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

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ABSTRACT

Purpose: To examine the association between exposure to surgery and 10-year change in cognitive functioning.**Methods:** Among 2351 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 1448 (62%) twins without surgery, using linear regression models adjusted for socioeconomic factors. Genetic and shared environmental confounding was addressed in intrapair 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 intrapair 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 intrapair analyses.

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Introduction

Cognitive impairment is commonly detected after surgery and anesthesia, 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% [4]–50% [5] of adult surgical patients, and the risk of POCD is found to be increasing with size of the surgical procedure [3,4,6] and age [2,6,7]. Three months after surgery, POCD is detectable in

approximately 12% of elderly patients [1,7]. The majority of studies on long-term POCD, that is POCD observed more than 3 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 anesthesia had more decline in several cognitive measures over a 5-year period compared with participants without surgery [13] raising concerns about the duration of POCD. To clarify whether there are long-term effects of surgery and anesthesia on cognitive functioning, there is a need for large longitudinal studies where adequate methods are also 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 8503 middle-aged and elderly twins [14]. Here, we report on a subsample of 2351 middle-aged twins

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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 Videnskabetiske 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 (MADTs) 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 [15]. The MADT represented a random sample of 120 intact twin pairs from each birth cohort from 1931 to 1952, in total 2640 intact twin pairs. Of the 5189 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 4299 (83%). Before the follow-up assessment beginning in 2008 and ending in 2011, 426 twins had died, reducing the sample size to 3873. Of these, 1475 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 2351 (61% of those

alive; Fig. 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 sociodemographic 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 [16]. 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 [17]. Thus, the register has nationwide coverage, and it is considered to have high validity, especially with regard to surgical procedures [18].

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 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 (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 I](#)). 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-minute 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-minute 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

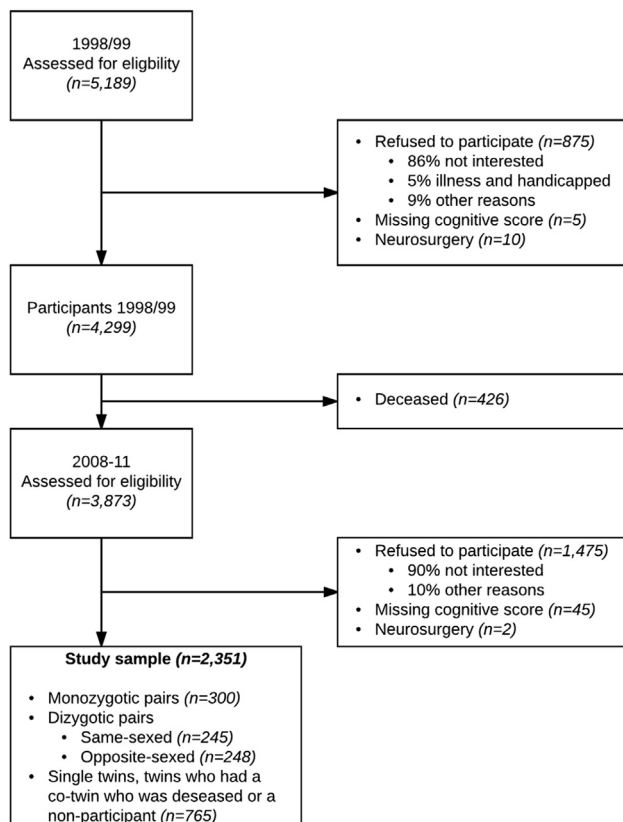


Fig. 1. Flow chart for the study of the middle-aged Danish twins.

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