variables included in the computation of the Framingham Risk Score as stratified by birth cohort.

| | Cohort | | |
|---|---|---|---|
| | 1901-02 | 1906-07 | 1930 |
| Framingham Risk score, M (SD)* | 39.22 (16.41) | 38.21 (17.81) | 32.68 (15.89) |
| Systolic blood pressure, M (SD)* | 168.47 (25.24) | 169.07 (22.16) | 155.16 (22.04) |
| Antihypertensive medication, n (%) | 76 (24.30) | 92 (24.10) | 120 (27.50) |
| Body mass index, M (SD)* | 25.97 (3.81) | 25.89 (3.64) | 26.83 (4.17) |
| Diabetes, n (%) | 16 (5.10) | 25 (6.60) | 41 (9.40) |
| Current smoker, n (%)* | 83 (26.50) | 60 (15.70) | 58 (13.30) |
| Gender, women n (%) | 183 (58.5) | 213 (55.9) | 261 (59.7) |

Note. *Significant cohort differences. See the main text for further details.

Table 3. Parameter estimates from multiple group latent growth curve models fitted to the spatial ability (Block Design test) data (N=1131)

| | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|
| Parameters | Estimates | *SE* | Estimates | *SE* | Estimates | *SE* |
| Intercept | | | | | | |
| Cohort 1901 | 12.60*** | 0.44 | 12.56*** | 0.45 | 12.61*** | 0.45 |
| Cohort 1906 | 14.73*** | 0.38 | 14.65*** | 0.39 | 14.65*** | 0.39 |
| Cohort 1930 | 17.31*** | 0.44 | 17.15*** | 0.47 | 17.19*** | 0.47 |
| Gender | 1.33*** | 0.41 | 1.55*** | 0.48 | 1.56*** | 0.48 |
| Education | 4.64*** | 0.49 | 4.65*** | 0.49 | 4.62*** | 0.49 |
| FRS | | | -0.12 | 0.14 | | |
| Cohort 1901 x FRS | | | | | -0.32 | 0.26 |
| Cohort 1906 x FRS | | | | | -0.13 | 0.20 |
| Cohort 1930 x FRS | | | | | 0.06 | 0.24 |
| Linear slope | | | | | | |
| Cohort 1901 | -0.27*** | 0.05 | -0.30*** | 0.05 | -0.30*** | 0.05 |
| Cohort 1906 | -0.46*** | 0.04 | -0.48*** | 0.05 | -0.48*** | 0.05 |
| Cohort 1930 | -0.52*** | 0.06 | -0.56*** | 0.06 | -0.56*** | 0.06 |
| Gender | -0.05 | 0.05 | 0.03 | 0.06 | 0.03 | 0.06 |
| Education | -0.11 | 0.06 | -0.11 | 0.06 | -0.11 | 0.06 |
| FRS | | | -0.04** | 0.02 | | |
| Cohort 1901 x FRS | | | | | -0.03 | 0.03 |
| Cohort 1906 x FRS | | | | | -0.04 | 0.02 |
| Cohort 1930 x FRS | | | | | -0.05 | 0.03 |
| Variability components | | | | | | |
| Intercept | 28.82 | 2.04 | 28.77 | 2.04 | 28.73 | 2.04 |
| Slope | 0.04 | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 |
| Covariance | 0.11 | 0.19 | 0.12 | 0.19 | 0.12 | 0.19 |
| Residual | 12.05 | 0.72 | 12.08 | 0.72 | 12.08 | 0.72 |
| Model fit indices | | | | | | |
| $\chi^2(df)$ | 69.54(40) | | 58.41(38) | | 57.10(34) | |
| CFI | 0.98 | | 0.99 | | 0.98 | |
| RMSEA [90% *CI*] | 0.03(0.02-0.04) | | 0.02(0.01-0.03) | | 0.03(0.01-0.04) | |

Note. * p < .05. ** p < .01. *** p < .001.

Table 4. Parameter estimates from multiple group latent growth curve models fitted to the reasoning ability (Figure Logic test) data (N=825)

| | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|
| Parameters | Estimates | *SE* | Estimates | *SE* | Estimates | *SE* |
| Intercept | | | | | | |
| Cohort 1901 | 11.94*** | 0.28 | 11.84*** | 0.29 | 11.90*** | 0.29 |
| Cohort 1930 | 15.23*** | 0.36 | 15.00** | 0.37 | 15.01*** | 0.37 |
| Gender | 1.06** | 0.36 | 1.53*** | 0.42 | 1.58*** | 0.41 |
| Education | 2.12*** | 0.43 | 2.12*** | 0.42 | 2.08*** | 0.42 |
| FRS | | | -0.29* | 0.13 | | |
| Cohort 1901 x FRS | | | | | -0.54*** | 0.15 |
| Cohort 1930 x FRS | | | | | 0.05 | 0.18 |
| Linear slope | | | | | | |
| Cohort 1901 | -0.08 | 0.05 | -0.08 | 0.05 | -0.08 | 0.05 |
| Cohort 1930 | -0.28*** | 0.06 | -0.28*** | 0.06 | -0.27*** | 0.06 |
| Gender | -0.05 | 0.06 | -0.07 | 0.07 | -0.07 | 0.07 |
| Education | -0.03 | 0.07 | -0.02 | 0.07 | -0.02 | 0.07 |
| FRS | | | 0.01 | 0.02 | | |
| Cohort 1901 x FRS | | | | | 0.03 | 0.03 |
| Cohort 1930 x FRS | | | | | -0.02 | 0.02 |
| Variability components | | | | | | |
| Intercept | 6.77 | 1.47 | 6.58 | 1.46 | 6.36 | 1.45 |
| Slope | 0.04 | 0.04 | 0.04 | 0.04 | 0.04 | 0.04 |
| Covariance | 0.21 | 0.19 | 0.22 | 0.19 | 0.23 | 0.19 |
| Residual | 13.95 | 0.94 | 13.96 | 0.94 | 13.94 | 0.94 |
| Model fit indices | | | | | | |
| $\chi^2(df)$ | 74.03 (24) | | 67.86 (22) | | 60.14 (20) | |
| CFI | 0.90 | | 0.91 | | 0.92 | |
| RMSEA [90% *CI*] | 0.05(0.04-0.06) | | 0.05(0.04-0.06) | | 0.05(0.04-0.06) | |

Note. * p < .05. ** p < .01. *** p < .001.

Figure caption

*Figure 1*. Graphical representation of the Latent growth Curve models fitted to the data.

*Figure 2*. Estimated change trajectories from multiple group LGCMs, conditioned on cardiovascular risk (FRS), and fitted to reasoning and spatial ability data from the H70. Groups are defined by birth cohorts.

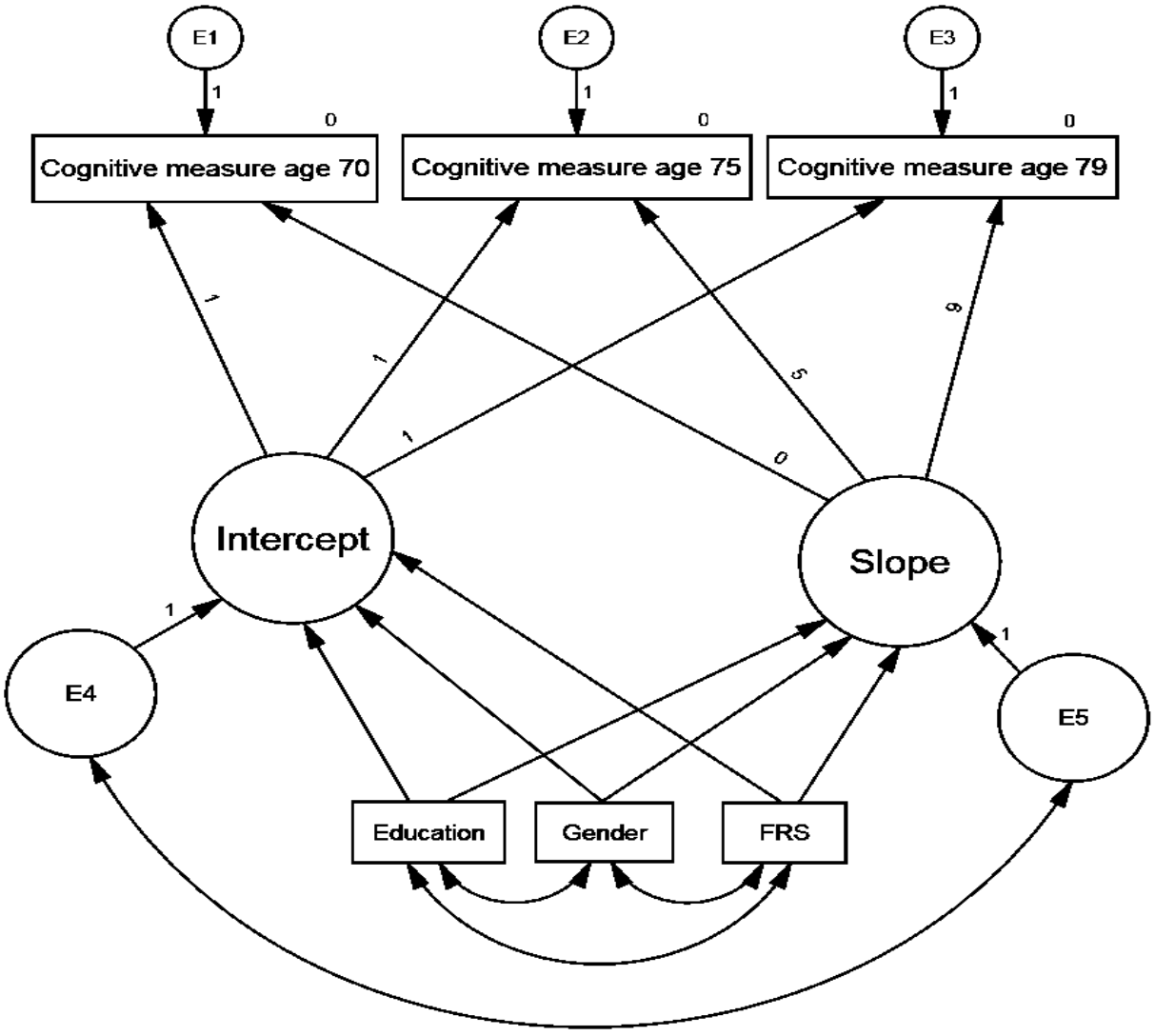
E1
E2
E3
1
1
1
0
0
0
Cognitive measure age 70
Cognitive measure age 75
Cognitive measure age 79
1
1
1
5
9
0
Intercept
Slope
1
1
E4
E5
Education
Gender
FRS

*Figure 1.*

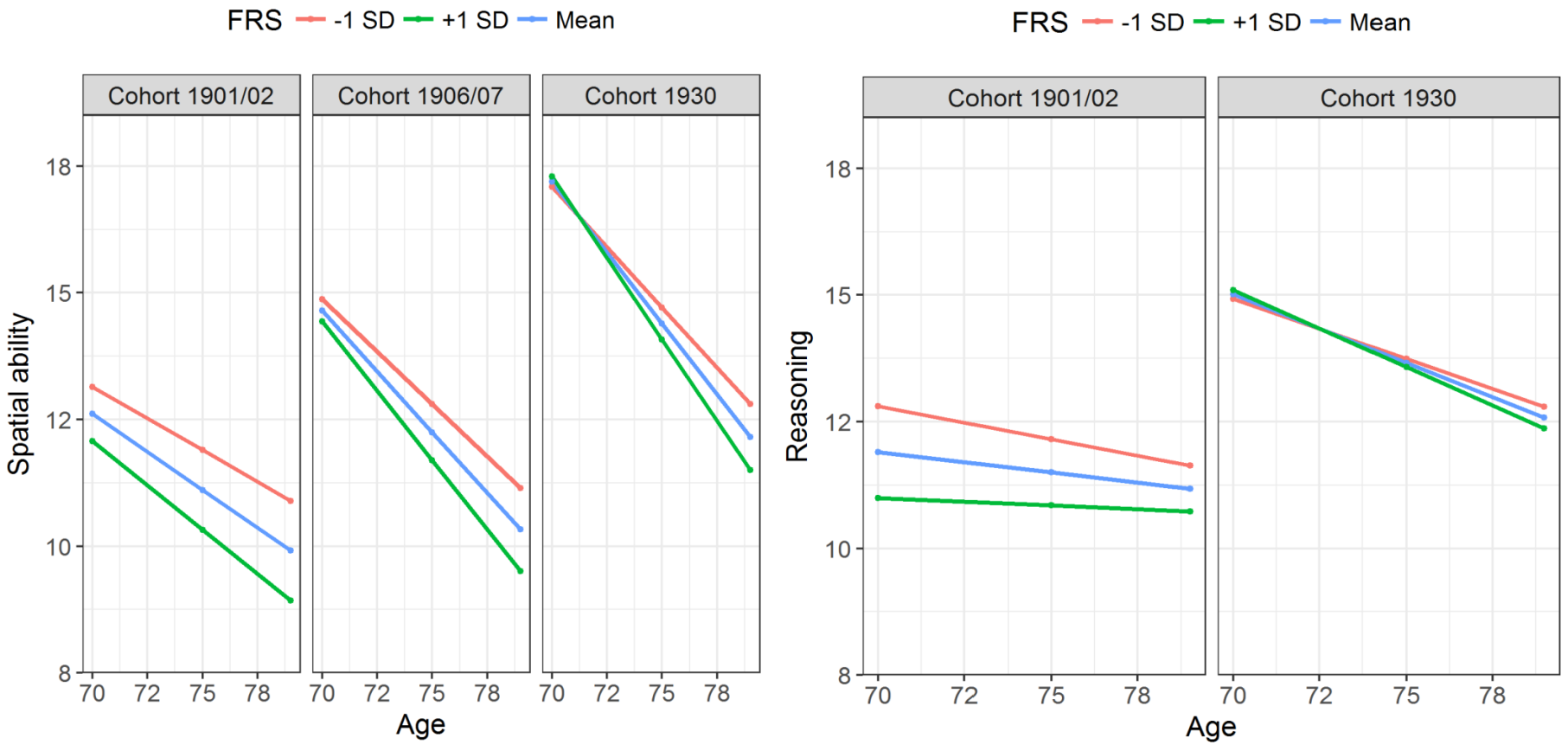
FRS
-1 SD
+1 SD
Mean
Cohort 1901/02
Cohort 1906/07
Cohort 1930
Spatial ability
Reasoning
Age
18
15
12
10
8
70
72
75
78

*Figure 2.*