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No impact of surgery on in cognitive function: a longitudinal study of middle-aged Danish twins

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Abbreviations

\textsuperscript{CI}: confidence interval
\textsuperscript{IQR}: interquartile range
\textsuperscript{MADT}: the Longitudinal Study of Middle-aged Danish Twins
\textsuperscript{NPR}: the Danish National Patient Register
\textsuperscript{OR}: odds ratio
\textsuperscript{POCD}: postoperative cognitive dysfunction
\textsuperscript{SD}: standard deviation
Abstract

Purpose
To examine the association between exposure to surgery and 10-year change in cognitive functioning.

Methods
Among 2,351 middle-aged twins, a 10-year change in composite cognitive scores derived from five cognitive tests was compared between 903 (38%) twins exposed to surgery classified as major, minor, knee and hip replacement, and other, and a reference group of 1,448 (62%) twins without surgery, using linear regression models adjusted for socioeconomic factors. Genetic and shared environmental confounding was addressed in intra-pair analyses of 48 monozygotic and 74 dizygotic same-sexed twin pairs.

Results
In individual-level analyses, twins with major surgery (mean difference, -0.37; 95% CI, -0.76 to 0.02) or knee and hip replacement surgery (mean difference, -0.54; 95% CI, -1.30 to 0.22) had a tendency of a negligibly higher rate of decline in cognitive score than the reference group.

In the intra-pair analyses, the surgery-exposed twin had a higher rate of cognitive decline than the co-twin in 55% (95% CI, 45% to 63%) of the pairs. The mean difference in cognitive decline within pairs was -0.21(95% CI, -0.81 to 0.39).

Conclusions
No significant associations were found between exposure to surgery and change in cognitive score either in individual-level or in intra-pair analyses.

Keywords: Surgery; postoperative period; cognition; aging
Introduction

Cognitive impairment is commonly detected after surgery and anaesthesia, and it occurs in adult surgical patients of all ages.\(^1\)\(^-\)\(^3\) In the literature this impairment is referred to as Postoperative Cognitive Dysfunction (POCD).

A growing body of research has aimed at quantifying the frequency and duration of POCD and also at identifying potential risk factors for this adverse condition. Early (7-day) POCD is observed in 7\(^\%\) to 50\(^\%\) of adult surgical patients, and the risk of POCD is found to be increasing with size of the surgical procedure\(^3\)\(^-\)\(^6\) and age.\(^2\)\(^-\)\(^7\) At three months after surgery, POCD is detectable in approximately 12\(^\%\) of elderly patients.\(^1\)\(^,\)\(^7\) The majority of studies on long-term POCD, i.e. POCD observed more than three months and up to several years after surgery, suggest that POCD is a temporary condition\(^6\)\(^,\)\(^8\)\(^-\)\(^12\), but follow-up is usually not complete. A recent study including 527 participants found that 182 patients exposed to various surgical procedures under general anaesthesia had more decline in several cognitive measures over a 5-year period compared to participants without surgery,\(^13\) raising concerns about the duration of POCD. To clarify whether there are long-term effects of surgery and anaesthesia on cognitive functioning there is a need for large longitudinal studies where also adequate methods are used to assess the potential impact of deaths and drop-outs.

Recently, we have shown that a history of major surgery was associated with a negligibly lower cognitive functioning in a large cross-sectional study of 8,503 middle-aged and elderly twins.\(^14\) Here we report on a subsample of 2,351 middle-aged twins cognitively tested twice at a 10-year interval, and the aim of this study was to examine whether exposure to surgery was associated with cognitive decline and to assess the potential impact of mortality and drop-out in the study period. The use of a twin design further enabled us to address potential confounding from genetic and shared environmental factors.
Methods

The existing data from two surveys used in this study were improved by the Danish Data Protection Agency [Datatilsynet], Copenhagen, Denmark; Journal number 2013-54-0299 and The Regional Committees on Health Research Ethics for Southern Denmark [De Videnskabsetiske Komitéer for Region Syddanmark]; Journal number S-VF-19980072.

This study was based on intake and follow-up data from the Longitudinal Study of Middle-Aged Danish Twins (MADT) with linkage to the Danish National Patient Register (NPR). In 1997, participants in the MADT were ascertained through the population-based Danish Twin Registry comprising twin pairs born from 1870 to 2004. The MADT represented a random sample of 120 intact twin pairs from each birth cohort from 1931 to 1952, in total 2,640 intact twin pairs. Of the 5,189 twins who were alive and residing in Denmark when the survey was conducted in 1998/99, 875 refused to participate, 10 were excluded due to neurosurgery and 5 had no cognitive measurement, reducing the sample size in 1998/99 to 4,299 (83%). Before the follow-up assessment beginning in 2008 and ending in 2011, 426 twins had died, reducing the sample size to 3,873. Of these, 1,475 refused to participate, 45 had no valid cognitive measurement and 2 were excluded due to neurosurgery in the follow-up period, reducing the sample size to 2,351 (61% of those alive) (Figure 1). The follow-up sample ranged in age from 56 to 80 years, with an average age of 66.7 years. Almost identical survey instruments were used in the MADT in both assessments including a questionnaire on socio-demographic factors, health and diseases, and lifestyle factors along with physical and cognitive tests.

Register Linkage

Since 1968, all Danish citizens have been assigned a unique civil registration number recorded in the civil registration system, and this number is the key to individual information in all official
registries covering the Danish population. Within Statistics Denmark, the civil registration number enables a linkage between all Danish registries, including the Danish NPR.

The Danish NPR comprises data on surgeries performed in Danish hospitals since 1977 along with data on diagnoses, and from 1995, data on outpatients and emergency patients were also included. Thus, the register has nationwide coverage, and it is considered to have high validity, especially with regard to surgical procedures.

Exposure assessment

Exposure status was determined by the linkage of survey data with surgery records in the NPR. The exposure time window was the period from 1998 where intake assessment took place and until follow-up assessment beginning 2008 and ending 2011. The exposure group comprised twins who had at least one surgical procedure between the two assessments and was further separated into four groups by type of surgical procedure according to the severity of the disease that led to surgery: (1) major surgeries, including cardiac, thoracic, laparotomy, central and peripheral vascular, and major fracture surgeries, (2) knee/hip replacement surgeries, (3) minor surgeries, and (4) other surgeries. Minor surgeries included outpatient procedures, surgeries followed by less than two days of hospitalisation, and, independently of the first two criteria, surgery codes representing eye, skin, endoscopic procedures along with biopsies and other small surgical procedures. The classification was performed by two experienced anaesthesiologists (T.G.H. and L.S.R.), who, independently of one another, went through the records of surgery codes in the study sample for the period from 1998 until 2011 (details can be found in the appendix). Twins who had more than one surgery were assigned to the groups using the following algorithm: (1) major surgery if any, (2) knee/hip replacement surgery if any, but no major surgery, and (3) other surgeries if any, but neither major nor knee/hip replacement surgery, and (4) minor surgery. The reference group in all analyses comprised twins without surgery in the period between the two assessments.
Outcome assessment

The outcome was a composite measure of cognitive functioning derived from a battery of five cognitive tests: a category fluency task, which involves the number of animals an individual can name in a 1-min interval, forward and backward digit span tests where individuals are read two times seven sequence of numbers with increasing list length and asked to repeat the same sequence back to the examiner in order (forward span) or in reverse order (backward span), immediate and delayed recall tests, which involves the number of words from the same 12-item list, immediately recalled and recalled after a 10-min delay. The composite cognitive score is a sum of z-scores of the five tests. The z-scores are based on means and SDs of all 45-49 year olds irrespective of the participants’ surgery exposure status. This measure of cognitive functioning has been shown to exhibit high validity and internal consistency reliability (0.75) and has been used in a series of previous studies.\textsuperscript{19, 20}

When the cognitive change was measured, individual-level change scores were formed by taking the difference between composite cognitive score at the first and the second assessment such that negative change scores indicated cognitive decline.

Covariates

Baseline age, sex, and vocational educational attainment were considered as potential confounding variables.\textsuperscript{1-3, 7} Educational level was self-reported and assessed using questions about highest grade of year of regular schooling and the highest degree earned. An ordinal measure was made by combining questions related to basic and vocational schooling. Age was included in the statistical models as a continuous variable and level of education as an ordinal variable with five coding categories, which ranged from ninth-grade education or less, coded as 2, to more than four years of academic education, coded as 6.
Intra-pair Analyses

To address genetic and shared environmental confounding, intra-pair analyses were performed in surgery-discordant twin pairs. Among the 2,351 twins in the study population we included 48 monozygotic and 74 same-sexed dizygotic pairs, of whom one twin had had a major surgery between the two cognitive measurements and the other no surgery, in order to obtain the biggest contrast in exposure.
Statistical Analyses

Baseline descriptive statistics were expressed as means/medians and SD/interquartile range (IQR) for continuous variables and as numbers and proportions for categorical variables.

The comparison of cognitive change scores between twins exposed for at least one surgery (major, minor surgery, knee/hip replacement surgery and other surgeries) and unexposed twins was performed using multivariate linear regression models adjusted for sex and age at intake in Model 1, and further adjustment for educational attainment in Model 2. In a third model we also adjusted for baseline cognitive score. Model assumptions were checked by residual plots and quantile-quantile plots of residuals.

In the intra-pair analyses the proportion of pairs in which the co-twin who had been exposed to anaesthesia and major surgery had also the higher cognitive decline was calculated including 95% CI using the binominal distribution. In addition, we assessed the numerical differences in cognitive decline within pairs using a Bland Altman plot and tested whether the mean difference in the 10-year cognitive change score within pairs was equal to zero using a one-sample t-test.

Attrition is inevitable in longitudinal studies and may pose a risk to both the internal and external validity. Selectivity of attrition in intake cognitive performance was examined with regression analyses to adjust for sex and age, as those factors may wholly or partially explain any observed inter-group difference. The risk of bias in the estimates of cognitive change due to attrition was addressed with logistic regression analyses to compare the odds of having had a surgery in one of the predefined exposure surgery groups in the follow-up period among non-participants and those deceased with the equivalent odds of having had a surgery among those who participated.
In all regression analyses the within-pair dependency of twin individuals was considered by estimating the standard errors using the cluster option of STATA (release 13; STATA Corp., USA).

Figure 1 Flow chart for the Study of the Middle-Aged Danish Twins
Results

A total of 2,351 Danish middle-aged twins with two valid cognitive measurements taken 10 years apart participated in the study. Their intake characteristics in the total sample and by surgery exposure group are given in Table 1 along with intake characteristics of those who dropped out before follow-up (n=1,475) and those who participated, but did not have a follow-up cognitive measure (n=45) or died before follow-up (n=426).

Table 1 Intake characteristics of the sample of the Study of Middle-Aged Danish Twins according to participation and non-participation in the follow-up assessment and death before follow-up, in totals and by surgery exposure group

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Totals</th>
<th>Surgical procedure groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Major surgery</td>
</tr>
<tr>
<td>n (%), Participants</td>
<td>2,351 (100)</td>
<td>194 (8)</td>
</tr>
<tr>
<td>Missing cog. score at follow-up</td>
<td>45 (100)</td>
<td>7 (16)</td>
</tr>
<tr>
<td>Non-participants</td>
<td>1,475 (100)</td>
<td>139 (9)</td>
</tr>
<tr>
<td>Deceased</td>
<td>426 (100)</td>
<td>59 (14)</td>
</tr>
<tr>
<td>Female, n (%), Participants</td>
<td>1,112 (47)</td>
<td>70 (36)</td>
</tr>
<tr>
<td>Missing cog. score at follow-up</td>
<td>18 (40)</td>
<td>3 (43)</td>
</tr>
<tr>
<td>Non-participants</td>
<td>793 (54)</td>
<td>61 (44)</td>
</tr>
<tr>
<td>Deceased</td>
<td>182 (43)</td>
<td>24 (41)</td>
</tr>
<tr>
<td>Age, year, median (IQR)</td>
<td>Participants</td>
<td>55.6 (10.2)</td>
</tr>
<tr>
<td></td>
<td>Missing cog. score at follow-up</td>
<td>60.1 (8.8)</td>
</tr>
<tr>
<td>Non-participants</td>
<td>57.5 (11.2)</td>
<td>60.7 (9.2)</td>
</tr>
<tr>
<td>Deceased</td>
<td>61.9 (9.9)</td>
<td>62.1 (10.6)</td>
</tr>
<tr>
<td>Cognitive score, Mean (SD)</td>
<td>Participants</td>
<td>-0.39 (3.30)</td>
</tr>
<tr>
<td></td>
<td>Missing cog. score at follow-up</td>
<td>-1.72 (3.24)</td>
</tr>
<tr>
<td>Non-participants</td>
<td>-1.69 (3.36)</td>
<td>-2.20 (3.34)</td>
</tr>
<tr>
<td>Deceased</td>
<td>-2.16 (3.64)</td>
<td>-1.73 (3.96)</td>
</tr>
</tbody>
</table>

In both sexes, all surgery groups and the reference group without surgery exhibited a statistically significant decline in cognitive scores over the approximately 10-year follow-up (Figure 2).
Figure 2 Change in composite cognitive score over the 10-year test-retest period according to exposure status (no surgery, minor, major and other surgery and knee and hip replacement surgery) and stratified on sex.

Compared with the reference group, no statistically significant differences were found in the 10-year cognitive change score in any of the surgery groups, when adjusted for sex and age (Model 1, Table 2). A tendency to a higher decline in composite cognitive score was found in twins with at least one major surgery (mean difference, -0.37, 95% CI, -0.76 to 0.02) and knee/hip replacement surgery (mean difference, -0.54, 95% CI, -1.30 to 0.23), corresponding to one tenth and one fifth of an SD, that is, negligible effect sizes. After further adjustment for educational attainment (Model 2) and baseline cognitive score (Model 3) similar results were found.
To further illustrate the effect size using the animal fluency test, the mean number of animals named in 1 min is 24.2 at intake meaning that a one tenth of an SD decline corresponds to naming 0.7 fewer animals at follow up, which represents a difference that must be considered clinically unimportant. When dichotomizing the cognitive change measure, using a cognitive decline over the 10-year period of two standard deviations as a threshold, the percentages with a decline larger than or equal to two SD were similar among operated and non-operated participants (results not shown). We further analysed the data according to those who had undergone surgery up to two years (n = 320), one year (n = 188), and three months (n = 59) preceding follow up assessment (results are shown in appendix II). Overall, the mean differences in cognitive decline in the surgery groups compared with those without surgery were rather similar across time strata, and the results indicated no interaction of time since surgery with the association between surgery and cognitive decline.

Table 2 Mean differences in 10-year change in composite cognitive score between middle-aged twins with major, minor, knee and hip replacement, or other surgeries and the reference group without surgery, (95 % CI)

<table>
<thead>
<tr>
<th>Surgical procedure groups</th>
<th>Differences in cognitive change scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Major†</td>
<td>194</td>
</tr>
<tr>
<td>Minor</td>
<td>515</td>
</tr>
<tr>
<td>Knee/hip replacement</td>
<td>51</td>
</tr>
<tr>
<td>Other</td>
<td>143</td>
</tr>
<tr>
<td>Without surgery</td>
<td>1,448 Reference</td>
</tr>
</tbody>
</table>

*Multiple linear regression analyses, adjusted for sex and age at intake (Model 1), sex, age at intake and educational attainment (Model 2), sex, age at intake, educational attainment and baseline composite cognitive score (Model 3).† Including cardiac, thoracic, laparotomy, central and peripheral vascular and fracture surgeries.

To further adjust for genetic and shared environmental confounding, we performed intra-pair analyses of surgery-discordant twin pairs. Overall, we found that the surgery-exposed twin had a higher decline in 67 out of 122 pairs corresponding to 55% (95% CI, 45 to 63%), suggesting that it was equally common for the surgery-exposed twin to have the higher and the lower cognitive decline (Figure 3 A). When the twin pairs were restricted according to magnitude of the intra-pair difference in cognitive decline to the top 75, 50 and 25 percentages, the results were similar. This was also the case when twins were stratified according to zygosity (data not shown). The mean
numerical intra-pair differences in cognitive change score were also assessed in 121 pairs using the Bland Altman Plot (Figure 3 B). The Bland Altman Plot revealed no specific patterns of the intra-pair differences and the mean difference in cognitive decline within pairs (the solid blue line) was -0.21 (95% CI, -0.81 to 0.39), i.e. the twins exposed to major surgery had a negligible higher 10-year cognitive decline compared to their unexposed co-twins.

Figure 3 (A) Proportion of twin pairs in which the twin exposed to major surgery during follow-up had a larger decline in the 10-year cognitive score compared to his/her unexposed co-twin for all 122 twin pairs and stratified according to the magnitude of intra-pair difference in cognitive change score. Above each line is the p-value from the binomial test, which tests whether the proportion of pairs in which the major surgery exposed twin had a higher decline than his/her unexposed co-twin equals to 0.5. (B) Bland Altman plot of the numerical differences in 10-year cognitive change score within twin pairs in which one twin was exposed to major surgery and the co-twin was unexposed. Each dot represents a twin pair; the mean cognitive change score of the two twins in a pair is on the x-axis and the difference in cognitive change score between the two twins in a pair is on the y-axis. The solid blue line represents the mean of all twin-pair differences in cognitive change score (mean -0.21).

With respect to selectivity in intake measures, minor differences were observed in the distribution of surgical exposure status, sex, median age and mean cognitive score at intake when non-participants and those deceased were compared to those who participated (Table 1). Non-participants and those deceased at follow-up had lower cognitive score at intake compared to those who participated also when adjusted for sex and age (Table 3).

Table 3 Mean differences in intake composite cognitive score between middle-aged twins not participating in the 10-year follow-up and twins deceased before follow-up and the reference group who participated in the 10-year follow-up, according to exposure status determined by follow-up date, (95 % CI)

<table>
<thead>
<tr>
<th>Differences in cognitive intake scores</th>
<th>Major surgery</th>
<th>Minor surgery</th>
<th>Knee/hip replacement</th>
<th>Other surgery</th>
<th>No surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
The odds of having had a major, minor, knee/hip replacement or other surgery, respectively, in the follow-up period among non-participants including those with a missing cognitive score and those who participated in the follow-up were similar (non-significantly odds ratios (ORs) between 1.11 and 0.96), when adjusted for age at intake, sex and baseline cognitive score, indicating no association between surgical exposure and non-participation at follow-up. However, the odds were higher for having had a major surgery (OR 1.50; 95% CI, 1.06 to 2.12) and lower for having had a knee/hip replacement surgery (OR 0.51; 95% CI, 0.22 to 1.19) for participants who died before follow-up than for those who participated in the follow-up assessment.

The 45 twins who had missing cognitive score at follow-up are included in the group of non-participants.
**Discussion**

In this study, no significant association was found between surgery, of whichever type, and a 10-year change in cognitive score.

Our results are in line with the findings in our recent cross-sectional study of 8,503 middle-aged and elderly twins with one cognitive assessment\(^1\), and so the present study adds to the evidence that surgical interventions in mid-life are not associated with accelerated subsequent long-term cognitive decline. Comparisons with other studies are to some extent hampered by differences in methodology including diversity of participants, types of surgeries, length of follow-up, methods of cognitive assessment, and outcome measures. Despite this diversity, our findings are in line with the majority of the studies assessing cognitive functioning more than six months postoperatively as summarised in systematic reviews and/or meta-analyses of cardiac\(^6-10\), non-cardiac\(^6, 10, 12\), and knee/hip replacement surgery\(^11\). Another study comparing the incidence of POCD at three months between different patient groups with coronary angiography under sedation (n=167), major non-cardiac surgery under general anaesthesia (n=157), and coronary artery bypass graft surgery under general anaesthesia (n=312) and a control group without surgery (n=32) found no difference in the incidence leading to the conclusion that POCD at three months was independent of type of surgery and anesthetic\(^22\).

The major strengths of our study are the use of a study sample from a population-based survey retrieved from the Danish Twin Registry\(^15\) and almost complete registrations in the Danish NPR\(^17, 18\), as this reduced the risk for selection bias. The use of a twin population should not be a concern with respect to generalisability of our results to a non-twin population as twins have the same general health and survival as singletons after the infancy period\(^23, 24\) and in recent cohorts also the same cognitive functioning\(^25\). However, as this study is performed in a relatively homogeneous Danish population with access to a National Health Care system with a minimum of
out-of-pocket expenses, caution is required in generalising our results to other settings, especially to countries with a health care system that is fundamentally different from the Danish health care system.

Even though we argue that the risk for selection bias is reduced, it is important to consider the sizeable attrition rate in this study. In total, 426 twins died before follow-up corresponding to 10% of those who participated in the intake assessment in 1998/1999 (n=4,299). The participation rate at follow-up given as the number of follow-up participants (n=2,351) divided by the number of surviving intake participants (n=3,873) was 61% (Figure 1) and thus somewhat lower than the participation rate at intake (83%). This difference in intake and follow-up participation rates can probably be explained by difference in location of the interviews as intake interview took place at the twins’ residence and the follow-up interview at a clinic, requiring the twins to travel. A comparison of participants, non-participants and those who were deceased by the time of follow-up on intake age and composite cognitive score showed the expected pattern, namely that those who were alive at follow-up were younger at intake and had a higher cognitive score than those who were deceased at follow-up, and those who participated in the follow-up were younger and had a higher cognitive score than non-participants (Table 1). The described pattern in cognitive score remained the same when adjusted for age and sex (Table 3). The magnitude of differences in intake measures between groups was rather small. In an association study, selection bias occurs if the exposure-outcome association differs between participants and non-participants. Although attrition in the current study is likely to underestimate the extent of cognitive decline over the 10-year period, the odds of having had any surgery, even a major surgery, in the follow-up period were similar among non-participants and participants, suggesting that the risk of bias due to attrition is minor. However, those deceased before follow-up had higher odds of having had a major surgery and lower odds of having had a knee/hip replacement surgery compared to those who
participated in the follow-up, indicating, as expected, that major surgery is associated with severe morbidity, and hence increased mortality and that knee/hip replacements are primarily given to individuals with a substantial remaining life expectancy. The odds of death being higher in those who underwent major surgery implicates that the effect on cognitive decline of major surgery may have been underestimated in this study.

To our knowledge, this is the largest study reporting on surgery and cognitive decline with up to 10 years following surgery in a population of middle-aged persons. The observed effect sizes, all below one sixth of an SD, were negligible and, even with a larger sample size that may have yielded statistically significant results in some of the surgery groups, the differences in cognitive change score were unlikely to be clinically relevant.

We used the co-twin design to adjust for childhood living conditions and genetic endowment, both known to be associated with cognitive decline later in life. Still, it may be that unmeasured comorbidity has confounded our finding of no association between surgery and cognitive decline as several diseases including cardiac diseases and cancer are important factors for both cognitive decline and undergoing surgery. If the operated participants have more diseases than the non-operated, which may be anticipated among the middle-aged and young elderly included in the study sample, the surgery-cognitive decline association will be overestimated. Contrarily, if the operated have less comorbidity the association will be underestimated, but we trust this scenario is more likely among very old persons because surgery is often not performed among those who are very frail. Furthermore, the lack of difference regardless of type of surgery exposure is supportive of our negative findings as there was no apparent dose-response effect of invasiveness of surgery.

In the interpretation of our results, alternative explanations related to the applied cognitive measure should also be considered. It may be that the measure has not been sufficiently
sensitive to detect differences in cognitive changes between groups over the test-retest-interval of 10 years. However, the composite cognitive score has been used in numerous studies for more than a decade and has proven sufficiently sensitive in a cross-sectional study to detect a normative age-related decline in cognition of 2.5 SD from age 45 to 90 years\textsuperscript{20}, and correlated with both physical functioning\textsuperscript{30} and survival\textsuperscript{31}. Although the cognitive composite measure primarily includes memory components implying that other specific cognitive domains may have been overlooked, it is important to emphasize that the measure is age sensitive and encompasses components that are crucial for daily living.

To conclude, in this sample of middle-aged twins no significant association was found between surgery, of whichever type, and change in cognitive score over the 10-year retest period in neither the individual level analyses nor in the intra-pair analyses. Our results suggest that surgery and anaesthesia in middle-aged patients do not accelerate long-term age-related cognitive decline.
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Authors’ contributions

U.D.: study design and planning, analysis and interpretation of data, drafting of manuscript, critical revision of manuscript; M.W.: statistical analysis, analysis and interpretation of data, critical revision of manuscript; M.T.: statistical analysis, analysis and interpretation of data, critical revision of manuscript; T.G.H.: study design and planning, analysis and interpretation of data, critical revision of manuscript; L.S.R.: study design and planning, analysis and interpretation of data, critical revision of manuscript; J. M-F.: study design and planning, analysis and interpretation of data, critical revision of manuscript; K.C.: study design and planning, analysis and interpretation of data, critical revision of manuscript.

Declaration of interest

None declared.

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References


10. Avidan MS, Evers AS. Review of clinical evidence for persistent cognitive decline or incident dementia attributable to surgery or general anesthesia. *Journal of Alzheimer’s disease : JAD* 2011; 24: 201-16


19. McGue M, Christensen K. The heritability of level and rate-of-change in cognitive functioning in Danish twins aged 70 years and older. *Experimental aging research* 2002; 28: 435-51


21. Van Breukelen GJ. ANCOVA versus change from baseline: more power in randomized studies, more bias in nonrandomized studies [corrected]. *Journal of clinical epidemiology* 2006; 59: 920-5
22 Evered L, Scott DA, Silbert B, Maruff P. Postoperative cognitive dysfunction is independent of type of surgery and anesthetic. *Anesthesia and analgesia* 2011; **112**: 1179-85


28 Eggermont LH, de Boer K, Muller M, Jaschke AC, Kamp O, Scherder EJ. Cardiac disease and cognitive impairment: a systematic review. *Heart* 2012; **98**: 1334-40


31 Arden R, Luciano M, Deary IJ, et al. The association between intelligence and lifespan is mostly genetic. *Int J Epidemiol* 2016; **45**: 178-85
## Appendix I: Surgery Codes according to the Nordic Classification of Surgical Procedures that Are Included in the Specified Surgery Groups: Major surgery, Minor surgery, Knee and Hip Replacement Surgery, and Other Surgeries

### Major surgeries

<table>
<thead>
<tr>
<th>Surgery Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac surgeries included codes</td>
</tr>
<tr>
<td>KFKD00, KFMD00, KFMD10, KFN000, KFCN10, KFCN20, KFCN30, KFCN40, KFN000, KFN096, KFNG00, KFNG02, KFNG02A, KFNG05, KFNG05A, KFNG30, KFNA00, KFNA96, KFXA00, KFXA96, KFXB00, KFXB96</td>
</tr>
<tr>
<td>Thoracic surgeries included codes</td>
</tr>
<tr>
<td>KGAB10, KGAC00, KGAC01, KGDA20, KGDA21, KGDB11, KGDB96, KGDC00, KGDC01, KJCC10, KJCC11</td>
</tr>
<tr>
<td>Central and peripheral vascular surgeries included codes</td>
</tr>
<tr>
<td>KPDC30, KPDG21, KPDH24, KPEF10, KPEH20, KPFH28, KPGH40</td>
</tr>
<tr>
<td>Laparotomies included codes</td>
</tr>
<tr>
<td>KJAH00, KJAL30, KJBC01, KJDA42, KJDA60, KJDD00, KJFB00, KJFB30, KJFB31, KJFB33, KJFB43, KJFB46, KJFG00, KJFG20, KJFG33, KJFG70, KJFH10, KJFK10, KJGB00, KJGB01, KJGB10, KJGB30, KJKA16, KJKA20, KJKA21, KJKB30, KJKD20, KJWD00, KKAB01, KKAC00, KKAC21, KKAS20, KKBJ80, KKCD10, KKCH01, KKCH42, KKCV22, KKB01, KLB00, KLA00, KLA01, KLC00, KLC10, KLC00, KLC04, KYKA01</td>
</tr>
<tr>
<td>Major fracture surgeries included codes</td>
</tr>
<tr>
<td>KNAG14, KNAG30, KNAG46, KNAG94, KNBJ11, KNBJ41, KNBJ51, KNBJ62, KNBJ71, KNBJ81, KNFJ24, KNFJ44, KNFJ51, KNFJ64, KNFJ70, KNFJ80, KNFJ81, KNGJ22, KNGJ40, KNGJ52, KNGJ59, KNGJ71, KNHJ42, KNHJ60, KNHJ62, KNHJ70, KNHJ74</td>
</tr>
</tbody>
</table>

### Minor surgeries

<table>
<thead>
<tr>
<th>Surgery Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Included all day-only procedures, surgeries followed by less than 2 days hospitalisation and irrespective of the first to criteria surgery codes that are compatible with, eye surgery, endoscopic and biopsy procedures, skin surgery and other small surgeries.</td>
</tr>
<tr>
<td>Eye surgeries included codes KCA, KCB, KCD, KCE, KCF, KCG, KCH, KCJ, KCK, KCW</td>
</tr>
<tr>
<td>Endoscopic and biopsy procedures included codes KUD, KUE, KUG, KUJ, KUK, KUL</td>
</tr>
<tr>
<td>Skin surgeries included codes KQA, KQB, KQC, KQD, KQW, KQX</td>
</tr>
<tr>
<td>Other small surgery procedures included codes KTA, KTB, KTC, KTD, KTE, KTF, KTA, KTH, KTA, KTK, KTL, KTM, KTN, KTP, KTQ</td>
</tr>
</tbody>
</table>

### Knee and hip replacement surgeries

<table>
<thead>
<tr>
<th>Surgery Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>KNFB12, KNFB20, KNFB30, KFNB40, KFNC20, KNFC21, KNGB14, KNGB20, KNGB30, KNGB40, KNGC30, KNGC40, KNGC99</td>
</tr>
</tbody>
</table>

### Other surgeries

<table>
<thead>
<tr>
<th>Surgery Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery codes that are not included in major, minor or knee/hip replacement surgeries</td>
</tr>
</tbody>
</table>
Appendix II  Mean differences in 10-year change in composite cognitive score between middle-aged twins with major, minor, knee and hip replacement, or other surgeries and the reference group without surgery with increasing restriction of our sample: participants who had undergone surgery up to 2 years, 1 year and 3 months preceding follow up examination, (95 % CI)

<table>
<thead>
<tr>
<th>Surgical procedure groups</th>
<th>Differences in cognitive change scores*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>2 years</td>
</tr>
<tr>
<td>Major†</td>
<td>44</td>
<td>-0.14 (-0.79 to 0.51)</td>
</tr>
<tr>
<td>Minor</td>
<td>230</td>
<td>-0.06 (-0.40 to 0.27)</td>
</tr>
<tr>
<td>Knee/hip replacement</td>
<td>15</td>
<td>-0.41 (-1.39 to 0.57)</td>
</tr>
<tr>
<td>Other</td>
<td>31</td>
<td>-0.65 (-1.36 to 0.06)</td>
</tr>
<tr>
<td>Without surgery</td>
<td>1,417</td>
<td>Reference</td>
</tr>
</tbody>
</table>

* Multiple linear regression analyses, adjusted for sex, age at intake, educational attainment and baseline composite cognitive score (Model 3 in the manuscript).† Including cardiac, thoracic, laparotomy, central and peripheral vascular and fracture surgeries.