SUPPLEMENTARY MATERIAL

Title: The StrokeCog Markov model: Projected prevalent and incident cases of stroke and post-stroke cognitive impairment to 2035 in Ireland

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The purpose of the supplementary material is to provide further detail on the background, methods and results for the StrokeCog model. Files containing R code to generate the model, and .xls files containing the input parameter estimates are available here: https://github.com/StrokeCog/EpiModel.

Supplementary Methods

1 Defining the model

The process of defining the model was influenced by consensus discussion with relevant experts and stakeholders, including stroke physicians, neuropsychologists, advocacy groups, with reference to pertinent clinical and epidemiological literature. We also carried out a review of published models of cognitive impairment progression, and a review of published models of stroke progression [1].

1.1 Models of Cognitive Impairment Disease Progression

Three databases were searched for articles describing relevant models – Pubmed, EMBASE and the National Health Service Economic Evaluations Database (NHS EED). Search terms relevant to decision models (e.g. "decision model", "state-transition", "cost-effectiveness") and cognitive impairment (e.g. "cognitive impairment", dementia, "Alzheimer disease") were used. These were searched as title and abstract terms, and were also mapped to keywords (e.g. MeSH). Articles published in English since 2000 were included. Reviews, commentaries and conference abstracts were excluded. 3107 abstracts were screened, with 185 full text articles reviewed for eligibility. 72 articles were ultimately included in the synthesis.

The dominant model type was a Markov cohort-level state transition model (k= 46/72, 64%). Disease progression was modelled as transition between categorical states of cognitive impairment, with a monthly or annual risk of transition to a worse or better state. Categories of cognitive impairment were defined based on score ranges on global impairment measures, or the number and type of domains of cognitive impairment. In 7/46 cohort-level studies, cognitive impairment was combined with a measure of functional impairment. A simplified illustrative representation is displayed in Figure I.

1.2 Stroke Models

The review of stroke models [1] has been published and can be accessed here:
https://www.karger.com/Article/FullText/506283, https://doi.org/10.1159/000506283.

1.3 Synthesis of cognitive impairment and stroke models

To date, epidemiological modelling of post-stroke cognitive impairment has been extremely limited. Current epidemiological models of stroke disease progression assume that patients remain stable unless there is a recurrent stroke. However, epidemiological evidence suggests that this assumption does not hold for cognitive impairment. Whilst recurrent stroke increases the risk of cognitive deterioration, there is substantial evidence that post-stroke cognitive function can deteriorate in the absence of recurrence (as outlined in Section 2 below). Epidemiological modelling of PSCI therefore requires a synthesis of two previous approaches: (i) Modelling the ongoing risk of transition to a worse cognitive

state, incorporating level of disability; and (ii) modelling the increased risk of deterioration associated with a recurrent stroke.

2 Assumptions

The epidemiological evidence base in relation to stroke has been used to inform the underlying design, structure and assumptions of the model. It is important to acknowledge some limitations in the epidemiological evidence-base for stroke and cognitive impairment – there is often a high-level of drop out (particularly for the sickest patients), and challenges in cognitive assessment in patients with language difficulties, or severe cognitive impairment. This implies that our estimates of the proportion of stroke patients with cognitive impairment are likely to be conservative. In addition, as stroke is a relatively rare event in the population, it is difficult to recruit and follow up large samples required for precise estimates. In this section, we outline the key assumptions in the model, and the evidence base used to justify each assumption.

2.1 Assumption 1: Cognitive impairment does not improve spontaneously after one-year post-stroke and Assumption 2: There is a risk of cognitive and functional decline after one-year post-stroke

There is considerable epidemiological evidence for both recovery of cognitive function within the first year post-stroke, and for delayed-onset cognitive impairment following stroke. In a systematic review of longitudinal studies of post-stroke cognitive trajectories, Tang et al (2018) [2] report that studies with a longer term follow-up (3-6 years) tend to report cognitive decline post-stroke, whereas studies that report a recovery-type trajectory tended to be hospital-based studies with a shorter follow-up (up to ~1 year). This supports the assumption that under baseline circumstances, substantial cognitive recovery does not occur after a year post-stroke. For example, in the Auckland Stroke Study, cognition improved in the first year post-stroke, but declined significantly by a mean 2.8 points on the MoCA by 48 months [3]. Pendlebury 2019 [4] et al report a steady increase in % of patients with dementia in five years after stroke, across levels of severity. They report an increase from 22.1% at 1 year, to 31% at 5 years. Age has a significant impact: at 5 years, 31% of people aged 75yr+ have dementia, compared with 9.3% of <75 years. There is also evidence that adults with prevalent stroke have an increased risk of dementia, with a pooled hazard ratio for all-cause dementia of 1.69 (95% confidence interval: 1.49–1.92) [5].

Delayed onset cognitive decline after stroke could be attributed to recurrent stroke. However, a number of studies show that cognitive decline occurs in a substantial proportion of patients who do not experience a recurrent stroke [4,6]. In a large study of 5673 stroke patients without dementia, 407 transitioned to dementia over a ~4 year period – the majority of these (n=301, 74%), did not experience a recurrent stroke [6].

There is some uncertainty regarding the extent to which post-stroke cognitive impairment (PSCI) and stroke could be symptoms of an ongoing vascular degenerative process that began prior to the stroke, and the extent to which the stroke itself has a causal role in the observed cognitive decline. Poorer pre-

stroke cognitive function is associated with an increased probability of post-stroke dementia [7] (ELSA data). Nevertheless, there is also evidence from the Oxford Vascular Study (OXVASC) that stroke increases risk of cognitive decline even in adults with high cognitive function pre-stroke, further supporting the causal role of the stroke in cognitive decline [4]. The evidence thus indicates that PSCI may be a consequence of both an ongoing degenerative process that began prior to the stroke, and the stroke itself – Dregan et al summarise this by describing PSCI as part of a "continuum of cognitive disorder that tends to deteriorate as people get older, and stroke may have a secondary effect by accelerating this early deterioration" [7] (Dregan, 2013, p. 3445).

2.2 Assumption 3: Recurrent stroke is associated with accelerated cognitive and functional decline

Systematic review evidence indicates that 40% of people with recurrent stroke have dementia, compared with 10-20% of survivors of a first ever stroke [4]. In longitudinal studies of stroke survivors, people who have a recurrent stroke have increased odds of dementia of 2.3, relative to those who do not have a recurrent stroke [4]. In the ESPIRIT trial, which included TIA patients and non-disabling ischemic stroke, patients who had a recurrent stroke during the 5 year follow up period were 2.45 times more likely to transition to dementia (adjusted for baseline cognitive status, age, baseline mRS, previous stroke) [8]. However, it is possible that the effect of recurrent stroke has been over-stated – Mahon et al. found no difference in the rate of PSCI between first-time and recurrent strokes [3].

Functional and Mortality Outcomes

Evidence on the fatality rate of recurrent stroke compared with first stroke is mixed. A Dublin-based population study (NDPSS) of recurrent strokes (46/518 stroke patients) found that recurrence was related to a greater deterioration in function (mRS), but was not associated higher fatality (Callaly et al, 2016) [9] although the number of recurrent strokes was low. Similarly, recurrent strokes ascertained at baseline in the NDPSS did not have a higher mortality rate relative to first-ever stroke (data collected 2005-2006). In contrast to this, in the Perth Community Stroke Study (PCSS) found a 2-fold higher 30-day case-fatality for recurrent stroke relative to first stroke [10].

We assumed that cognitive and functional outcomes are worse after a recurrent stroke, relative to a first ever stroke. We also assumed that recurrent stroke is not associated with an increased fatality rate, but varied this assumption in sensitivity analysis by using the PCSS figure of a 2-fold higher case-fatality for recurrent stroke.

2.3 Assumption 4: After 30-days post-stroke, people who had a stroke have an increased risk of death relative to the age and sex matched population

Case-fatality due to stroke is generally defined as death within ~30 days post-stroke (Feigin et al, 2009) [11]. After this, we assume that mortality reflects the background mortality of the same age and sex group, but with an increased risk associated with having had a stroke. A review by Singh et al (2018) [12] concluded that mortality risk for stroke patients is 10-12 times higher than the matched general population in the first year, and remains 2-3 times higher in subsequent years. This could be due to cardiovascular or nonvascular causes.

There is also evidence that post-stroke CIND and dementia increase the risk of mortality post-stroke relative to NCI [13]. In the base case, we made the conservative assumption that background mortality does not vary by physical or cognitive function, but varied this assumption in sensitivity analysis.

2.4 Assumption 5: Age-specific probabilities remain stable and do not vary over time (calendar trend or time since stroke)

To be conservative, we have assumed that current age-specific annual risks of stroke incidence, the incidence of post-stroke cognitive impairment, transition probabilities, mortality, risk of stroke recurrence will remain stable to 2035. In addition, we have assumed they remain stable regardless of time since stroke. Whilst these assumptions are somewhat implausible, data limitations mean that it is difficult to reasonably estimate the relevant trends or trajectories. As part of future work, we will develop a set of alternative plausible scenarios for future trends in stroke and stroke outcome risks, and examine ways to incorporate time since stroke.

2.5 Assumption 6: Data on stroke patient populations in England can be applied to the Irish stroke population.

Evidence from international sources is frequently used in epidemiological modelling (e.g., Global Burden of Disease studies). However, it is best practice to use local epidemiological data where possible. For a number of parameter estimates in the StrokeCog model, there was either no Irish-specific data available (e.g., stroke recurrence rate, excess mortality), or the available Irish data was based on small samples, making it difficult to disaggregate by age and resulting in imprecise estimates (e.g. case fatality). We therefore based some parameter estimates on data from one of Ireland's closest geographical neighbours, England, where necessary. In particular, we used data from the English Longitudinal Study on Ageing (ELSA). This assumption was validated by comparing the estimates from English sources with local epidemiological data (The Irish Longitudinal Study on Ageing, TILDA, and the North Dublin Population Stroke Study, NDPSS) and published estimates. In addition, we used the Irish estimates in sensitivity analysis.

2.6 Assumption 7: Stroke incidence, prevalence and case-fatality vary by sex, and the effect of sex on other model inputs is uncertain

Higher age-specific incidence of stroke in men is a well-established finding [14]. However, age-specific prevalence may be higher in women due to their longer life expectancy. The evidence in relation to stroke severity, or stroke outcomes, is not as clear. There is some evidence for higher case fatality in women, but this appears to be associated with differences in age and stroke subtype, rather than sex [14]. Evidence for the effect of sex on post-stroke cognitive decline is mixed, with significant effects reported in either direction (review by Tang et al 2018) [2]. In identifying parameter estimates for the model, we tested this assumption by examining sex differences in the relevant data sources.

2.7 Assumption 8: Age has a significant effect on stroke incidence, prevalence and outcomes

Age has an important influence on a range of aspects of stroke epidemiology, including incidence, prevalence and outcomes. Age is a strong predictor of cognitive outcomes post-stroke – in the Auckland Stroke Outcomes study participants aged over 75 years were 13.4 times more likely to be cognitive impaired than those aged <50 years [3]. To reflect these important age differences, model input parameter estimates were disaggregated by age as far as possible. However, at times this may be constrained by the limitations of the data sources. Particularly if sample sizes are small, higher levels of disaggregation result in less precise estimates. There may therefore be a trade-off between capturing age variation, and maintaining precision. Where appropriate, these trade-offs were tested in sensitivity analysis.

3 Model Design

3.1 Model Structure

The model begins in 2014, where the population is categorised as disease-free, or with prevalent stroke (disaggregated by health state). No outcomes such as deaths are calculated for end of 2014 – it is assumed that the prevalence estimates relate to the total number of stroke people alive at the end of that year.

In 2015, an estimated risk of incident stroke is applied to the disease-free population, in addition to tracking the health-state transitions of people with prevalent stroke in 2014. It is assumed that events/transitions occur at the end of the year. For example, an incident stroke in 2015 is assumed to happen at the end of the year, with the 12-month outcomes of this stroke captured in 2016. The model cycle length is one year, which means that events can only occur once a year.

Each year, the disease-free population has a risk of having an incident stroke, and of dying of another cause. The cohort who have an incident stroke have a risk of dying of stroke (within 30 days) or of another cause (30 days to 1 year), of surviving in one of five health states (NCI with or without disability;

CIND with or without disability, dementia with or without disability, dementia), or of having a recurrent stroke within one year. The population in each of the four non-dementia health states have an annual risk of moving to a worse health state, of dying of a non-stroke cause, or of having a recurrent stroke. The cohort with dementia have an annual risk of dying of a non-stroke cause, or of having a recurrent stroke.

The population who have a recurrent stroke stay in a "tunnel state" for one year. This cohort has a risk of dying within one year, of having another recurrent stroke within one year, or of surviving in one of the five health states. The model includes separate tunnel states for each health state, allowing the transition following the tunnel state to be dependent on the health state before the recurrent stroke. For example, patients who had dementia before the recurrent stroke stay in that state following the recurrence. Patients cannot improve their health state following a recurrent stroke. The model allows for up to 3 recurrent strokes. The model predicts a very low incidence for a third recurrent stroke, and the incidence of a fourth recurrence is thus negligible. In the Perth Community Stroke Study, only 1/251 participants had a third recurrent stroke, over 10 years post-stroke follow-up [10].

Although the results are only calculated for the age 40-89 age group, the model generates estimated outcomes for the 90-99 age group to facilitate calculation of life expectancies. Certain parameters are calculated specifically for this group, including stroke incidence, and proportion living in nursing homes for the purposes of prevalence calculation. For other parameters, the estimate for the oldest age group (e.g. age 75+, age 85+) is applied.

3.2 Definition of Health States

Definition of Dementia

The most widely used definitions of dementia in stroke are the DSM-IV criteria and the NINDS-AIREN criteria. More recently, the DSM-V has been proposed as a revised set of criteria for dementia appropriate for use in stroke [15].

The DSM-V criteria were operationalized in ELSA and TILDA as outlined below. Similar criteria were used in a previous modelling study [16].

Dementia criteria:

Substantial impairments in one or more of the following cognitive domains: orientation to time, immediate and delayed memory, verbal fluency and visual search.

> (defined as a score >2 SD below the mean for the same age group and level of education, following Sachdev et al, 2014 [15]).
>
> If the participant is too impaired to take part in cognitive testing, then an IQCODE score >= 3.6 is defined as indicative of dementia [17].

AND

Impairment in IADLs

(defined as a difficulty with the following activities: managing money and/or taking medications)

There are two options for defining IADL impairment: requiring impairment in **either** managing money OR taking medications for a dementia classification, or requiring impairment in **both** of these activities.

OR

Self-reported doctor diagnosis of dementia

Please note: these criteria are for classifying people as having dementia for epidemiological modelling purposes, and do not equate to a diagnosis. The more conservative definition (requiring impairment in both IADLs) was used in the base case model, with the alternative definition used as a sensitivity analysis.

Cognitive Impairment no Dementia (CIND) criteria:

Modest impairment in one or more of the following cognitive domains: orientation to time, immediate and delayed memory, verbal fluency and visual search (with or without functional impairment)

(impairment defined as a score 1.5-2 SD below the mean for the same age group and level of education)

OR

IQCODE score 3.3-3.6

OR

Substantial impairment (defined as >2SD below the mean for the same age group and level of education, or IQCODE >3.6), but not meeting the IADL impairment criteria for dementia.

No cognitive impairment (NCI) criteria:

Any level of cognitive impairment that does not meet the criteria for CIND or dementia (with or without functional impairment).

NOTE: There was some variation in the cognitive tests available across data sources and measurement occasions. Visual search was not assessed in TILDA, or in ELSA waves 7 and 8. Verbal fluency was not assessed in ELSA wave 6. The IQCODE was not included in TILDA wave 2.

Definition of disability

Previous stroke models have defined disability on the basis of overall function or dependency, for example using the Modified Rankin scale or the Barthel Index [1]. Neither of these measures are available in TILDA or ELSA. However, both studies capture need for assistance in basic activities of daily living. Disability was defined as needing assistance in one or more of these basic activities: Walking across a

room; Bathing or showering; Eating, such as cutting up your food; Getting in or out of bed; Using the toilet, including getting up or down.

4 Parameters

Each set of parameter estimates are assigned a label P1 to P9, which are also used to label the relevant .xls input files, and within the modelling code .r files (see https://github.com/StrokeCog/EpiModel). Sensitivity analyses in relation to P*N* are labelled as S*N*.1, S*N*.2 etc. A description of the data sources used for each parameter, and associated sensitivity analyses, is provided in this section. The assumptions and uncertainty analysis for each parameter are displayed in Table I. The following assumptions apply across parameters: 1) Irish data sources are representative of the relevant target population (e.g. TILDA is representative of the Irish population aged 40-89) and 2) parameters remain stable over time, unless stated otherwise.

Data sources for parameters were identified through an initial systematic review of the prevalence of post-stroke cognitive impairment no dementia [18], through consultation with experienced researchers and clinicians in this field, and through ongoing monitoring of literature alerts set up in Pubmed and Google Scholar, with the search terms related to stroke (e.g. “stroke”, “cerebrovascular”) and cognitive impairment (e.g., “cognitive impairment”, “dementia”).

4.1 P1: Population Estimates and Projections

Sex and age specific population estimates for 2014-2018, and population projections for 2019-2035, were obtained from the CSO (2018)[19] (statbank.cso.ie). Alternative sets of CSO population projections are available based on variation in assumption related to fertility and migration patterns. Assumptions related to fertility have no impact on the projections for age 40+, and the F1 assumption of high fertility used in all analysis. In the base case, we assume high net inward migration +30,000 per annum in 2017/2051 (M1F1 scenario). In sensitivity analysis, we assume low net inward migration of +10,000 per annum in 2017/2051 (M3F1 scenario).

Sensitivity Analysis:

- S1.1: Alternative assumptions for population projections: M3F1 (high fertility, low migration)

4.2 P2-3: Prevalence estimates

To estimate changing prevalence of stroke, post-stroke cognitive impairment and dementia in the Irish population, we need an estimate of the initial or “starting” prevalence of these health states. These estimates relate to the number of people who have had a stroke at the end of that year, and therefore include people who had an incident stroke in the same year. To avoid double counting, these prevalence estimates were applied to the population in 2014, and incident strokes were not included in the model until the following year (2015). In addition, when 40 year olds enter the model, prevalence alone is calculated for the first year, and not incidence.

As prevalence is likely to vary in the community and in nursing homes, we first estimated the proportion of the population resident in nursing homes in 2014, disaggregated by age and sex. These estimates were developed by the Economic and Social Research Institute from administrative data supplied by the HSE Social Care Division, Department of Health and HIQA. Further details are available from Wren et al [20]. Separate community and nursing home prevalence estimates were then applied to these estimated proportions of the total population.

P2.1: Community Stroke Prevalence

Prevalence of stroke in the community was estimated using data from the Irish Longitudinal Study on Ageing (TILDA)[21], based on wave 3 (collected in 2014) (n=6,530) and data from the Irish Quarterly National Household survey (QNHS)[22] (collected in 2010) (n=15,673) . The first wave of TILDA (2009-2010) excluded people with dementia, although participants who were subsequently diagnosed with dementia were included in waves 2 and 3. This exclusion of people with dementia at wave 1 in TILDA, along with a likely selection bias against people who have had a stroke in both data sources, means that the prevalence estimates are likely to be conservative.

Prevalent stroke was assessed in TILDA and QNHS based on self-reported doctor diagnosis – "Has a doctor ever told you that you have had a stroke?" This approach to stroke ascertainment has limitations (e.g., recall bias), but has been demonstrated to be broadly valid and reliable [7]. The prevalence was estimated by sex and age group. In TILDA, participants who had ever disputed their stroke diagnosis, or were aged 90+ or <50, were excluded from the analysis. Only age aggregated data was available from QNHS, by four age groups: 18-24yrs; 25-44 yrs; 45-64 yrs; and 65+ years. The QNHS is less recent than the TILDA data, but includes a larger sample size for the 45-64 age group (n=5,203), compared with n=3,036 for age 50-64 in TILDA.

We combined the TILDA and QNHS data sources in two ways:

1) The QNHS estimate for age 25-44 was applied to the 40-49 year age group in the model, with TILDA data used for the 50-64, 65-74 and 75+ age groups (TILDA approach)

2) The QNHS estimate for age 25-44 years was applied to the 40-45 year age group in the model, and the estimate for the 45-64 year age group to the same age group in the model. The TILDA estimates were then applied for age 65-74 and 75+ (QNHS approach).

As part of model validation, the projected stroke prevalence generated by these two approaches were compared with an approach that used the DisMod II tool[23] to generate baseline prevalence estimates. This tool, developed by the World Health Organisation, allows prevalence to be estimated from data on incidence and mortality. It was not possible to use DisMod prevalence estimates in the base case model, as these could not be disaggregated by setting to allow for application of nursing home and community specific estimates of cognitive impairment. However, we were able to check the total stroke prevalence estimated by the model against those generated using our incidence and mortality estimates, as a validation.

This analysis indicated that the TILDA approach appeared to under-estimate prevalence for men, while the QNHS approach under-estimated prevalence for women (see Figure II). However, the divergence

was greater for the TILDA approach, and we therefore used the QNHS approach. The TILDA approach was used in sensitivity analysis.

Sensitivity Analysis:

- *PSA:* Prevalence rate (Beta distribution)
- S2.1: TILDA estimate for age 50+, QNHS estimates for age 40-49

P3.1: Post-stroke CI and dementia in the community

The total sample of stroke survivors available in TILDA is small (n ~140), and we therefore used data from the English Longitudinal Study on Ageing (ELSA)[24] to estimate the distribution of the five health states within the population of prevalent strokes. The five health states were defined and operationalised as outlined in Section 3.2 above.

There were 458 participants with prevalent stroke aged <90 in ELSA wave 5. Prevalent stroke was based on self-reported doctor diagnosis – "Has a doctor ever told you that you have had a stroke?", and participants who later disputed their stroke diagnosis were excluded. After excluding participants resident in a nursing home (n=26), and with missing data on cognitive impairment (n=49), there were 387 eligible for inclusion in the analysis. (50-75, n= 198; 75+ n= 189). As ELSA does not recruit adults aged 40-49, we applied estimates for age 50-69 to the 40-49 year old age group.

To evaluate the extent to which ELSA data reflects local prevalence, the health state distribution was compared against the distribution observed in people with stroke in TILDA wave 3 (data collected in 2014/2015, n=134) (Table II). Although the cognitive profiles are similar, the disability profiles are more divergent. Although ELSA estimates were used in the base case, due to the larger sample size and greater precision, TILDA estimates were used in a sensitivity analysis.

Sensitivity Analysis:

- PSA: Distribution of health states (Dirichlet distribution)
- S3.1: Alternative definitions for CI and dementia
    - S3.1.1: Use a cut-off of 1SD below the mean for CIND classification (1.5 SD in the base case)
    - S3.1.2: Require only one IADL deficit (managing money OR taking medications) for dementia classification
- S3.2: TILDA estimates

P2.2; P3.2: Prevalence of stroke and PSCI in nursing homes

As outlined above, the prevalence of stroke among people in nursing homes was estimated by using data on the total proportion of the Irish population living in nursing homes by age in 2015, disaggregated by age and sex. To this data, we applied estimates of the proportion of stroke residents

who have had a stroke, disaggregated by age (<75, 75+) and level of cognitive impairment (NCI, CIND and dementia). These estimates were based on the StrokeCog Nursing Home survey[25], which involved collecting data from a representative sample of nursing homes in Ireland (n=13), relating to 643 residents. Information was collected on stroke diagnosis, and cognitive function status (NCI, CIND and dementia).

Sensitivity Analysis:

- PSA: Prevalence rates (Beta distribution)
- PSA: Distribution of health states (Dirichlet distribution)

4.3 P4: Stroke Incidence

Annual age and sex-specific stroke incidence in Ireland was estimated using data from the Hospital Inpatient Enquiry (HIPE) system. The HIPE database records admissions to public acute hospitals in the Republic of Ireland, and collects a range of data including diagnostic information coded using ICD-10-AM, and demographic information [26]. We included the number of discharges with a principal or secondary diagnosis of ischaemic or haemorrhagic stroke, or stroke not-specified, in 2015 (ICD codes I60-I61, I63-64), disaggregated by 5-year age groups and sex. As recommended based on previous work [27], we excluded 1) rehabilitation hospital discharges or with a principal diagnosis of rehabilitation, 2) discharges with a LOS < 1 day that were transferred to another hospital or home and 3) discharges with an area of residence outside Rep. of Ireland. This helped to ensure that multiple discharges arising from the same stroke episode were excluded. This number of discharges were applied to population data for that year from the Central Statistics Office to estimate an age and sex specific annual stroke incidence for the Irish population.

However, this estimate did not include incident strokes that do not result in a hospital admission. This could occur, for example, where the person died before reaching hospital, or for a person in long-term care with multiple co-morbidities where hospital admission may not benefit the patient. We used the NDPSS data to estimate the proportion of out-of-hospital (OOH) strokes in people aged 40-89, again following the methodology proposed by Wren & Kelly [27]. In the NDPSS, the highest rate of OOH strokes was in age 40-49 (15.4%) and 90+ (27.3%). However, the size of the age 40-49 group was small (n=26), and within the 40-89 age group, the effect of age was not statistically significant (based on logistic regression analysis adjusted for age^2 and sex, OR for age = 0.91, p=0.474). The OOH rate is 10% in age 40-89 age group (95% CI 7.6%-13.0%). We therefore increased the stroke incidence rate estimate in each age/sex group by the same percentage.

A further issue with HIPE data is that it includes both first ever and recurrent strokes, whereas we need to estimate first-ever strokes. Again, we used the NDPSS data to estimate the proportion of total incident strokes in Ireland that are recurrent strokes. 15.6% of incident strokes in the age 40-89 age group were recurrent strokes (95% CI 12.7-19.1). Logistic regression (adjusted for sex) indicated a significant effect for age (continuous): OR= 1.05; 95% CI 1.02-1.08). The proportion appeared to increase linearly with age, so we applied a separate estimate for age groups (40-59, n=95; 60-69, n=114; 70-79,

n=156 and 80-89, n=135). This estimate of the percentage of recurrent strokes was applied to reduce the overall stroke incidence rate, to reflect the incidence of first-ever stroke.

HIPE was used as the primary source for stroke incidence estimates instead of NDPSS as it is more recent (2015 for HIPE v 2005-2006 for NDPSS). In addition, the NDPSS reports higher incidence rates than those observed in other European countries, which may relate to higher vascular risk in the North Dublin population [28].

Sensitivity Analysis:

- PSA: Crude incidence rate (Beta distribution)
- PSA: OOH rate (Beta distribution)
- PSA: Proportion of incident strokes that are recurrent (Beta distribution)

4.4 P5: Cognitive and functional impairment at 1 year post-stroke

Three key systematic reviews and meta-analyses have been conducted on the prevalence of post-stroke CIND and dementia in the first year post-stroke. The meta-analysis by Pendlebury et al [29] of the prevalence of dementia in the first year post-stroke reported a prevalence of 23% (95% CI 21.4-24.7) in hospital-based studies and 12.5% (95% CI 9.6-14.4) in population-based studies. A more recent review [30] explicitly based on the DSM-V criteria (see Section 3.2) reported a post-stroke dementia prevalence of 16.5% (95% CI: 12.1–20.8) 3-18 months post-stroke. The same review reported a post-stroke CIND prevalence of 36.4% (95% CI: 29–43.8). Our own systematic review of post-stroke CIND prevalence [18] indicated a very similar pooled prevalence of post-stroke CIND, 38% [95% CI 32– 43%], with a prevalence of 39%, [95%CI 35–42%] observed in a homogenous group of higher quality studies. Further unpublished analysis of the studies included in our review[18] indicated a post-stroke dementia prevalence of 18% (95% CI 14-23), or 14% (95% CI 11-18) in the higher quality studies.

However, although these meta-analysis results are useful, they do not provide age-specific estimates of cognitive impairment prevalence at 12 months post-stroke. Pendlebury et al (2019)[4] indicate a steep age gradient in post-stroke dementia. For this reason, we used ELSA data to estimate the prevalence of CIND and dementia at 1 year post-stroke, disaggregated by age. A further advantage of ELSA is the availability of individual-level data on age, CIND, dementia and disability, thus allowing us to estimate all the health states from the same data source. It also allowed us to exclude individuals aged 90+, and recurrent stroke. We included participants in waves 2-5 who were having their first interview after an incident, first-ever stroke, including those living in the community and in nursing homes (n=287). This could have occurred any time in the previous 2 years, with a mean/median follow up of 1 year. The results based on time since stroke are compared below.

The definition of CIND and dementia outlined in Section 3.2 above was used. If a participant disputed their stroke diagnosis in a subsequent wave, they were excluded from the analysis. Waves 6-8 were not used due to the omission of some cognitive tests (animal naming in w6, letter cancellation in w6-8). Stroke was ascertained as outlined in Section 4.2.

Multinomial logistic regression in ELSA, adjusted for age, indicated that women had a decreased risk being classified as CIND relative to NCI. However, this effect was only statistically significant for CIND no disability (p=0.016). To optimize precision, it was thus decided to disaggregate by age and not sex in the base case, although we did explore sex differences in sensitivity analysis.

The ELSA analysis was replicated using TILDA data. As the inclusion criteria were relatively selective, including only participants having their first interview after an incident, first-ever stroke, the sample size was small (n=60). Table III displays a comparison of the cognitive impairment and disability profile of ELSA and TILDA at 1 year post-stroke, and the three available meta-analyses [18,29,30]. The proportions with CIND are similar in ELSA (34%) and TILDA (37%), and close to published estimates (36-39%). However, the proportion with dementia in TILDA (18%) is approximately double the estimate in ELSA (9%). The TILDA estimate was closer to published estimates (12.5-23%). The proportion with disability was similar in ELSA and TILDA (~40%). As the TILDA sample size was too small for any disaggregation by age, the ELSA data was used in the model, disaggregated by under and over age 75 years. However, it should be noted that the estimated proportion of people with dementia is conservative, and lower than other available estimates.

To investigate the effect of time since stroke, we compared the distribution of cognitive and disability outcomes among all interviews that took place in the 0-2 years after stroke, with those occurring within a year post-stroke. The results are similar (see Table IV), and a chi2 test indicated no statistically significant association (chi2, (df=8, n=287) = 11.30, p=0.185). We used the estimates based on all interviews 0-2 yrs post-stroke in the model, to have a larger sample to allow for disaggregation by age.

Women participants were less likely to be classified as having CIND, relative to men, in the first interview post first ever stroke in ELSA (see Table V). In multinomial logistic regression adjusted for age, this was a significant difference (B= -1.05; p <0.001). As this sex difference has not been previously documented in the literature, we did not disaggregate this parameter estimate by sex in the base case model. We explored the impact of disaggregated this estimate by sex in sensitivity analysis, but the results should be treated with caution, as they may be due to sample-specific variation.

In ELSA, in the 40-89 age group, the proportion with CIND (33.5%) and dementia (9.1%) were lower than the estimates based on meta-analysis. This is not unexpected as the ELSA stroke sample is likely to be healthier than the general stroke population. By using the ELSA estimates, we are therefore taking a conservative approach with regard to cognitive outcomes.

As an alternative, less conservative approach, we also used recent published data from the population-based OXVASC study[4], which uses multiple methods of case ascertainment to identity stroke cases, thus reducing selection and attrition biases. A prevalence of dementia at 1 year post-stroke of 20.7% (95% CI 17.3% - 24.6%) is reported in OXVASC (Table S3)[4], similar to that reported in the meta-analyses described above. Data stratified by under and over age 75 years is reported in Table S5. The OXVASC estimate includes individuals aged 90+, and those with recurrent stroke, and therefore may be an over-estimate for the group aged 40-89 with first-ever stroke. In addition, the OXVASC study used a relatively

inclusive definition of dementia (MMSE<24). We therefore used the OXVASC estimate in a sensitivity analysis, rather than as the base case.

Sensitivity Analysis

- PSA: Distribution of health states (Dirichlet distribution)
- S5.1: Alternative definitions for CI and dementia (As S3.1 above)
- S5.2: Include ELSA waves 7-8. These are excluded in the base case as they exclude the letter cancellation cognitive test. Wave 6 is not included even in sensitivity analysis, as it also excludes the verbal fluency test.
- S5.3: Disaggregate by sex
- S5.4: OXVASC estimates for dementia

4.5 P6: Stroke Recurrence

Mohan et al 2009 [31] examined data from the South London Stroke Register (SLSR) collected between 1995 and 2004. They reported a cumulative recurrence at one year of 7.1% (95% CI 6.0 to 8.3) (n=2,874), at 5 years of 16.2% (95% CI 14.4 to 18.1) (n=1,143). This is equivalent to an annual rate of 2.3%. The 10-year cumulative rate in the SLSR was 24.5 (21.3 to 27.9). This compares with the study by Hardie et al (2004)[10] (Perth Community Stroke Study) which found a 10-year cumulative recurrence of 43% in 1989-1999, consistent with the hypothesis of declining recurrence rates.

Other sources: In a population-based study of stroke patients in Ireland (NDPSS) the rate of recurrence in stroke patients (n=518) was 8.5% at 1 year and 10.8% at 2 years (Callaly et al., 2016) [9]. This corresponds to a rate of 2.3% in the second year post-stroke which is identical to the annual rate observed in the Mohan SLSR study. The 1-year rate observed in NDPSS (8.5%) is slightly higher than the 7.1% observed in SLSR. A more recent source is data from OXVASC on recurrent ischaemic stroke for patients with an incident stroke from 2002-2014 (n=1242) [32]. The recurrent stroke rate @ 1 year was 10.5% (slightly higher than Mohan et al), and 1.7% thereafter up to 5 years (slightly lower than the rate reported by Mohan et al).

The SLSR estimate is used in the base case model, with OXVASC estimates used in sensitivity analysis. The NDPSS estimate was not used in sensitivity analysis as it was so close to the base case estimate. The effect of age on recurrence in SLSR was not statistically significant, and the estimates are therefore not disaggregated by age in the base model, but this is varied in sensitivity analysis.

Effect of cognition on recurrence: Sibolt et al [33] examined the effect of PSCI on stroke recurrence risk, using data from the Helsinki Stroke Ageing and Memory (SAM) cohort (ischaemic stroke) (follow-up over 12 years, n=446 patients). Post-stroke dementia (ascertained at 3 months) was associated with a HR of 1.84 (95% CI 1.34-2.54) for recurrent stroke, adjusted for covariates. There was no increased risk of recurrence associated with CIND (relative to NCI). To be conservative, we assume that there is no

increased risk of recurrence associated with dementia in the base case. However, we examine the potential effect of this in sensitivity analysis.

Sensitivity analysis

- PSA: Recurrent stroke rate (Beta distribution)
- S6.1: Disaggregate Mohan et al estimates by age
- S6.2: OXVASC estimates
- S6.3: Increased risk of recurrence for dementia

4.6 P7: Transition probabilities for cognitive impairment and disability health states

To estimate annual probability of transition between the five health states, we again used data from the English Longitudinal Study on Ageing (ELSA). We included participants in ELSA waves 1-5, age 50-89, who ever had a stroke at any point in the past, and who participated in at least two consecutive waves of data collection. Stroke was ascertained as described in Section 4.2. The five health states were defined and operationalised as outlined in Section 3.2 above.

The unit of observation was the transition between two waves or interview occasions. A single participant could therefore contribute multiple observations. Institutional and community interviews were included. Transitions in which a recurrent stroke occurred were excluded from the analysis (n=225, see Section 4.7). Waves 6-8 were excluded due to a change in the cognitive testing regime, but waves 7 and 8 were included in a sensitivity analysis. In total, there were 465 participants included with 937 transitions. Total follow up time ranged from 1 to 10 years. Transition probabilities were estimated from a transition probability matrix.

Rules for back transitions: We assumed that spontaneous recovery of cognitive impairment and disability are not possible after the first year post-stroke (Assumption 2). If a participant was classified as having cognitive impairment on a single measurement occasion, and then transitioned to better cognitive function, we assumed that the original cognitive impairment was transient, and re-classified it as NCI. However, if cognitive impairment was present for more than one occasion, and absent for a subsequent occasion, it is assumed that the NCI classification is incorrect and that the person still had CI. The same approach was applied to participants moving from disability to no disability. If cognition or disability improved in the same year that a proxy was used, assumed the original impairment is still present (i.e. the self-report is valid). Particularly for cognition, change could be due to change in measurement, e.g. cognitive tests to IQCODE.

There were 183 transitions that involved an improvement in cognitive function or disability. 8/183 of these “mismatch” transitions involved a move to proxy, and it was assumed that the self-report in the previous wave was correct. The remainder involved transient states – the cognitive/disability state prior to the improvement was observed in one wave only, and was therefore classified as transient. These

adjustments were conservative, as patients were re-classified from a worse health state to a better health state. A small number of transitions involving a move from NCI to dementia were excluded (n=7). As the average time between interviews was 2 years, we divided each transition probability by 2 to calculate the annual transition probability. The transition probability matrix following adjustments is displayed below (Table VI).

The same analytic strategy was implemented in TILDA. In total, there were 165 participants included with 311 transitions. The resulting transition probability matrix following adjustments is displayed in Table VII. Total follow up time ranged from 1 to 8 years. The TILDA estimates are used in sensitivity analyses. Combining disability groups, there was an annual risk of transition from NCI to CIND in ELSA of 7.1%, and 5.6% in TILDA. Published estimates of the annual risk of transition from NCI to CIND after the first year post-stroke include 10% [34], 14% [35], and 5.6% [36]. **The ELSA estimate for NCI to CIND is thus in the mid-range of available estimates.**

Combining disability groups, there was an annual risk of transition from CIND to dementia in ELSA of 3.6%, and 4.3% in TILDA. Published estimates of the annual risk of transition from CIND to dementia after the first year post-stroke include 2% [6], 4.3% [35], 8% [36] and 11% [34]. One study distinguished risk of transition to dementia from mild CIND 1.3% and moderate CIND 6.6% [8]. **The ELSA estimate for CIND to dementia is thus at the lower end of the range of available estimates.**

The tables for all ages (Tables VI and VII) are presented for the purpose of comparing with other data sources. However, the estimates used in the model were disaggregated by age 75+ and age <75. We considered using predicted probabilities by single year of age: however, we judged that the sample size was not sufficient to make such fine-grained predictions. Regression analysis based on multinomial logistic regression indicated that transition probabilities did not vary significantly by sex. However, age (continuous) was significantly associated with increased probability of transition from NCI no disability to CIND no disability (p=0.004), and from CIND no disability to dementia (p = 0.012).

We examined cognitive and disability transitions among participants who had at least 3 observations in the dataset. In these participants, there is a greater opportunity to identify transient states, due to additional follow-up. In wave 2-5 of ELSA, there are 390 participants with at least 3 observations, with a total of 862 transitions. Transition probabilities are highly similar, with an estimated annual probability of transition from NCI to CIND of 6.7% (versus 7.1% in the base case), and an estimated annual probability of transition from CIND to dementia of 3.9% compared with 3.6% in the base case. The input parameters were so similar that it was not deemed necessary to re-run the model with these estimates.

As a sensitivity analysis, we also explored the effect on model outputs of assuming that there were no health state transitions in the absence of recurrent stroke, by setting the transition probabilities to zero, consistent with previous modelling studies in this area [1].

Sensitivity Analysis

- S7.1: Alternative definitions for CI and dementia (As S3.1 above)
- S7.2: Include ELSA waves 7-8 (As S5.2 above)

- S7.3: Use TILDA estimates
- S7.4: No health state transitions in the absence of recurrent stroke

4.7 P8: Recurrent Stroke Outcomes

There is a deficit in the evidence base in relation to health state transitions when a recurrent stroke occurs. Previous epidemiological models of stroke have tended to base these transitions on assumption – for example, that there is an equal likelihood of transitioning to each of the worse possible states [1]. No empirical evidence has been provided for this assumption [1]. In longitudinal cohorts of stroke survivors, a recurrent stroke is associated with a two-fold increase in the probability of having dementia, relative to those who do not have a recurrent stroke. However, there is limited published evidence available for the probability of transitioning from NCI to CIND or dementia, or from CIND to dementia, for people who have a recurrent stroke.

In the ELSA cohort (waves 1-5), we identified 225 transitions where a participant who had a prevalent stroke, had a recurrent stroke between interview waves, and complete health state data for both waves. This involved 179 individual participants, as some participants had multiple recurrent events. Stroke was ascertained as described in Section 4.2, and health states were defined as described in Section 3.2. Assumptions in relation to transitions to better states were applied as described in Section 4.6. The health state definitions were varied in sensitivity analysis, and waves 7-8 were also included in a sensitivity analysis. TILDA included only 11 recurrent events among stroke participants in wave 1-4, and we therefore did not replicate the analysis in TILDA.

Based on the estimates derived from ELSA, the risk of transitioning from NCI to CIND is only slightly elevated for recurrent strokes. Combining disability groups, the overall risk of transitioning from NCI to CIND was 9.7%, compared with 7.1% in the absence of recurrent stroke. However, the risk of transitioning from CIND to dementia appears to be 2.3 times higher in the presence of recurring stroke (8.2% compared with 3.6% in the absence of a recurrent stroke). This estimate derived from ELSA are consistent with published estimates of the increased risk of dementia associated with recurrent stroke. This includes an estimate derived from a systematic review and meta-analysis (OR=2.3, 95% CI: 1.5–3.5)) [29], and from the ESPIRIT trial, which included TIA patients and non-disabling ischemic stroke (HR=2.45, 1.02-5.92) [8].

We also allowed for transition from NCI to dementia where there is a recurrent stroke, but this risk was very small (1.3%). These estimates are likely to be conservative as participants who transition to worse cognitive states as a result of their recurrent stroke are arguably more likely to drop out, relative to those who maintained their cognitive or physical function.

- S8.1: Alternative definitions for CI and dementia (As S3.1 above)
- S8.2: Include ELSA w7-8 (As S5.2 above)

4.8 P9: Mortality

There are two components of mortality to be estimated. Case fatality is defined as mortality within the first month post-stroke. Following this, mortality is estimated based on general population sex and age-specific mortality rates, with an increased mortality risk applied based on stroke and health state.

4.8.1 *P9_1: Case Fatality*

Case fatality can be defined as death within 21, 28, 30 days or and 1 month, and there are negligible differences depending on which time period is used [11]. 28-day case fatality in the North Dublin Population Stroke Study was 21% (n=485) (collected 2005-2006) [28]. This included ischaemic and haemorrhagic stroke, and first-ever (85%) and recurrent stroke [28]. Analysis by age indicates that under 80yrs, the fatality rate is 17%, compared with 29% after age 80.

A larger sample size of events, making more precise disaggregation by age possible, is available from English hospital episode statistics (HES) linked with national mortality statistics, and published in Seminog et al (2019) [37]. This study used data from and to examine stroke case fatality by age (10 year age groups) and sex for 2010, with a sample size of 93,867 events. The case-fatality rate for all ages in the Seminog et al dataset of was 25.4%, higher than the rate observed in NDPSS data. However, this could be accounted for by the older age of the patients in the Seminog et al data - a mean age of 79 for men and 84 for women, compared with an overall mean age of 70 in the NDPSS. Comparing these estimates to other published data, a systematic review by Feigin et al (2009) [11] found a mean case fatality of 19.8% among studies in high income countries conducted in 2000-2008, with the majority of studies falling within the range of 17 to 30%.

The Seminog et al estimates were used in the base case StrokeCog model, due to the disaggregation by age and sex. We assumed that this data was generalizable to the Irish context. However, we used the NDPSS data in sensitivity analysis. In the base case model, we assumed that recurrent strokes were associated with the same case fatality rate as first-ever stroke, but varied this in sensitivity analysis, by applying a 2-fold increase in risk, based on Perth Community Stroke Study[10].

Estimating reductions in stroke case fatality

There is considerable evidence to suggest that stroke case fatality has declined in recent decades. The Irish National Audit of Hospital mortality (INAHM) reports a 38% reduction in ischaemic stroke (IS) mortality 2009-2018, and a 17% reduction in SAH/ICH mortality over the same period. As IS accounts for 80% of total strokes in NDPSS, and SAH/ICH accounts for 20%, this relates to an overall decrease in mortality of 34%, or 3.4% per year. Seminog et al report a reduction of 40% in case fatality in England in the previous decade, 2001-2010. Similarly, Wafa et al [38] report an annual decline in case fatality of 3.8% for ischaemic stroke in the South London Stroke Register during 2000–2015.

We assume that the age-specific case fatality rates observed in 2010 in England also applies to Ireland in 2010. We then estimate an annual decline in the case fatality rate based on the INAHM (3.4%) until

2018, after which we assume that the rate remains stable. To simplify the programming, we apply the 2018 reduced rate in 2015-2017. In sensitivity analysis, we used the NDPSS data, and apply the same estimate of annual decline.

Sensitivity Analysis

- PSA: Case fatality rate (Beta distribution)
- S9.1.1: Use NDPSS data
- S9.1.2: Increased case fatality associated with recurrent stroke (2-fold increase based on Perth Community Stroke Study [10]

4.8.2 *P9_2 - P9_3: Background and excess mortality*

Baseline mortality rates by age and sex are obtained from the Central Statistics Office Vital Statistics Yearly Summary 2016 [39]. A review by Singh et al (2018) [12] concluded that mortality risk for stroke patients is 10-12 times higher than the matched general population in the first year, and remains 2-3 times higher in subsequent years. Studies included in the Singh review include the WHO MONICA study (data collection = 1982-1989) [40] and the Perth Community Stroke Study (data collection: 1989-1999) [41,42].

Although we can reasonably assume that the increased risk of death associated with stroke decreases with age (as the baseline risk is higher), there is limited availability of age-specific data. Brønnum-hansen et al report a standardized mortality ratio (SMR) of 3.14 for adults aged 25-69 in 1-5 yrs after stroke, and 1.99 for adults aged 70+ (WHO MONICA study; data collection = 1982-1989).

There is also evidence that post-stroke CIND and dementia increase mortality risk relative to those with no cognitive impairment post-stroke [13]. In the Helsinki Stroke Ageing and Memory (SAM) study, post-stroke dementia was a significant independent predictor of mortality, 3 months to 12 years post-stroke (HR=1.53, p = 0.003). In the same study, excluding cases with dementia and those who were not assessed, CIND was associated with an increased mortality risk relative to those with NCI, with a similar effect size (HR=1.63, p=0.01). As this was based on only a single study, in the base case we assumed no variation in mortality by level of cognitive impairment, but varied this in sensitivity analysis.

In the base case we assume no variation in age, sex or health state, and apply the all ages hazard ratio reported in the 5-year Perth Community Stroke data (RR = 2.5, 95% CI = 2.1-3). In sensitivity analysis, we explore the impact of varying the risk ratio by age and cognitive status. Although the Helsinki SAM study observed an increased risk for both CIND and dementia, to be conservative we apply an increased risk for dementia only.

Sensitivity Analysis

- PSA: Risk ratio (truncated lognormal distribution - truncated to ensure RR>1)
- S9.2.1: Variation in risk ratio by age (based on Brønnum-hansen data)
- S9.2.2: Variation in risk ratio by age and dementia status

4.9 Bias in case ascertainment and loss to follow up

It is likely that many of the datasets used to estimate the input parameters involved incomplete case ascertainment of post-stroke CIND and dementia. This participant group, particularly those with dementia, may be less likely to volunteer to participate in research studies or may be excluded due to difficulty participating.

The estimate of baseline community prevalence of stroke, post-stroke CIND and dementia, based on ELSA and TILDA, is likely to be an under-estimate. This is due to likely selection bias in these general population surveys against individuals who have had a stroke, particularly those with worse cognitive function. The comparison with figures generated through DISMOD (see Section 4.2) indicate that overall community prevalence of stroke is under-estimated by TILDA. This likely under-estimation of baseline prevalence has minimal impact on the projections for later years. However, it does indicate that estimates of percentage increases over the time period may over-estimate the extent of change, and should be treated with caution.

As noted in Section 4.4, the estimated prevalence of post-stroke dementia at 12 months based on ELSA data is lower than other data sources, and is therefore likely to be conservative. An alternative estimate based on OXVASC, which is likely to have more complete case ascertainment, was used in sensitivity analysis (S5.4).

As noted in Section 4.6 and 4.7, the estimates of risk of transition from NCI to CIND and from CIND to dementia, generated from ELSA data, are also likely to be conservative. Individuals who experienced cognitive decline may have been more likely to drop out of the study between interviews, relative to those whose cognition remained intact. The loss to follow up by health state is displayed in Table VIII. Overall, the loss to follow up was 21%, with individuals in the CIND no disability category having the highest rate of loss to follow up (37.6%). Logistic regression analysis indicated that CIND was associated with a higher odds of loss to follow up, relative to those in the NCI category (OR=2.6, $p<0.001$).

Of the 319 cases that were lost to follow up, the most frequent reason was refusal (n=119, 37.3%) followed by ineligible (n=104, 32.6%). Ineligibility includes participants who declined consent to be contacted for a subsequent survey wave. The next most common reasons were “unable to participate”, (n=40, 12.5%), “unable to contact” (n=22, 6.9%), “in institution” (n=10, 3.1%) and other (n=3, 0.9%). 21 (6.6%) were interviewed in the subsequent wave, but did not provide sufficient cognitive data for inclusion in this analysis.

5 Analysis

5.1 Calculating life expectancy

The life expectancy calculations followed the method outlined by the UK Office of National Statistics (https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandlifeexpectancies/methodologies/guidetocalculatingnationallifetables). Life table versions of the model were generated, for the cohort of stroke survivors at age 50, 65 and 75. These were closed versions of the model, with no incident or prevalent stroke included above the selected age, and no new 40 year old cohorts entering the model. This allowed us to follow a cohort of stroke survivors at a specific age and calculate life expectancy for that cohort.

First, the total number of person years lived at each individual age was calculated. This was equivalent to the number of people living with prevalent or incident stroke at that age. Assuming deaths occur evenly over the course of a year, this was calculated as an average of the current and following year. The total number of life years left to live was then calculated, by summing the total number of years lived from the selected age, to the oldest age in the lifetable (age 99). To calculate life expectancy for a given age, the number of life years left to live was divided by the total number of people at that age in the lifetable.

We also calculated dementia free life expectancy, or the number of expected years of life free of dementia. The total number of person years lived free of dementia at each individual age was first calculated. This was equivalent to the number of people living with prevalent or incident stroke, in a non-dementia state, at that age. Dementia free life expectancy was then calculated in the same way as above. Cognitive impairment free life expectancy, or the number of expected years of life free of both CIND and dementia, was also calculated using the same method.

5.2 Validation

Validation of the model was informed by the relevant ISPOR guidance (Eddy et al (2012), [43]). Transparency was ensured by providing sufficient non-technical documentation to provide an understanding of the model to a non-specialist reader, with further, more detailed, comprehensive technical documentation available. Face validity has been assured by regular consultation on the model structure and design with relevant experts who are members of the project steering group (e.g. stroke clinician, neuropsychologist, experienced stroke researchers). To obtain independent expert input, preliminary forms of the model have been presented at relevant national and international conferences. Verification of the technical aspects of the model has been achieved in StrokeCog by programming early versions of the model in two separate packages – Excel and R, and by maintaining complete and up-to-date code documentation.

External validation was also carried out by comparing model outputs to other data sources. Model predicted stroke deaths for 2017, by age group and sex, were compared against official statistics from

the CSO on stroke mortality for the same year (see statbank.cso.ie, Table VSA08). 2017 was the most recent year available from the CSO, and is also the first year in which recurrent stroke outcomes are counted in the model, and stroke deaths are therefore fully counted.

Data on hospital discharges for stroke in 2016-2019 was obtained from the HIPE system. 2015 data from this system was used to estimate rates of sex and age-specific stroke incidence for the model (see Section 4.3), but the data from 2016-2019 was not used as input data, and is therefore external. We applied the same selection criteria to the 2016-2019 data as we used for the 2015 data, excluding likely duplicate and non-resident discharges so that the number of discharges would reflect the number of stroke episodes. As this data still only captured hospital-based incidence, we ran a version of the model excluding out-of-hospital incident strokes.

We also validated the model projections for stroke prevalence against an alternative approach using the DisMod II tool [23] to generate baseline prevalence estimates. This tool, developed by the World Health Organisation, allowed us to generate an alternative estimate for baseline stroke prevalence from our estimates of stroke incidence, case fatality, background mortality and excess mortality in stroke survivors. It was not possible to use these DisMod prevalence estimates model, as these could not be disaggregated by setting to allow for application of nursing home and community specific estimates of cognitive impairment. However, we were able to compare modelled projections for overall stroke prevalence when the DisMod II baseline prevalence estimates were used, against our base case model estimates. This provided a validation of the extent to which our prevalence projections are consistent with our model input estimates for incidence and mortality.

6 GATHER Checklist

Item #	Checklist item	Reported on page #
Objectives and funding		
1	Define the indicator(s), populations (including age, sex, and geographic entities), and time period(s) for which estimates were made.	Main paper, P5
2	List the funding sources for the work.	Title page
Data Inputs		
For all data inputs from multiple sources that are synthesized as part of the study:		
3	Describe how the data were identified and how the data were accessed.	P15 of supplementary material; Source info tab in .xls files (available in Github repository[1]) for each parameter estimate
4	Specify the inclusion and exclusion criteria. Identify all ad-hoc exclusions.	Detailed information given on data sources for each parameter in supplementary Section 4
5	Provide information on all included data sources and their main characteristics. For each data source used, report reference information or contact name/institution, population represented, data collection method, year(s) of data collection, sex and age range, diagnostic criteria or measurement method, and sample size, as relevant.	
6	Identify and describe any categories of input data that have potentially important biases (e.g., based on characteristics listed in item 5).	
For data inputs that contribute to the analysis but were not synthesized as part of the study:		
7	Describe and give sources for any other data inputs.	Supplementary Section 4
For all data inputs:		
8	Provide all data inputs in a file format from which data can be efficiently extracted (e.g., a spreadsheet rather than a PDF), including all relevant meta-data listed in	.xls files for each input parameter,

	item 5. For any data inputs that cannot be shared because of ethical or legal reasons, such as third-party ownership, provide a contact name or the name of the institution that retains the right to the data.	including relevant metadata, available on Github[1]
Data analysis		
9	Provide a conceptual overview of the data analysis method. A diagram may be helpful.	P5, Fig 1, supplementary Section 3
10	Provide a detailed description of all steps of the analysis, including mathematical formulae. This description should cover, as relevant, data cleaning, data pre-processing, data adjustments and weighting of data sources, and mathematical or statistical model(s).	Analysis used to produce parameter estimates provided in supplementary section 4.
11	Describe how candidate models were evaluated and how the final model(s) were selected.	Process for model design described in supplementary section 2.
12	Provide the results of an evaluation of model performance, if done, as well as the results of any relevant sensitivity analysis.	Sensitivity analysis and validation results – P15
13	Describe methods for calculating uncertainty of the estimates. State which sources of uncertainty were, and were not, accounted for in the uncertainty analysis.	Main paper P7-8, more detail in Supplementary Table I & section 4
14	State how analytic or statistical source code used to generate estimates can be accessed.	R code used to generate the model available in github repository[1]. Code used to generate parameter estimates available from the corresponding author on request.
Results and Discussion		

15	Provide published estimates in a file format from which data can be efficiently extracted.	.xls files of results available in github repository[1]
16	Report a quantitative measure of the uncertainty of the estimates (e.g. uncertainty intervals).	Uncertainty intervals provided in Tables 2 and 4, and in .xls files[1]
17	Interpret results in light of existing evidence. If updating a previous set of estimates, describe the reasons for changes in estimates.	Discussion P16-17
18	Discuss limitations of the estimates. Include a discussion of any modelling assumptions or data limitations that affect interpretation of the estimates.	Discussion P17-18

[1] https://github.com/StrokeCog/EpiModel

7 Supplemental Tables

Table I: Parameter Assumptions and Sensitivity Analyses

Parameter	Assumptions	Uncertainty (Sensitivity Analysis)
P1. Population estimates/projections	M1F1: high fertility, high inward migration	PSA: N/A S1.1: M3F2 – high fertility, low migration
P2. Stroke prevalence		PSA: Prevalence rate (Beta)S2.1: TILDA estimate for age 50+, QNHS for age 40-49
P3. Prevalence of post-stroke cognitive impairment, dementia and disability	ELSA data applies to Irish population All NH residents have disability	PSA: Distribution of health states (Dirichlet) S3.1: Alternative definitions for CI and dementia S3.2: TILDA estimates
P4. Stroke incidence		**PSA:** Incidence rate (Beta); OOH rate (Beta); Recurrent stroke rate (Beta)
P5. Cognitive and disability health states at 1 year post-stroke (first-stroke)	ELSA data applies to Irish population Distribution up to 2 years post-stroke not different from distribution at 1 year No sex differences	PSA: Distribution of health states (Dirichlet) S5.1: Alternative definitions for CI and dementia S5.2: Include ELSA 7-8 S5.3: Disaggregate by sex
P6. Stroke recurrence	No age or sex variation Rate of recurrence declines after first year post-stroke and remains stable after that Data from SLSR applies to Ireland	PSA: Recurrence rate (Beta) S6.1: Disaggregate estimates by age S6.2: OXVASC estimates S6.3: Increased risk of recurrence for dementia
P7. Post-stroke transitions probabilities for cognitive and disability states	ELSA data applies to Irish population No variation by sex Cognition and disability do not improve after the first-year post-stroke	PSA: Transition probabilities (Dirichlet) S7.1: Alternative definitions for CI and dementia S7.2: Include waves 6-8 (different cognitive tests) S7.3: TILDA data S7.4: No transitions
P8. Cognitive and disability health states at 1 year post-stroke (recurrent stroke)	ELSA data applies to Irish population No variation by age or sex	PSA: Transition probabilities (Dirichlet) S8.1: Alternative definitions for CI and dementia S8.2: Include ELSA w7-8 S8.3: ESPIRIT data: recurrent stroke 2.5 times likely to transition to dementia
P9.1 Case fatality (30-day)	English hospital episode data applies to Ireland Case fatality rates declined 2010-2018, stable after that	PSA: Case fatality rate, Beta distribution S9.1.1: Use NDPSS data S9.1.2: Increased case fatality associated with recurrent stroke

P9.2 Background mortality		N/A
P9.3 Excess mortality after stroke (relative risk)	No variation by age or sex No increased risk associated with cognitive impairment or disability	PSA: Hazard ratio (log-normal) S9.3.1: Variation in risk ratio by age (data) S9.3.2: Variation in risk ratio by health state

Table II: Distribution of Health States for Prevalent Stroke in ELSA and TILDA

	TILDA wave 3 (2014/2015)	**%**	**ELSA wave 5 (2010/2011)**	**%**
	N = 134		N = 387	
NCI	85	63.4%	209	54%
CIND	38	28.3%	138	35.7%
Dementia	11	8.2%	40	10.3%
Disability (including dementia)	39	29.1%	189	48.8%

Table III: Cognitive and disability outcomes in the first interview post first ever stroke, ELSA and TILDA, compared with alternative sources

	Data Sources		**Meta-Analyses**			
	ELSA (n=287)	TILDA (n=60)	Pendlebury (population)	Pendlebury (hospital)	Barbay	Sexton
Total NCI %	57.5	45				
Total CIND %	33.5	36.7			36.4	39[a]
Total Dementia %	9.1	18.3	12.5	23	16.5	14 [a]
Total disability* %	40.8	41.7				

*Includes dementia. NCI = no cognitive impairment; CIND = cognitive impairment no dementia

[a]Based on homogenous group of high quality studies

Table IV: Cognitive and disability outcomes in the first interview post first-ever stroke, 0-2 and 1 year post-stroke

	ELSA 0-2 yrs post-stroke (n=287)	ELSA 1 yr post-stroke (n=116)
Total NCI %	57.5	55.2
Total CIND %	33.5	37.9
Total Dementia %	9.1	6.9
Total disability* %	40.8	42.3

*Includes dementia. NCI = no cognitive impairment; CIND = cognitive impairment no dementia

Table V: Cognitive and disability outcomes in the first interview post first ever stroke in ELSA, by sex

	Men (n=287)	Women (n=122)
Mean Age		
Total NCI %	49.3	66.7
Total CIND %	42.1	23.7
Total Dementia %	8.6	9.6
Total disability* %	36.8	45.2

***Includes dementia. NCI = no cognitive impairment; CIND = cognitive impairment no dementia**

Table VI: Annual transition probabilities (adjusted), ELSA wave 1-5

		Wave n + 1				
	All Ages	NCI no disability	NCI disability	CIND no disability	CIND disability	Dementia
Wave n	NCI no disability (n=409)	0.90	0.04	0.06	0.01	0.00
	NCI disability (n=191)	0.00	0.92	0	0.08	0.00
	CIND no disability (n=153)	0.00	0.00	0.90	0.07	0.03
	CIND disability (n=122)	0.00	0.00	0.00	0.96	0.04
	Dementia (n=55)	0.00	0.00	0.00	0.00	1.00

Table VII: Annual transition probabilities (adjusted), TILDA wave 1-4, n=311

		Wave n + 1				
	All Ages	NCI no disability	NCI disability	CIND no disability	CIND disability	Dementia
Wave n	NCI no disability (n=205)	0.90	0.04	0.05	0.00	0.00
	NCI disability (n=27)	0.00	0.87	0.00	0.13	0.00
	CIND no disability (n=44)	0.00	0.00	0.91	0.05	0.05
	CIND disability (n=27)	0.00	0.00	0.00	0.94	0.06
	Dementia (n=7)	0.00	0.00	0.00	0.00	1.00

Table VIII: Loss to follow up, ELSA wave 1-5

			Wave n + 1					
		All Ages	Included		Died		Lost to follow up	
			n	%	n	%	n	%
Wave n		NCI no disability (n=605)	476	78.7	18	3.0	111	18.3
		NCI disability (n=291)	244	83.8	10	3.4	37	12.7
		CIND no disability (n=335)	183	54.6	26	7.8	126	37.6
		CIND disability (n=228)	165	72.4	18	7.9	45	19.7

Table IX: Sensitivity analysis S1.1: M3F1 population projections – high fertility, low migration

		2016	95% Uncertainty Intervals		2035	95% Uncertainty Intervals		% diff 2016	% diff 2035
Stroke Prevalent Cases,	Base Case	14,073	11,888	16,667	18,276	17,367	19,201		
	S1.1	14,073	11,888	16,667	17,958	17,067	18,865	*0*	*1.7*

Table X: Sensitivity analysis S2.1: TILDA data for starting stroke prevalence for age 50-64

		2016	95% Uncertainty Intervals		2035	95% Uncertainty Intervals		% diff 2016	% diff 2035
Stroke Prevalent Cases, Age 40-89	Base Case	37,448	34,306	41,174	69,051	65,361	72,626		
	S2.1	33,453	30,717	36,352	66,993	63,752	70,451	*-10.7*	*3*

Table XI: Sensitivity analysis S3.2: TILDA data for distribution of health states in community prevalent stroke

		2016	95% Uncertainty Intervals		2035	95% Uncertainty Intervals		% diff 2016	% diff 2035
CIND Prevalent Cases	Base Case	11,193	9,848	12,882	25,274	22,431	28,275		
	TILDA	10,205	8,763	11,890	25,388	22,498	28,445	*-8.8*	*<1*
Dementia – Prevalent Cases	Base Case	4,875	4,191	5,611	12,442	10,135	14,989		
	TILDA	4,105	3,474	4,818	12,076	9,806	14,605	*-15.8*	*-2.9*

Table XII: Sensitivity Analyses S3.1, S5.1, S7.1, S8.1: Alternative definitions for CI and dementia

		2016	95% Uncertainty Intervals		2035	95% Uncertainty Intervals		% diff 2016	% diff 2035
CIND Prevalent Cases	Def 1, 1.5 SD (Base case)	11,193	9,848	12,882	25,274	22,431	28,275		
	1 SD	17,651	15,652	19,990	36,783	33,785	40,012	*57.7*	*45.5*
	Def 2	9,653	8,425	10,980	20,462	17,805	23,231	*-13.8*	*-19.0*
Dementia – Prevalent Cases	Def 1, 1.5 SD (Base case)	4,875	4,191	5,611	12,442	10,135	14,989		
	1 SD	4,823	4,204	5,607	11,921	9,683	14,281	*-1.1*	*-4.2*
	Def 2	6,395	5,589	7,394	17,034	14,407	19,869	*31.2*	*36.9*
CIND – Annual Incident Cases	Def 1, 1.5 SD (Base case)	2,487	2,239	2,766	3,832	3,546	4,091		
	1 SD	3,248	3,000	3,510	4,736	4,489	4,951	*30.6*	*23.6*
	Def 2	2,325	2,086	2,582	3,572	3,310	3,838	*-6.5*	*-6.8*
Dementia – Annual Incident Cases	Def 1, 1.5 SD (Base case)	828	677	993	1,715	1,427	2,005		
	1 SD	817	671	980	1,634	1,368	1,925	*-1.4*	*-4.7*
	Def 2	1,120	937	1,348	2,193	1,904	2,518	*35.3*	*27.9*

Notes: 1SD = Varying the cut-off for CIND by using 1 standard deviations (SD) below the mean, instead of 1.5 SD below the mean. Def 2 = In definition 2, a person who has had a stroke and severe cognitive impairment (2SD below the mean), and reports an impairment with either managing money or medications, is classified as having dementia. In definition 1, they must have an impairment in **both** managing money and taking medications. Definition 2 is therefore a more sensitive and less specific approach to defining dementia.

The definitions of CIND and dementia are used in parameter estimates for distribution of outcomes in prevalent stroke (P3), 12-month outcomes (P5), and health state transitions in the absence of recurrent stroke (P7) and with recurrent stroke (P8). To ensure consistency in model outputs, when we vary these definitions we vary them for all four parameters simultaneously.

Table XIII: Sensitivity analyses S5.2, S7.2, S8.2: Inclusion of ELSA data from wave 7 and wave 8

		2016	95% Uncertainty Intervals		2035	95% Uncertainty Intervals		% diff 2016	% diff 2035
CIND – Prevalent Cases	Base Case (w2-5)	11,193	9,848	12,882	25,274	22,431	28,275		
	w2-5, 7&8	10,981	9,624	12,608	24,317	21,800	27,253	*-1.9*	*-3.8*
Dementia - Prevalent Cases	Base Case (w2-5)	4,875	4,191	5,611	12,442	10,135	14,989		
	w2-5, 7&8	4,789	4,145	5,554	11,599	9,550	14,071	*-1.8*	*-6.8*
CIND – Annual Incident Cases	Base Case (w2-5)	2,487	2,239	2,766	3,832	3,546	4,091		
	w2-5, 7&8	2,302	2,090	2,536	3,655	3,434	3,878	*-7.4*	*-4.6*
Dementia – Annual Incident Cases	Base Case (w2-5)	828	677	993	1,715	1,427	2,005		
	w2-5, 7&8	747	622	913	1,554	1,310	1,826	*-9.7*	*-9.4*

Table XIV: Sensitivity analysis S5.3: Vary cognitive and disability outcomes at one year post-stroke by sex

		2016	95% Uncertainty Intervals		2035	95% Uncertainty Intervals		% diff 2016	% diff 2035
CIND – Prevalent Cases	Base Case	11,193	9,848	12,882	25,274	22,431	28,275		
	Vary by sex	11,166	9,821	12,830	25,738	22,354	29,081	*-0.2*	*1.8*
Dementia – Prevalent Cases	Base Case	4,875	4,191	5,611	12,442	10,135	14,989		
	Vary by sex	4,836	4,144	5,590	12,892	10,137	15,865	*-0.8*	*3.6*
CIND – Annual Incident Cases	Base Case	2,487	2,239	2,766	3,832	3,546	4,091		
	Vary by sex	2,439	2,171	2,738	3,694	3,389	3,968	*-1.9*	*-3.6*
Dementia – Annual Incident Cases	Base Case	828	677	993	1,715	1,427	2,005		
	Vary by sex	795	623	985	1,636	1,312	1,950	*-3.9*	*-4.6*

Table XV: Sensitivity analysis S5.4: OXVASC estimate for dementia prevalence at one year post-stroke

		2016	95% Uncertainty Intervals		2035	95% Uncertainty Intervals		% diff 2016	% diff 2035
Dementia – Prevalent Cases	Base Case	4,875	4,191	5,611	12,442	10,135	14,989		
	OXVASC	5,369	4,727	6,113	16,394	14,268	19,104	*10.1*	*31.8*
Dementia – Annual Incident Cases	Base Case	828	677	993	1,715	1,427	2,005		
	OXVASC	1,322	1,192	1,489	2,401	2,171	2,678	*59.6*	*40.0*

Table XVI: Sensitivity analysis S6.1: Recurrent stroke rate disaggregated by age

		2016	95% Uncertainty Intervals		2035	95% Uncertainty Intervals		% diff 2016	% diff 2035
Total Stroke Prevalent Cases	Base Case	37,448	34,306	41,174	69,051	65,361	72,626		
	S6.1	37,455	34,325	41,186	69,093	65,341	72,706	*<1*	*<1*
CIND Prevalent Cases	Base Case	11,193	9,848	12,882	25,274	22,431	28,275		
	S6.1	11,188	9,850	12,828	25,358	22,580	28,248	*<1*	*<1*
Dementia Prevalent Cases	Base Case	4,875	4,191	5,611	12,442	10,135	14,989		
	S6.1	4,856	4,190	5,653	12,368	10,070	15,103	*<1*	*<1*
Annual Incident Recurrent Stroke	Base Case	1,105	944	1,290	2,009	1,729	2,348		
	S6.1	1,112	943	1,308	2,041	1,745	2,369	*<1*	*1.6*

Note: In this sensitivity analysis, we disaggregated the 12 month stroke recurrence rate by 3 age groups, <65, 65-74 and 75+, based on a published analysis of the SLSR [31]. We did not disaggregate the annual

Table XVII: Sensitivity analysis S6.2: OXVASC data source for recurrent stroke rate

		2016	95% Uncertainty Intervals		2035	95% Uncertainty Intervals		% diff 2016	% diff 2035
Total Stroke – Prevalent Cases	Base Case	37,448	34,306	41,174	69,051	65,361	72,626		
	OXVASC	37,490	34,355	41,230	69,174	65,411	72,793	*<1*	*<1*
(CIND) – Prevalent Cases	Base Case	11,193	9,848	12,882	25,274	22,431	28,275		
	OXVASC	11,149	9,755	12,771	25,198	22,411	28,236	*<1*	*<1*
Dementia Prevalent Cases	Base Case	4,875	4,191	5,611	12,442	10,135	14,989		
	OXVASC	4,842	4,204	5,633	12,445	10,005	15,381	*<1*	*<1*
Recurrent Stroke Incident Cases	Base Case	1,105	944	1,290	2,009	1,729	2,348		
	OXVASC	1,183	1,025	1,368	2,103	1,837	2,399	*<1*	*4.7*

Note: In this sensitivity analysis, we applied estimates of the recurrent stroke rate from OXVASC (10.5% up to 1yr post-stroke and 1.7% annually thereafter (n=1242). This compares to the base case rate of 7.1% at 1 year and an annual rate 2.3%. As with the base case model, a probabilistic sensitivity analysis based on the Beta distribution was performed for both parameters.

In addition, in the model stroke patients are not classified as having dementia until 12 months post-stroke. There was an increase in the projected number of incident recurrent strokes in 2035 (+10.8%), but minimal impact on overall projected prevalent cases of stroke, post-stroke CIND and post-stroke dementia

Table XVIII: Sensitivity analysis S6.4: Increased risk of recurrence for dementia

		% diff 2016	95% Uncertainty Intervals		2035	95% Uncertainty Intervals		% diff 2016	% diff 2035
Total Stroke Prevalent Cases	Base Case	37,448	34,306	41,174	69,051	65,361	72,626		
	S6.4	37,436	34,301	41,166	68,868	65,266	72,462	*<1*	*<1*
(CIND) Prevalent Cases	Base Case	11,193	9,848	12,882	25,274	22,431	28,275		
	S6.4	11,168	9,812	12,771	25,288	22,417	28,276	*<1*	*<1*
Dementia Prevalent Cases	Base Case	4,875	4,191	5,611	12,442	10,135	14,989		
	S6.4	4,865	4,207	5,585	12,304	10,007	14,721	*<1*	*-1.1*
Recurrent Stroke – Incident Cases	Base Case	1,105	944	1,290	2,009	1,729	2,348		
	S6.4	1,192	1,008	1,408	2,225	1,890	2,620	*7.9*	*10.8*

Note: This estimate was varied using probabilistic sensitivity analysis, based on a log-normal distribution. To be conservative, it was applied to the annual risk of recurrence after 12 months, not the estimate of recurrence within 12 months.

Table XIX: Sensitivity analysis S3.2: TILDA data for transition probability estimates

		2016	95% Uncertainty Intervals		2035	95% Uncertainty Intervals		% diff 2016	% diff 2035
CIND – Annual Incident Cases	Base Case	2,487	2,239	2,766	3,832	3,546	4,091		
	TILDA	2,818	2,468	3,242	4,051	3,745	4,337	*13.3*	*5.7*
Dementia – Annual Incident Cases	Base Case	828	677	993	1,715	1,427	2,005		
	TILDA	1,231	903	1,595	2,372	1,849	2,828	*48.7*	*38.3*

Table XX: Sensitivity analysis S7.4: No health state transitions in the absence of recurrent stroke

		2016	95% Uncertainty Intervals		2035	95% Uncertainty Intervals		% diff 2016	% diff 2035
CIND – Annual Incident Cases	Base Case	2,487	2,239	2,766	3,832	3,546	4,091		
	No transitions	1,653	1,486	1,822	2,683	2,426	2,939	*-33.5*	*-30.0*
Dementia – Annual Incident Cases	Base Case	828	677	993	1,715	1,427	2,005		
	No transitions	562	447	693	960	775	1,174	*-32.2*	*-44.0*

Note: As outlined in Section 2.1 the assumption that there is no transition between health states after 12 months post-stroke is not consistent with the available epidemiological evidence. However, this sensitivity analysis highlights how applying the assumptions used in previous modelling studies [1] could have resulted in an under-estimate of the projected incidence of post-stroke CIND and dementia.

Table XXI: Sensitivity analysis S9.1.1: NDPSS estimate of case fatality

		% diff 2016	95% Uncertainty Intervals		2035	95% Uncertainty Intervals		% diff 2016	% diff 2035
Total Stroke Prevalent Cases	Base Case	37,448	34,306	41,174	69,051	65,361	72,626		
	SA 9.1.1	37,514	34,405	41,245	69,414	65,517	73,155	<1	<1
Annual estimated stroke deaths	Base case	986	944	1,031	1,614	1,542	1,689		
	SA 9.1.1	875	771	994	1,411	1,241	1,592	-11.2	-12.6

Table XXII: Sensitivity analysis S9.1.2: Increased case fatality for recurrent stroke

		2016	95% Uncertainty Intervals		2035	95% Uncertainty Intervals		% diff 2016	% diff 2035
Total Stroke – Prevalent Cases	Base Case	37,448	34,306	41,174	69,051	65,361	72,626		
	SA 9.1.2	37,364	34,225	41,073	67,314	63,769	70,739	*<1*	*-2.5*
Annual estimated stroke deaths	Base case	986	944	1,031	1,614	1,542	1,689		
	SA 9.1.2	1,089	1,029	1,154	1,901	1,800	2,012	*10.5*	*17.8*

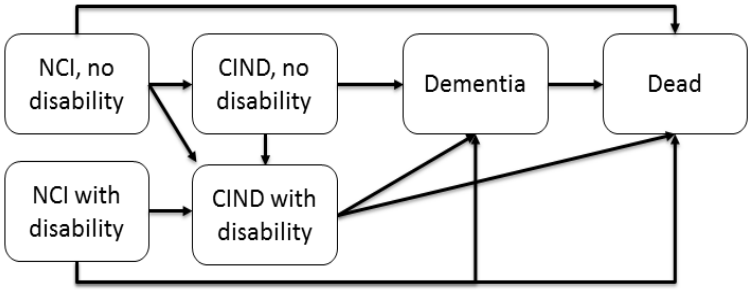
Table XXIII: Sensitivity analysis S9.2.1: Variation in risk ratio for background mortality by age

		2016	95% Uncertainty Intervals		2035	95% Uncertainty Intervals		% diff 2016	% diff 2035
Total Stroke – Prevalent Cases	Base Case	37,448	34,306	41,174	69,051	65,361	72,626		
	S9.2.1	38,131	34,991	41,867	71,394	68,666	73,989	*1.8*	*3.4*
Annual estimated non-stroke deaths	Base case	2,598	2,268	3,001	5,551	5,298	5,800		
	S9.2.1	2,308	2,066	2,578	5,296	5,100	5,495	*-11.2*	*-4.6*

Table XXIV: Sensitivity analysis S9.2.2: Relative risk for background mortality disaggregated by age and dementia status

		2016	95% Uncertainty Intervals		2035	95% Uncertainty Intervals		% diff 2016	% diff 2035
Total Stroke Prevalent Cases	Base Case	37,448	34,306	41,174	69,051	65,361	72,626		
	SA 9.2.2	37,702	34,572	41,363	68,974	66,212	71,749	*<1*	*<1*
Annual estimated non-stroke deaths	Base case	2,598	2,268	3,001	5,551	5,298	5,800		
	SA 9.2.2	2,494	2,220	2,795	5,472	5,262	5,695	*-4.0*	*-1.4%*
Dementia Prevalent Cases	Base case	4,875	4,191	5,611	12,442	10,135	14,989		
	SA 9.2.2	4,618	3,982	5,412	10,919	8,924	4,618	*-5.2*	*-12.2*

8 Supplemental Figures



NCI = No cognitive impairment; CIND = Cognitive Impairment No Dementia

Figure I: Simplified, illustrative representation of current models of CI disease progression

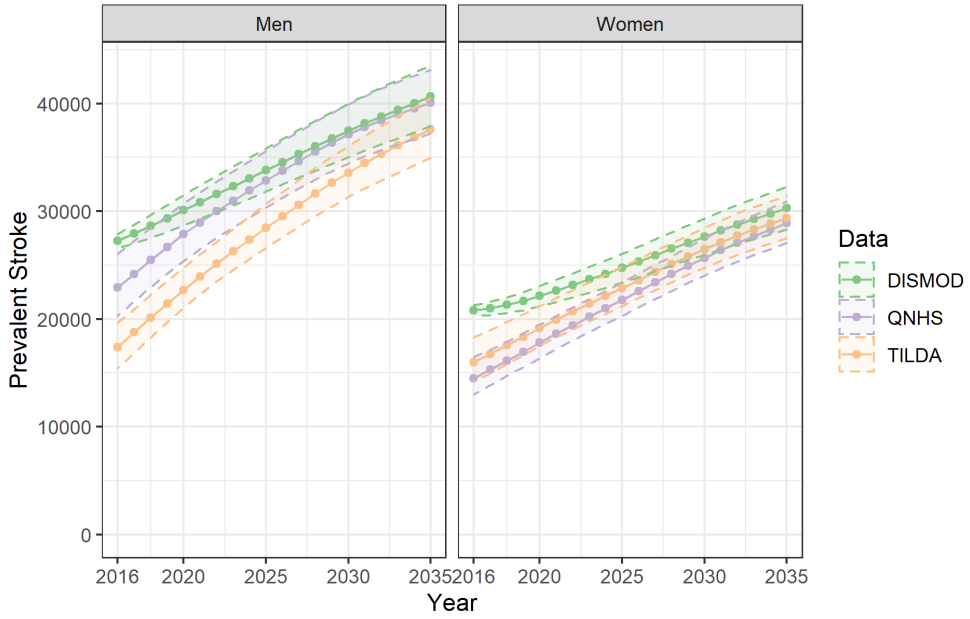


Figure II: Comparison of projected prevalence estimates generated using TILDA and QNHS data for 50-64 yrs age group, against estimates generated using DisMod

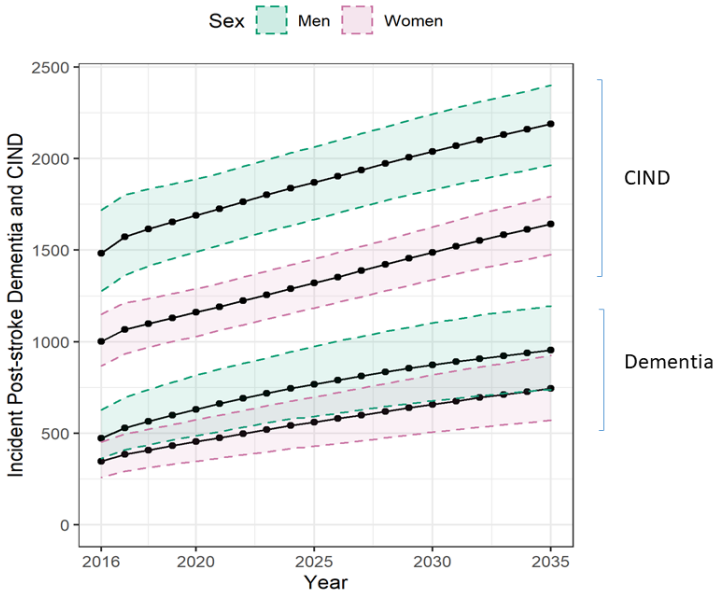


Figure III: Projected annual incident cases of post-stroke Dementia and CIND, 2016-2035, by sex, with 95% UI

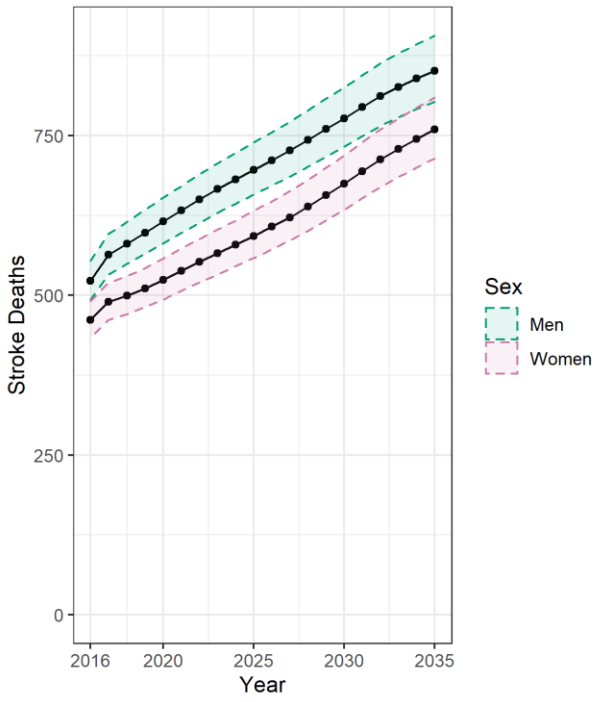


Figure IV: Estimated and projected deaths due to stroke 2016 to 2035 by sex, with 95% UI

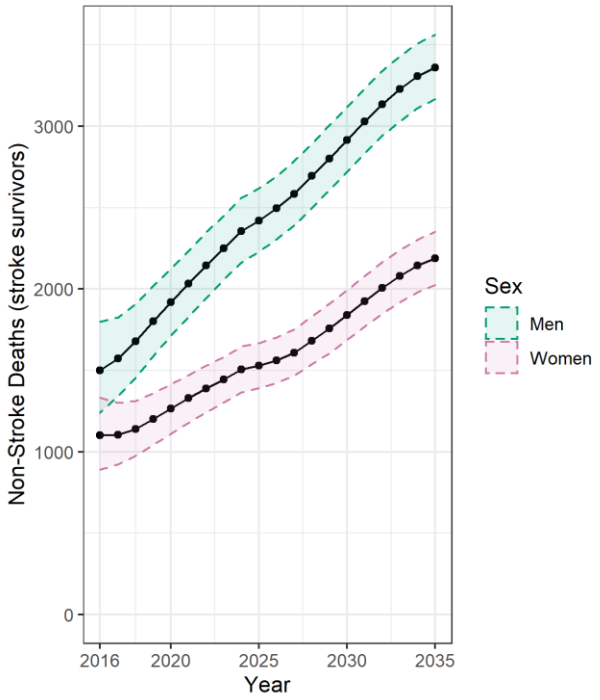


Figure V: Estimated and projected deaths due to other causes in stroke survivors, 2016 to 2035 by sex, with 95% UI

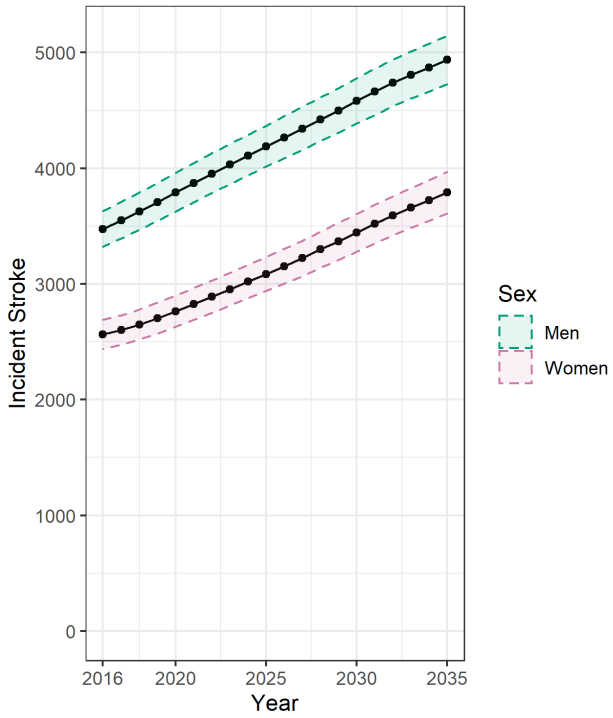


Figure VI: Estimated and projected first-ever incident strokes, 2016 to 2035 by sex, with 95% UI

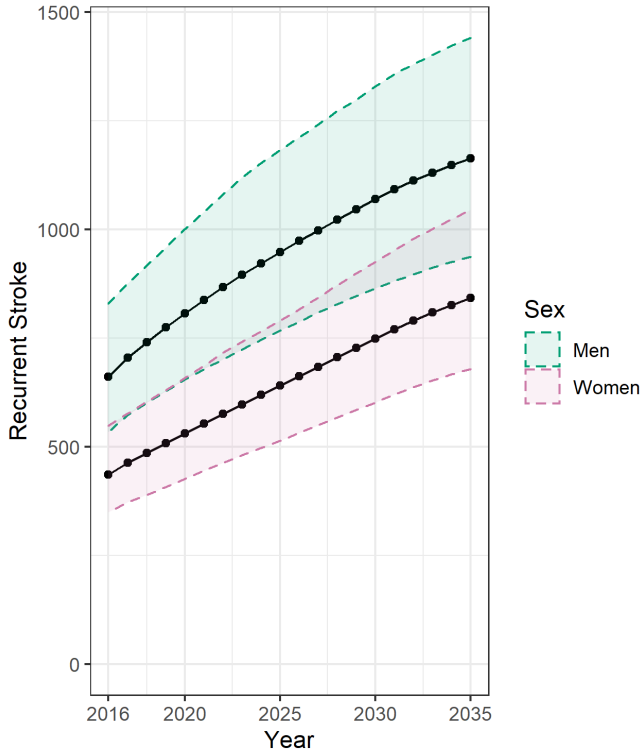


Figure VII: Estimated and projected recurrent strokes, 2016 to 2035 by sex, with 95% UI

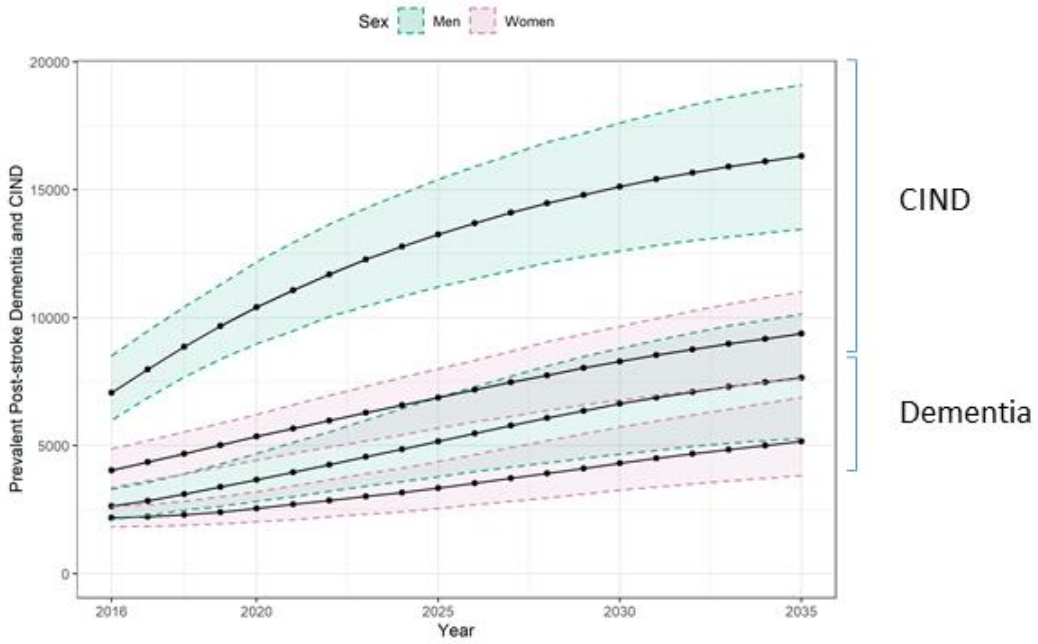


Figure VIII: Prevalent post-stroke dementia and CIND for sensitivity analysis S5.3: Vary cognitive and disability outcomes at one year post-stroke by sex

Note: This possible sex difference in post-stroke CIND should be treated with caution, as it is based on a single data source (ELSA) and may reflect sample-specific variation rather than population differences.

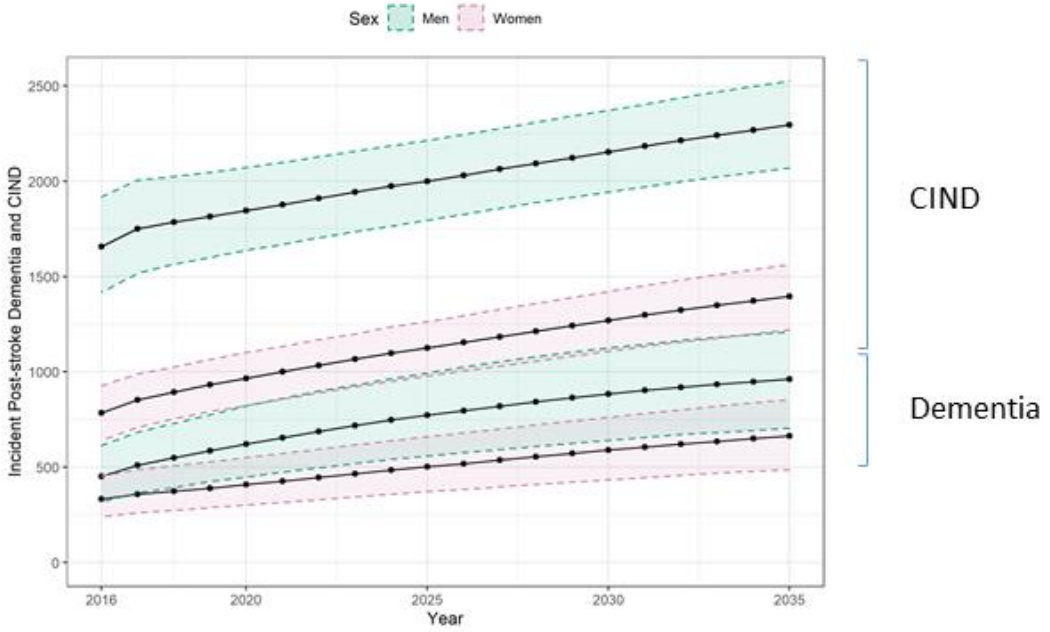


Figure IX: Incident post-stroke dementia and CIND for sensitivity analysis S5.3: Vary cognitive and disability outcomes at one year post-stroke by sex

Note: This possible sex difference in post-stroke CIND should be treated with caution, as it is based on a single data source (ELSA) and may reflect sample-specific variation rather than population differences.

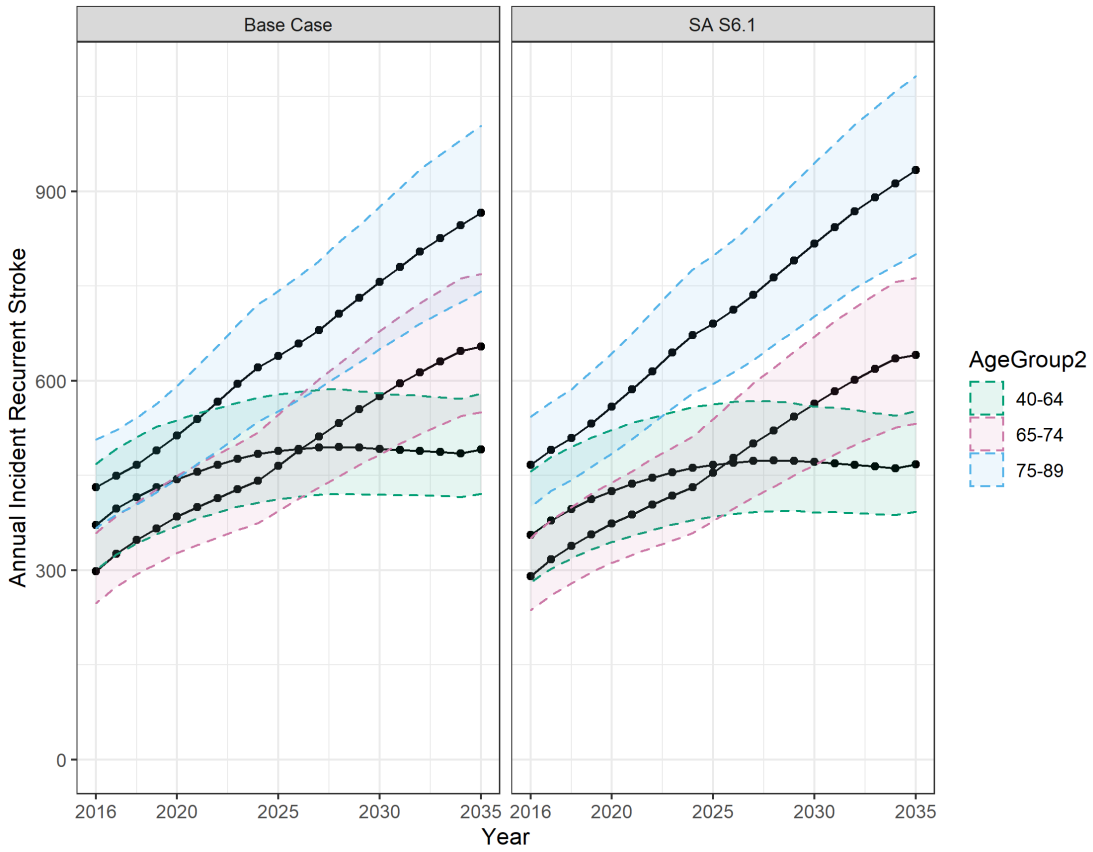


Figure X: Sensitivity analysis S6.1: Recurrent stroke rate disaggregated by age

Note: In this sensitivity analysis, we disaggreated the 12 month stroke recurrence rate by 3 age groups, <65, 65-74 and 75+, based on a published analysis of the SLSR [31]. We did not disaggregate the annual rate after 12 months by age, as there was insufficient data in the published paper to perform a PSA for the age disaggregated estimates.

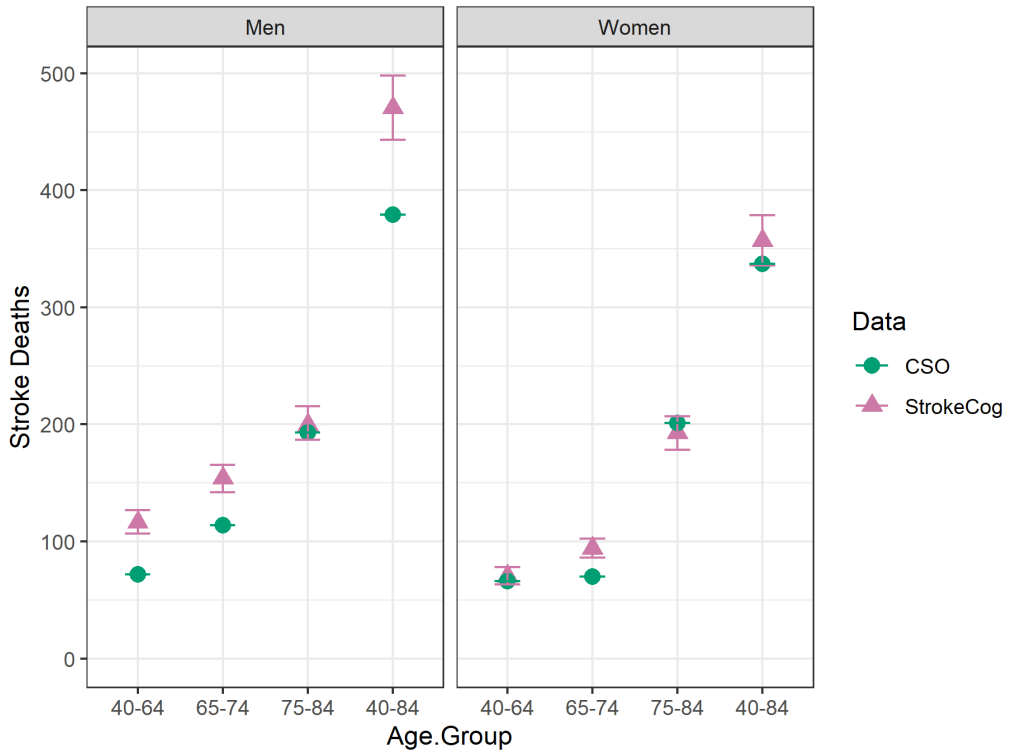


Figure XI: Estimated stroke deaths in StrokeCog model compared with stroke deaths recorded in CSO official statistics, 2017

Note: Figure XI displays the model-predicted stroke deaths for 2017, against the number of stroke deaths recorded in official statistics, by age group and sex. The estimates are close for women, with the total deaths within the uncertainty intervals of the model output estimate. However, the model appears to over-estimate deaths for men aged 40-74. Overall, the number of deaths recorded for men aged 40-84 (n=379) is 19% lower than the model estimate (n=470).

Figure XII: Estimated hospital-based stroke incidence in StrokeCog model compared with stroke discharges recorded in HIPE, age 40-89, 2016-2019

Figure XII displays the model-predicted hospital-based stroke incidence for 2016-2019 against the number of stroke hospital episodes reported in official statistics (the HIPE system). The estimate based on HIPE is generally within the uncertainty intervals of the model output estimate, with the exception of the prediction for men in 2019.

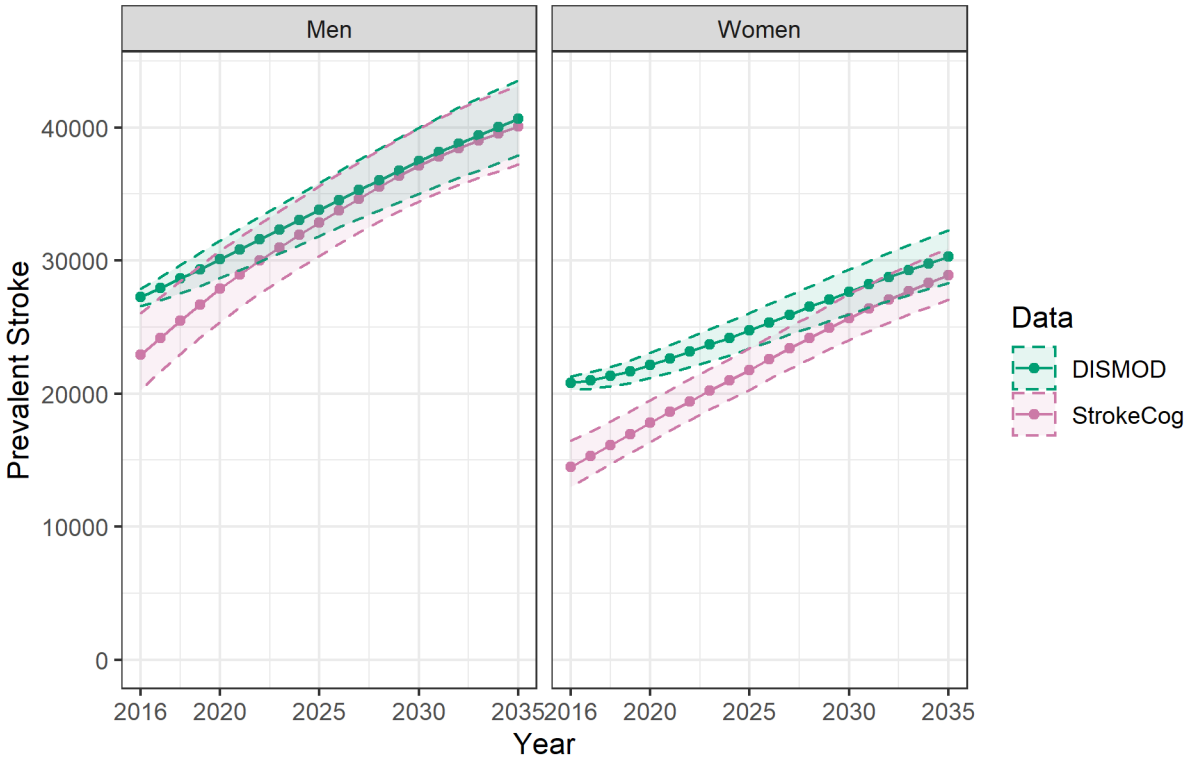


Figure XIII: Estimated stroke prevalence in base case StrokeCog model compared with estimates generated using DISMOD starting prevalence estimates

Results of the validation of the base case model predictions for stroke prevalence 2016-2035, against model predictions based on DisMod II starting prevalence estimates, are displayed in Figure XIII. The StrokeCog model underestimates baseline prevalence relative in 2016 to DisMod II, but by 2035 the estimates have converged.

9 Supplemental References

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