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Cognitive functioning after surgery in middle-aged and elderly Danish twins

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Abstract

Background—Postoperative cognitive dysfunction is common, but it remains unclear whether there are long-term adverse cognitive effects of surgery combined with anesthesia. We examined

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the association between exposure to surgery and level of cognitive functioning in a sample of 8,503 middle-aged and elderly twins.

Methods—Results from five cognitive tests were compared in twins exposed to surgery, classified as either major, minor, hip and knee replacement, or other, with those of a reference group without surgery using linear regression adjusted for sex and age. Genetic and shared environmental confounding was addressed in intra-pair analyses of 87 monozygotic and 124 dizygotic same-sexed twin pairs in whom one had a history of major surgery and the other did not.

Results—Statistically significantly lower composite cognitive score was found in twins with at least one major surgery compared with the reference group (mean difference -0.27 [95% CI: -0.48 ; -0.06]), corresponding to one tenth of a standard deviation, i.e., a negligible effect size. In the intra-pair analysis the surgery-exposed co-twin had the lower cognitive score in 49% [95% CI: 42%; 56%] of the pairs. None of the other groups differed from the reference group except the knee and hip replacement group that tended to have higher cognitive scores (mean difference 0.35 [95% CI: -0.18 ; 0.87]).

Conclusions—A history of major surgery was associated with a negligibly lower level of cognitive functioning. The supplementary analyses suggest that preoperative cognitive functioning and underlying diseases were more important for cognitive functioning in mid and late life than surgery and anesthesia.

Introduction

Cognitive impairment is a well-known complication after surgery with delirium and postoperative cognitive dysfunction (POCD) as the most common disorders.¹ Early (7-day) POCD occurs in adult surgical patients of all ages, but elderly patients are at higher risk, and at three months after surgery, cognitive impairment is still detectable in patients above 60 years.^{2–5} POCD may be present for longer than six months in some patients⁶ with potential long-term implications for the patient including impaired quality of life,^{7,8} increased mortality risk,^{3,9} higher prevalence of time receiving welfare benefits, and increased risk of leaving the labor market prematurely.⁹

In recent years, POCD has received increasing attention in the literature, and several pathophysiological factors and pathways have been suggested, including anesthetics and inflammatory response to the surgical trauma.¹⁰ Animal studies suggest that general anesthetics are a possible pathogenic factor of POCD as brain cell damages, apoptosis and decrease in cognitive skills are seen in animals after prolonged exposure.^{11–15} Based on evidence from human studies, type of surgery is suggested as a risk factor of POCD as the incidence of early POCD after minor surgery was significantly lower than after major surgery.¹⁶ Several explanations for this finding have been proposed including non-resolution of the inflammatory response following surgery.^{10,17} Moreover, the disease prompting the surgery may be responsible for the cognitive impairment as two very common diseases among the elderly, namely cardiac disease and cancer, are found to be associated with cognitive impairment.^{18–20} A longitudinal study has shown that patients with coronary artery disease showed significant declines in different cognitive domains after six years of follow-up, regardless of whether they had on-pump coronary artery bypass graft (CABG)

surgery, off-pump CABG surgery or no surgery.¹⁹ Furthermore, the incidence of cognitive impairment in colorectal cancer patients prior to chemotherapy is more than three times that of aged-matched healthy controls.²⁰ No differences were found by disease stage or between patients pre- and postoperatively, indicating that factors other than surgery and anesthesia were responsible for the higher proportion of cognitive impairment in these patients at baseline. Mild cognitive impairment with memory deficits has been shown to associate with subsequent dementia, particularly Alzheimer's disease (AD)²¹, and it has further been suggested that POCD and dementia share some of the perioperative risk factors, including anesthetics.²² However, a meta-analysis²³ including 15 case control studies found that a history of exposure to general anesthesia was not associated with an increased risk of AD, and also in a recent cohort study it was not possible to ascertain an association between POCD and dementia.²⁴

Our aim was to examine the association between exposure to surgery and subsequent level of cognitive functioning in a very large population of middle-aged and elderly twins with almost complete records of surgeries since 1977, hereby enabling us to test for more subtle differences in cognitive functioning. The use of a twin design further enabled us to address potential confounding from shared environmental and genetic factors as an approach to adjust for preoperative cognitive functioning.

Materials and Methods

The present study was based on the linkage of the intake examination data of the Longitudinal Study of Middle-Aged Danish Twins (MADT) and the Longitudinal Study of Aging Danish Twins (LSADT) with the Danish National Patient Register (NPR) in Copenhagen. Both studies included an assessment of cognitive functioning and have previously been described in detail elsewhere.^{25–27} In brief, participants in the MADT and the LSADT were ascertained through the Danish Twin Registry (DTR) comprising twin pairs born in 1870–2004 and considered representative of the general population in Denmark.^{28,29} The MADT represented a random sample of 120 intact twin pairs from each birth cohort from 1931 to 1952. The LSADT was initiated in 1995 and included Danish twins aged 75 years or older and residing in Denmark by January 1995. Further cohorts aged at least 70 years were added in 1997, 1999 and 2001. The MADT and the LSADT included a questionnaire on socio-demographic factors, health and diseases, life style factors along with physical and cognitive tests. We excluded patients who had undergone neurosurgery.

Register linkage

Since 1968, all Danish citizens have been assigned a unique 10-digit identifier, the civil registration number (the CPR number), which is the key to individual information in all official registries covering the Danish population.³⁰ Within Statistics Denmark, the CPR number enables the linkage between Danish registries, including the Danish National Patient Register. The Danish National Patient Register comprises data on surgeries performed in Danish hospitals since 1977 along with data on diagnoses. Until 1996, the Danish National Board of Health's Classification of Surgeries was used to classify surgeries, and from 1996, the Nordic Classification of Surgical Procedures (NCSP) was used. Data on outpatients and

emergency patients was added in 1995.³¹ Thus, the register has nation-wide coverage and is considered to have high validity, especially with regard to surgical procedures.³²

Exposure assessment

The exposure group encompassed twins who had at least one surgical procedure within 18 to 24 years before intake cognitive examination. The exposure group was separated into four groups by type of surgical procedure taking into account the severity of the underlying disease: 1) major surgeries, including cardiac, thoracic, laparotomy, central and peripheral vascular and major fracture surgeries, 2) knee and hip replacement surgeries, 3) minor surgeries, and 4) other surgeries. Minor surgeries included all-day only procedures, surgeries followed by less than two days of hospitalization 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 anesthesiologists (TGH and LR), who, independently of one another, went through the records of surgery codes in the study sample for the period from 1977 and until intake examination (details can be found in Appendix 1). Twins who had more than one surgical procedure were assigned to the groups using the following algorithm: 1) major surgery if any, 2) knee and hip replacement surgery if any, but no major surgery and 3) other surgeries if any, but neither major nor knee and hip replacement surgery. The reference group in all analyses comprised twins with no surgical procedures from 1977 and until intake examination. The exposure was reassessed employing three more narrow time frames to assess whether time since surgery modified the association between exposure to surgery and cognitive performance: 1) two years 2) one year and 3) three months preceding intake examination.

Also the effect of cumulative exposures was investigated based on type of surgical procedures carried out from 1977 and until cognitive examination. Five exposure groups were defined according to both type and number of surgeries performed: 1) minor surgeries, 2) one major/other surgery, 3) two major/other surgeries, 4) three major/other surgeries and 5) more than three major/other surgeries.

Outcome measurement

The outcome was cognitive functioning assessed by a five-component test battery. The specific tasks included in the test battery were 1) a category fluency task, in which individuals were asked to name as many animals as they could during a one-minute interval, 2) forward and 3) backward digit span and 4) immediate and 5) delayed recall of a twelve-item list. An overall composite measure of cognitive functioning was computed by adding the five standardized scores (using mean and standard deviation from participants aged 45–49 years) of each of the five component tasks.³³ The composite cognitive score has been used in a series of previous studies. It has been shown to be a valid, reliable and very age-sensitive measure of cognitive functioning, though moderately stable over a two-year interval (.60), and it has a high internal consistency reliability (.75).^{33–36}

Covariates

Potential confounders were identified in other similar studies,^{5,37} including sex, age and educational attainment. However, as the effect sizes were similar regardless of whether educational attainment was included in the statistical model, this covariate was omitted in the analyses.

Intra-pair analyses

To address genetic and shared environmental confounding and to take preoperative cognition into account, intra-pair analyses were performed. The 8,503 twins in the study population consisted of 1,065 monozygotic pairs and 1,179 dizygotic, same-sexed twin pairs, as well as 4,015 twin individuals from opposite-sexed pairs and “single twins”, i.e. twins who had a co-twin who was either deceased or a non-participant. To avoid confounding by sex, the intra-pair analyses only included same-sexed pairs. To obtain the biggest contrast in exposure, the intra-pair analyses only included pairs in whom one had a history of major surgery and the other no surgery. Among the 1,065 monozygotic pairs, a total of 87 such pairs were identified, whereas the corresponding number for dizygotic twins was 124 among 1,179 pairs. Consequently, 211 exposure-discordant pairs were included in the intra-pair analyses.

Statistical analyses

Descriptive statistics were expressed as means and standard deviations for continuous variables and as numbers and proportions for categories. The comparisons of composite cognitive scores between twins exposed for at least one surgery (major, minor surgery, knee and hip replacement surgery, other surgeries) before examination of cognitive functioning and twins not exposed were performed using multivariate linear regression models adjusting for sex and age at examination. The within-pair dependency of twin individuals was considered by estimating the standard errors using the cluster option of STATA (release 13). 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 anesthesia and major surgery also had the lower composite cognitive score was calculated including the 95% confidence interval using the binomial distribution.

Results

A total of 8,527 Danish twins with a valid cognitive score were included: 4,309 of 4,314 from the MADT (< 70 years) and 4,218 of 4,731 from the LSADT (≥ 70 years).

Of these participants, 65% had at least one surgery preceding intake examination. We excluded 24 twins with neurosurgery from the study: 10 from the MADT and 14 from the LSADT, reducing the sample sizes to 4,299 and 4,204, respectively (Table 1).

Major surgery was slightly more common in twins aged 70 years and above compared with twins younger than 70 years (20% vs. 17%). The unadjusted mean cognitive scores varied slightly between exposure groups, whereas the cognitive scores were substantially lower for older compared to younger participants, as expected. However, twins aged 70 years and

above with knee and hip replacement surgery had the highest cognitive score (1.68) of surgery groups (ranging from 0.88 to 1.68) and even higher than the reference group (1.24).

Compared with the reference group, twins with major surgery preceding intake examination had slightly lower cognitive scores when adjusted for sex and age (mean difference: -0.27, CI: -0.48; -0.06) (Table 2), which is equivalent to about one tenth of a standard deviation (Table 1), i.e., negligible effect size³⁸. In contrast, we found that those with knee and hip replacement surgery had higher cognitive score at intake (mean difference: 0.35, CI: -0.18; 0.87), although the difference did not reach significance. For twins with minor or other surgical procedures, no differences were found in cognitive score in comparison with the reference group. Analyses stratified on overall age (< 70 years and ≥ 70 years) yielded similar estimates.

To further illustrate the effect size associated with major surgery (0.1 SD), we analyzed separately one of the cognitive tests included in the cognitive composite score, namely the animal fluency test (i.e. mention as many animals as possible in one minute). Here, one tenth of a standard deviation corresponds to 0.7 named animal. In MADT, the mean number of animals named in one minute is 24.2, and this means that a tenth of a standard deviation lower score corresponds to 23.5, which represents a difference that must be considered clinically unimportant. In comparison, the difference in cognitive score between the group below 70 years and that above 70 years is about a 0.9 standard deviation (Table 1), which in the animal fluency test would correspond to a six-word difference.

We also analyzed data according to those who had undergone surgery up to two years (n=1,738), one year (n=1,109) or three months (n=391), respectively, preceding intake examination (Figure 1). Overall, the mean differences in cognitive scores in the surgery groups compared with those without surgery in the same periods were similar across strata. Although the majority of estimates did not reveal statistical significance, the results indicated no interaction of time since surgery with the association between surgery and cognitive score at intake examination. When we stratified on overall age (< 70 years and ≥ 70 years), the analyses yielded similar estimates in each of the age groups.

In addition, analyses were stratified on type and number of surgical procedures to investigate the dose-response pattern of cumulative exposure to surgery and anesthesia on cognitive impairment (Table 3). We found that exposure to three or more surgeries was associated with significantly lower score, about one fifth of a standard deviation.

The intra-pair analysis of twin pairs in whom one had a history of major surgery and the other had no surgery was included to further adjust for genetic and shared environmental factors. In the analysis of all 211 discordant pairs, we found that the surgery-exposed twin had a lower cognitive score than the co-twin in 49% [95% CI: 42%; 56%] of the pairs (Figure 2), suggesting that it was as common to have the higher cognitive score when exposed to surgery as it was to have the lower cognitive score. When twin pairs were restricted according to the magnitude of the intra-pair differences in cognitive score to the top 75%, 50% and 25%, respectively, the analyses yielded similar results. This was also the case when the twins were stratified by zygosity (not shown).

Discussion

In this study comprising 8,503 twins, major surgery was associated with a negligibly lower level of cognitive functioning. Thus, the study provides evidence against a clinically relevant association between exposure to surgical procedures and anesthesia and subsequent cognition in mid and late life.

Twins who had undergone major surgery had slightly lower cognitive scores, corresponding to one tenth of a standard deviation, compared with the reference group, but in the intra-pair analysis where genetic and shared environmental factors were adjusted for by design, no association was observed. Twins who had undergone hip or knee replacement had slightly higher cognitive scores, although not significantly so, whereas no differences were found in the minor or other surgery group when compared with the reference group.

The time interval between surgery and cognitive examination had no impact on effect sizes and no dose-response pattern for number of surgeries was found, albeit having had three or more major/other surgeries was significantly associated with a lower cognitive score corresponding to one fifth of a standard deviation.

Our results are reassuring in relation to long-term adverse cognitive effects of exposure to major surgery and anesthesia in adulthood for two reasons: First, effect sizes of one tenth to one fifth of a standard deviation are very subtle and may be clinically irrelevant; secondly, our large sample size ensures estimates with high confidence. Cognitive impairment is a feared aspect of aging,³⁹ and thus our finding of a subtle yet persistent cognitive impairment following surgery and anesthesia may be a concern. However, the results from the intra-pair analysis and across surgical procedures suggest that factors other than surgery and anesthesia are important. In the intra-pair analysis, the association between major surgery/anesthesia and cognitive score disappeared and along with evidence of high correlation in cognitive scores among twins,⁴⁰ this suggest that long-term postoperative cognitive functioning is primarily determined by the preoperative cognitive functioning. The severity of the underlying diseases across surgery groups are diverse with the more severe diseases in twins belonging to the major surgery group (e.g. cardiac and vascular surgeries and laparotomies) than to the minor (e.g. eye and laparoscopic surgeries) and knee and hip replacement surgery groups. Thus, the observations of a lower cognitive score in the major, no difference in the minor and other surgery groups and even a higher score in the hip and knee replacement group in comparison with the reference group indicate that the underlying disease is a major determining factor.

There was a tendency to better cognitive scores in the hip and knee replacement group compared with all other groups including the reference group. This is most likely due to the fact that the best functioning individuals are offered hip and knee replacements. Furthermore, it could also be explained by reduction in pain and increased mobility after successful joint replacements and subsequent improvement in level of functioning.

Comparisons with other studies are hampered by differences in methodology, including differences in design, endpoints and of length of follow-up. The present study reports mean differences in composite cognitive score whereas most other studies report dichotomous

outcomes, primarily incidence of POCD. Moreover, the present study has longer follow-up (up to 24 years) than other studies.⁴¹

Despite the methodological differences our findings across surgical procedures and in the intra-pair analyses are to a large extent in line with other studies that assessed cognition more than six months postoperatively.^{16,37,42} Still, a recent cohort study⁴³ (n=192) found an increased incidence of POCD in surgical patients above 60 years compared with age-gender matched controls at one year postoperatively, and a meta-analysis of 17 studies⁴⁴ concluded that no impairment in cognitive performance could be documented at three to six months after hip and knee replacement. However, only two small studies that included control groups assessed cognitive functioning at three months of follow-up in this meta-analysis, and that conclusion may therefore not be justified. Another study of 270 elderly patients undergoing elective orthopedic surgery found improvements in some verbal cognitive tasks including immediate and delayed verbal recall and either deterioration or no differences in other tasks at follow-up at approximately one year.⁴⁵ Hence, our findings of a tendency to a slightly higher composite cognitive score in the hip or knee replacement group could be considered to be in agreement with these findings. However, caution in this interpretation is warranted as the effect size in our study is small and non-significant. In addition, even if surgery successfully treats chronic pain and restores both physical and cognitive functioning in this patient group,^{46,47} the recovery may take time and is only registered by longer follow-up.

Our finding of no effect of time interval between surgery and cognitive examination on effect sizes does not support the current evidence of a gradual resolution of POCD between three months and one to two years,^{6,37} but the confidence intervals are quite wide.

Exposure to three or more surgeries seemed to be a risk factor but may be explained by underlying disease(s) or complications after surgery. Interestingly, a cross-sectional study⁴⁸ found no association between number of general anesthetic exposures and cognitive deficits in 606 participants aged 75 years or more. Likewise, a case-control study of 1,010 participants found no association between cumulative number of exposures of general anesthesia and AD.⁴⁹

Major strengths of the present study are the use of study samples from population-based surveys retrieved from the Danish Twin Registry²⁸ and the completeness of the Danish National Patient Register,^{31,32} which minimized the risk for selection bias. The Danish national health care system with no out-of-pocket expenses further minimizes bias from different access to health care depending on educational and socioeconomic factors that are known to be strongly associated with cognitive performance. On the other hand, the study is performed in a relatively homogeneous Northern European population, and thus the results should be replicated in other settings.

The large sample size of more than 8,500 twins is another strength as this enabled us to detect even very subtle cognitive score differences with high accuracy. In the literature there is a compelling body of evidence that twins are similar to the general population with regard to health and survival^{50–54} and in recent cohorts also with regard to cognitive functioning.⁵⁵

An observed, slightly lower cognitive functioning in older cohorts⁵⁶ should not affect the associations in this study as the comparisons are conducted within a twin population. In addition, we have no reason to believe that the effect of surgery and anesthesia differs between twins and singletons and so, our findings are likely generalizable to the non-twin population.

The use of the co-twin design has a number of strengths. Firstly, it is statistically powerful, reflected in the narrow confidence interval on the effect measure (proportion of pairs in which the major surgery-exposed twin had the lowest score: 49%; 95% CI 42–56%) despite that only 211 pairs were included. Furthermore, the design controls for childhood socioeconomic status and genetic endowment, both known to be strongly associated with cognitive functioning in mid- and late life.^{57,34} Finally, due to the high correlation in cognitive performance within twin pairs, especially within monozygotic twin pairs, the co-twin is the best matched control.

Even though we argued that the risk of selection bias is small in this study, selection bias due to mortality and non-attendance should be considered when interpreting the results. The non-attendance of 518 twins (6%) in the cognitive examination may be explained by severe cognitive or physical impairments.³⁶ An explorative data analysis (not shown) revealed that non-attendees had 1.3 times higher odds of having had any surgery than attendees. Hence, it cannot be ruled out that a small fraction of surgery-exposed twins may be particularly susceptible to surgery and anesthesia or disadvantaged in other ways.

The cross-sectional design of this study did not allow us to consider selective mortality, i.e., those with cognitive decline may have less chance of surviving to the study intake. Results were similar when restricting the analyses to surgeries performed less than three months before intake and hence minimizing the risk of survival bias. We did not assess cognition preceding surgery/anesthesia. However, in the intra-pair analysis, preoperative cognition was taken into account to some degree as the intra-pair similarity of intelligence is high.⁴⁰

Unmeasured co-morbidity is likely to represent an important factor for cognitive performance. If the operated participants have less co-morbidity than the non-operated (which may be anticipated among the oldest in the cohort since surgery is often not performed among those who are very frail) the surgery-cognition association will be underestimated. However, if the operated participants have more co-morbidity (which may be anticipated among middle-aged and younger elderly), the association will be overestimated. We see no such age-dependence in our study (Table 2). A limitation of the exposure measure is that information about outpatient procedures performed prior to 1995 is not available. This could mean inclusion of exposed cohort members in the unexposed group and tend to bias the results towards null. However, major surgery very rarely took place in an outpatient setting before 1995.

Finally, alternative explanations related to the cognitive measure used in this study should be considered in the interpretation of our findings. Low sensitivity may be associated with an inability to detect cognitive deficits that may have been picked up by other cognitive test batteries. It is noteworthy that the composite cognitive score used is shown to be very age-

sensitive with a difference of 2.5 standard deviation from age 45 to age 90.³³ Although the composite cognitive score does not capture exactly the same cognitive domains as the psychometric test batteries used to detect POCD, it reflects elements that are pivotal for daily living, including working memory.

In conclusion, exposure to major surgery and anesthesia was associated with a negligible reduction in cognitive functioning among middle-aged and elderly twins. This finding substantiates the current evidence of no long-term major adverse cognitive effect of surgery and anesthesia as the very large sample size along with the sensitive cognitive measure allow us to detect very subtle effect sizes.

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Twins exposed to surgery:

- Major
- ◆ Minor
- Hip and knee replacement
- ▲ Other

vs non-exposed twins

Figure 1.

Mean differences in composite cognitive scores between twins who had undergone major, minor, knee and hip replacement or other surgical procedures up to 24 years (n=5,538), two years (n=1,738), one year (n=1,109) or three months (n=391) preceding intake examination, and the non-exposed group. Panel A: Participants age <70 years, Panel B: Participants ≥ 70 years, Panel C: All participants.

Figure 2.

Proportion of twin pairs in which the twin exposed to major surgery had a lower composite cognitive score for all twin pairs and stratified according to magnitude of intra-pair difference in cognitive score. Above each line is the *P*-value from the binomial test, which tests whether the proportion equals to 0.5.

Table 1

Characteristics and summary statistics for composite cognitive scores among participants from the Study of Middle-Aged Danish Twins (< 70 years) and the Longitudinal Study of Aging Danish Twins (> 70 years), in totals and by type of surgical procedure

Characteristics	Totals	Surgical procedure groups			
		Major surgery*	Minor surgery	Knee and hip replacement	Other surgery
n (%)					Without surgery
All	8,503 (100)	1,546 (18)	1,729 (20)	171 (2)	2,092 (25)
< 70 years	4,299 (100)	732 (17)	1,004 (23)	38 (1)	1,043 (24)
70 years	4,204 (100)	814 (20)	725 (17)	133 (3)	1,049 (25)
Female sex					
n (%)					
All	4,560 (54)	1,011 (65)	837 (48)	112 (66)	1,144 (55)
< 70 years	2,106 (49)	561 (77)	430 (43)	13 (34)	567 (54)
70 years	2,454 (58)	450 (55)	407 (56)	99 (74)	577 (55)
Age, yr.					
Mean (SD)					
All	67 (12)	68 (12)	65 (12)	74 (8)	67 (12)
< 70 years	57 (6)	57 (6)	57 (6)	61 (5)	56 (6)
70 years	77 (5)	77 (5)	77 (5)	77 (5)	77 (5)
Cognitive score					
Mean (SD)					
All	2.89 (3.95)	2.58 (4.02)	3.17 (4.05)	2.26 (3.78)	2.94 (4.01)
< 70 years	4.59 (3.50)	4.47 (3.63)	4.62 (3.70)	4.26 (3.61)	4.73 (3.45)
70 years	1.15 (3.60)	0.88 (3.58)	1.17 (3.63)	1.68 (3.65)	1.17 (3.74)

* Including cardiac, thoracic, laparotomy, central and peripheral vascular and fracture surgeries

Table 2

Mean differences in composite cognitive scores between twins with major, minor, knee and hip replacement or other surgical procedures and the reference group

Surgical procedure groups	n	Total Differences in cognitive scores* (95 % CI)	n	< 70 years Differences in cognitive scores* (95 % CI)	n	70 years Differences in cognitive scores* (95 % CI)
Major [†]	1,546	-0.27 (-0.48;-0.06)	732	-0.27 (-0.59;0.04)	814	-0.30 (-0.59;-0.01)
Minor	1,729	-0.06 (-0.27;0.14)	1,004	-0.03 (-0.30;0.25)	725	-0.09 (-0.39;0.20)
Knee and hip replacement	171	0.35 (-0.18;0.87)	38	0.16 (-1.05;1.36)	133	0.35 (-0.23;0.92)
Other	2,092	-0.08 (-0.27;0.10)	1,043	-0.06 (-0.33;0.20)	1,049	-0.04 (-0.30;0.23)
Without surgery	2,965	Reference	1,482	Reference	1,483	Reference

* Multiple linear regression analysis adjusted for sex and age at intake examination

[†] Including cardiac, thoracic, laparotomy, central and peripheral vascular and fracture surgeries

CI=Confidence interval

Table 3

Mean differences in composite cognitive scores between twins with minor surgery, one major/other surgery, two major/other surgeries, three major/other surgeries or more than three major/other surgeries and the group without surgery preceding intake examination

Number/type of surgical procedures	n	Total Differences in cognitive scores* (95 % CI)	n	<70 years Differences in cognitive scores* (95 % CI)	n	70 years Differences in cognitive scores* (95 % CI)
>3 major/other	478	-0.50 (-0.84;-0.15)	225	-0.67 (-1.19;-0.15)	253	-0.33 (-0.79;0.13)
3 major/other	437	-0.47 (-0.79;-0.16)	203	-0.17 (-0.64;0.30)	234	-0.70 (-1.13;-0.26)
2 major/other	948	0.04 (-0.21;0.29)	424	-0.10 (-0.46;0.26)	524	0.16 (-0.18;0.50)
1 major/other	1,946	-0.07 (-0.26;0.12)	961	-0.03 (-0.30;0.24)	985	-0.07 (-0.34;0.19)
Minor	1,729	-0.06 (-0.26;0.14)	1,004	-0.03 (-0.30;0.25)	725	-0.09 (-0.39;0.20)
No surgery	2,965	Reference	1,482	Reference	1,483	Reference

* Multiple linear regression analysis adjusted for sex and age at intake examination

CI=Confidence interval

Appendix 1

Surgery codes according to the Danish National Board of Health's Classification of Surgeries and Treatments and 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
<p><i>Cardiac surgeries, included codes</i> Danish National Board of Health's Classification of Surgeries and Treatments: 30009, 30019, 30029, 30039, 30049, 30059, 30069, 30079, 30089, 30099, 30119, 30120, 30149, 30200, 30240, 30241, 30350, 30354, 30700, 30780, 31020, 31119, 31130, 31268, 31269, 31699, 32400, 32920, 32940, 32960 Nordic Classification of Surgical Procedures: KFKD00, KFMD00, KFMD10, KFNA00, KFNA20, KFNC10, KFNC30, KFNC40, KFNC50, KFNE96, KFNG96, KFXB96</p>
<p><i>Thoracic surgeries, included codes</i> Danish National Board of Health's Classification of Surgeries and Treatments: 34100, 34140, 34260, 34420, 34960, 35080, 35160, 35180, 35300, 35340, 35380, 35740, 40540, 40549 Nordic Classification of Surgical Procedures: KGAB10, KGAB13, KGAC50, KGDB11, KGDC00, KJCC10</p>
<p><i>Central and peripheral vascular surgeries, included codes</i> Danish National Board of Health's Classification of Surgeries and Treatments: 86080, 86300, 86550, 86552, 86560, 86570, 86585, 86670, 86700, 86740, 86760, 86772, 86875, 86911, 86912, 86920, 86950, 86951, 86952, 86963, 86970, 86971, 86972, 87000, 87015, 87020, 87050, 87052, 87055, 87064, 87070, 87072, 87073, 87074, 87075, 87076, 87163 Nordic Classification of Surgical Procedures: KPAP21, KPBH10, KPDP30, KPDG10, KPDG24, KPDH24, KPEG10, KPEH10, KPEH20, KPEH30, KPFH22, KPFH26, KPFH27</p>
<p><i>Laparotomies, included codes</i> Danish National Board of Health's Classification of Surgeries and Treatments: 40190, 40220, 40350, 40400, 40450, 40480, 40510, 40560, 40569, 40600, 40680, 40960, 41120, 41300, 41500, 41720, 41740, 41760, 41800, 41880, 41890, 41980, 42000, 42100, 42140, 42180, 42240, 42260, 42280, 42330, 42340, 42380, 42620, 42680, 42720, 42740, 42749, 43120, 43140, 43380, 43420, 43440, 43460, 43540, 43660, 43680, 43700, 43740, 43780, 43787, 43800, 43820, 43840, 43860, 43880, 43900, 44020, 44060, 44120, 44150, 44160, 44200, 44400, 44480, 44600, 44790, 44840, 44860, 44900, 44920, 44940, 44960, 44980, 45020, 45060, 45080, 45100, 45120, 45160, 45180, 45200, 45240, 45320, 45340, 45480, 45560, 45680, 45780, 45800, 45840, 45860, 45880, 46020, 46060, 47020, 47089, 47280, 47340, 47360, 47365, 47580, 47640, 47740, 47960, 48140, 48420, 48550, 48700, 48880, 48900, 48960, 48980, 49000, 50400, 50440, 50480, 50660, 50700, 50740, 50800, 51340, 51360, 51440, 51680, 51760, 52440, 52660, 52680, 52760, 54060, 55150, 57480, 58040, 58060, 58100, 58700, 60020, 60040, 60060, 60100, 60120, 60140, 60180, 60200, 60240, 60280, 60300, 60320, 60340, 60360, 60380, 60400, 60420, 60460, 60480, 60500, 60520, 60560, 60580, 60700, 60940, 60960, 61000, 61020, 61100, 61380, 61400, 61440, 61520, 61540, 61549, 62400 Nordic Classification of Surgical Procedures: KJAH00, KJAL30, KJDA00, KJDB00, KJDE00, KJEA10, KJFB00, KJFB60, KJFC00, KJFC30, KJFF10, KJFF13, KJFF23, KJFF27, KJFG00, KJFG10, KJFH10, KJFK10, KJFL10, KJGB00, KJGB10, KJGB20, KJGB30, KJJB00, KJKA20, KJKA21, KJWD00, KJWW96, KKAC00, KKAC20, KKBA10, KKB10, KKB160, KKCA00, KKCC10, KKCD10, KKKB10, KLAE10, KLAF00, KLB00, KLCC10, KLCD00, KLCD11</p>
<p><i>Major fracture surgeries, included codes</i> Danish National Board of Health's Classification of Surgeries and Treatments: 73700, 75109, 75119, 75201, 75203, 75204, 75205, 75209, 75210, 75211, 75212, 75213, 75230, 75231, 75232, 75234, 75241, 75242, 75243, 75244, 75245, 75249, 75250, 75252, 75253, 75255, 75259, 75279, 75319, 75329, 75339, 75349, 75379, 75389, 75636, 75637, 75638, 75660, 76640, 82271, 82275, 82375, 82377 ICD-10: KNAG30, KNAG42, KNB151, KNB171, KNB181, KNF161, KNF180, KNF182, KNF183, KNF184, KNF185, KNGJ22, KNGJ40, KNGJ53, KNHJ40, KNHJ60, KNHJ62, KNHJ63, KNHJ70, KNHJ71, KNHJ72, KNHJ77</p>
Minor surgeries
<p>Included all day-only procedures, surgeries followed by less than two days of hospitalization* and irrespective of the first two criteria surgery codes that are compatible with eye surgery, endoscopic and biopsy procedures, skin surgery and other small surgeries. Danish National Board of Health's Classification of Surgeries and Treatments: Eye surgeries, included codes 10000–1990 Endoscopic and biopsy procedures, included codes 90900–93190 Skin surgeries, included codes 89520–90860 Nordic Classification of Surgical Procedures: Eye surgeries, included codes CA, CB, CD, CE, CF, CG, CH, CJ, CK, CW Endoscopic and biopsy procedures, included codes UD, UE, UG, UJ, UK, UL Skin surgeries, included codes QA, QB, QC, QD, QW, QX Other small surgery procedures, included codes TA, TB, TC, TD, TE, TF, TG, TH, TJ, TK, TL, TM, TN, TP, TQ</p>
Knee and hip replacement surgeries
<p><i>Knee and hip replacement surgeries, included codes</i> Danish National Board of Health's Classification of Surgeries and Treatments:</p>

Major surgeries
70030, 70031, 70032, 70033, 70034, 70039, 70041, 70042, 70043, 70044, 70131, 70132, 70133, 70134, 70142, 70143, 70144, 70232, 70332, 70340, 70342, 70343, 70431, 70439, 70540, 70939, 70949, 71239, Nordic Classification of Surgical Procedures: KNFB30, KNFB40, KNFC01, KNFC12, KNFC20, KNFC21, KNFC40, KNGB13, KNGB20, KNGB30, KNGB40, KNGC13, KNGC21, KNGC43
Other surgeries
Danish National Board of Health's Classification of Surgeries and Treatments and Nordic Classification of Surgical Procedures: Surgery codes that are not included in major, minor or knee and hip replacement surgeries

* Due to unavailability of the exact date of surgery in NPR before 1996, the date was considered to be the date of hospital admission plus one day. From 1996 onwards, date of surgery was available in the Danish National Patient Register and therefore accordingly used.