

Association of Major Surgical Admissions With Quality of Life

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Supplemental Methods

Study Design and Participants

The study was approved by University College London Hospital Committee on the Ethics of Human Research, reference number 85/0938, and University of Wisconsin, Madison, USA institutional review board (IRB no. 2018-0658). The Whitehall II study is a prospective cohort study of British civil service employees who worked in London offices. 10,308 people (6895 men and 3413 women) were recruited between 1985-1988 at ages of 35-55 years old. Health questionnaires, including the quality of life scale SF-36, were included in waves of data collection 3-5 years apart. The age span during follow-up was 44-86 years (median age 64) with a mean 3.9 assessments per person and a maximum follow-up of 19.4 years (mean 14.7 years).

Exposures

Our exposure of interest was major surgical or medical admissions, defined as requiring at least a two-night stay (excluding outpatient events) based on length of stay from Hospital Episode Statistics (HES) registry of National Health Service hospitals. Since 1997, high quality HES data has been available. Audits of discharge reports indicate that HES data is 96% accurate¹. Surgical admissions in HES data were defined by Office of Population, Censuses and Services (OPCS) codes (as per our previous report)². Emergency admissions were identified by specific OPCS codes designated as an emergency procedure. Medical admissions were identified by ICD-10 codes and similarly required a hospital admission of at least two nights. Any admissions within 14 days were linked together to limit the effect of any intra-hospital transfers. If OPCS codes were identified, the entire admission was designated as a surgical admission to ensure that complications of surgical admissions were grouped with the operations. The reader should note that this may weight the analysis towards exaggerating any effect of surgery. Out of 45,936 HES entries during the study period (for 7,592 subjects), 36,915 remained after linkage. 9,476 HES entries were deemed “major” events.

Outcomes

The primary outcome was the SF-36 quality of life score collected in 1997-1999, 2002-2004, 2007-2009, 2012-2013, and 2015-2016. As SF-36 is typically analyzed in two orthogonal domains, the mental component score (MCS) and physical component score (PCS), designated a conservatively corrected significance threshold of $p < 0.025$ based on Bonferroni correction of a nominal $\alpha = 0.05$.

Covariates

Covariates included age, age², and the total number of SF-36 assessments. Additional covariates were included in sensitivity analyses: ethnicity, sex, education level, occupational position, diabetes mellitus, smoking history, married/cohabitating status, and Framingham cardiovascular disease risk score³. Education level, occupational position, and smoking history

were treated as constant for individual subjects, taking the maximum or positive score across observations. Framingham score and married/cohabitating status were variable across observation points.

Statistical models

We use a statistical approach that models quality of life changes over the adult lifespan as a function of Age and Age², and with major hospital admissions as possible moments of immediate and persistent change in quality of life, similar to a previous study of cognitive performance². We model the cumulative major surgical, medical, and stroke-related association with fixed effects for each admission category representing the number of admissions at the time of SF-36 assessment. We include baseline adjustments for major admissions throughout the entire observation period and for the number of completed assessments (as a categorical factor) to avoid spurious associations with initial conditions and bias in outcomes for early study drop outs. We included additional covariates as mentioned above as a sensitivity analysis.

As in the prior study, we also assume that individuals vary both in their non-age-related quality of life as well as their linear change in quality of life (QoL) with age (random intercepts for subject and random slopes for age per subject).

The described approach results in a linear model of the form:

$$\text{QoL}_{ij} = \beta * [1 + \text{Age}_{ij} + \text{Age}_{ij}^2 + \text{EverSurgery}_i + \text{EverMedical}_i + \text{EverStroke}_i + \text{nAssessments}_i + \text{Surgery}_{ij} + \text{Medical}_{ij} + \text{Stroke}_{ij} + \text{Covariates}_i + \text{Covariates}_i * \text{Age}_{ij} + \text{CovariatesTD}_{ij}] + \gamma_i * [1 + \text{Age}_{ij}] + \epsilon_{ij}$$

Subscript i indicates predictors that vary across subjects; subscript j indicates predictors that vary across cognitive assessments within one subject. Covariates_i are constant per subject; CovariatesTD_{ij} are time-dependant covariates. The primary coefficients of interest are those representing the number of surgery, medical, and stroke admissions prior to the quality of life measurement.

Separate models for each outcome measure (composite MCS/PCS measures or SF-36 subdomains) were fit using the R package MCMCglmm⁴ using 103000 iterations (3000 burn-in trials, thinned per 10 trials). Model convergence was confirmed via autocorrelation plots and Gelman-Rubin diagnostic⁵⁻⁷.

Interpretation of model parameter estimates

We report posterior means and Bayesian 95% credible intervals that indicate the range of parameter estimates that are probable given the data. We also report p-values for the hypothesis that there is no association between each major hospitalization category and quality

of life, though we caution that p-values may be misinterpreted⁸, and note these p-values are uncorrected across our multiple outcome measures. We advise the reader to consider primarily the CIs rather than only the p-value⁹.

Missing Data

Study waves in which SF-36 was not collected were omitted from analysis. When performing sensitivity analyses involving covariates secondary to our objectives, we used the R package MICE¹⁰ to impute missing covariate data 100 times and report credible intervals across all of the imputed models¹¹.

Identifying substantial decline

As a secondary outcome, we tested for substantial (rather than average) decline in quality of life by observing large deviations from the pre-admission trajectory. For this approach, we selected only individuals who had no major hospital admissions prior to their third quality of life assessment, and additionally excluded subjects with any stroke, leaving 4140 subjects. For each individual, we predicted MCS and PCS scores for the last SF-36 assessment (either the fourth or fifth study wave, “final”) by extrapolating from the first three assessments (“baseline”). We fit linear mixed effects models to the “baseline” with Age and Age² as fixed effects, and Subject as a random effect with random slopes for Age. The predicted “final” SF-36 scores for each patient were subtracted from the actual “final” SF-36 scores, and these residuals z-scored across subjects. In accordance with our prior work on cognition², we defined subjects with z-scored residuals less than -1.96 as those experiencing “substantial decline” relative to the predicted trajectory. We fit a logistic regression for occurrence of “substantial decline” as a function of four possible categories: those who had no major admissions before the final assessment, those who had only surgical admissions, those who had only medical admissions, and those who had both. As a further sensitivity analysis we conducted a similar analysis using a threshold of -1.5 as a substantial decline in quality of life.

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