Can the effect of income on survival after stroke be explained by access to secondary prevention?

A mediation analysis on data from the Swedish stroke register

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Abstract

In Sweden, research has shown that socially underprivileged groups have poorer access to stroke care, both in the acute stage and secondary prevention after stroke, and are more likely to have adverse outcomes. The aim of this thesis is to study the causal mechanisms behind the association between low income and death after having a stroke. More specifically, to what extent is the effect of income on death mediated through treatment according to guidelines? To do this, mediation analysis have been applied to a data material from Riksstroke, the Swedish stroke register. The results of a mediation analysis rely on confounding assumptions that cannot be verified using observed data and it is important to quantify the effects of violations. Sensitivity analysis has therefore been applied to investigate how sensitive the results are to unobserved confounding. The results show that a small part of the effect of having low income on the probability of death 29 days to 1 year after stroke is mediated by treatment according to guidelines. This effect is significant positive for the study population. The same results were shown for patients with high risk of dying after stroke. However, there were no evidence of a mediated effect for patients with low risk of dying after stroke. The sensitivity analyses indicate that the estimated effects for the population are non-significant or reversed for certain levels of unobserved confounding. This must be considered when interpreting the results.

Sammanfattning

Titel: Kan effekten av inkomst på överlevnad efter stroke förklaras av tillgång till sekundärpreventiv behandling? – En mediationsanalys baserad på data från Riksstroke

Popular scientific summary

Each year, around 28 000 people in Sweden suffer a stroke. It is a leading cause of death and disability that affects all population groups and requires substantial health care resources. In Sweden, research has shown that socially underprivileged groups have poorer access to stroke care, both in the acute stage and secondary prevention after stroke, and are more likely to have adverse outcomes. It has also been shown that patients with low income have a lower probability of survival after stroke compared to patients with high income. These differences are established and it is of interest to further investigate why they occur and how they can be prevented.

The data material used in this thesis is from Riksstroke, the Swedish stroke register. This register covers all Swedish hospitals that admit acute stroke patients and around 25 000–26 000 admissions for stroke is registered each year. The main purpose of the register is to support quality improvement of the stroke care in Sweden.

The aim of this thesis is to study the association between low income and death after stroke by using a method called mediation analysis. This method enables a decomposition of the relationship between income and death into direct and indirect effects. We can therefore study to what extent the effect of income on death takes the pathway through another variable, if the patient received treatment according to guidelines. Mediation analysis requires assumptions that cannot be evaluated using the observed data and the results relies heavily on them. It is therefore important to investigate how sensitive the results are to violations of the assumptions.

The results showed that a small part of the effect of having low income on death after stroke goes through treatment according to guidelines. The effect was positive, which suggests that having low income decreases the probability of receiving treatment according to guidelines which in turn increases the probability of death after stroke. This result was also obtained for the study population and for patients with high risk of dying after stroke. However, this effect could not be established for patients with low risk of dying after stroke. When investigating how sensitive the results were to violations of the assumptions, it was shown that the effect could be non-significant or even reversed for certain levels of unobserved variables. This must be considered when interpreting the results.
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1 Introduction

Each year, around 28,000 people in Sweden suffer a stroke. This means that on average, three people are affected every hour (The Swedish Heart-Lung Foundation 2017). Stroke is the third most common cause of death behind heart attack and cancer. Given the amount of people affected and the severity of the disease, it requires substantial care. The annual number of days in hospital is close to one million, which makes stroke the one somatic, i.e. physical, disease that accounts for most treatment days in Swedish hospitals. The total societal cost of stroke has been estimated to around 18.3 billion SEK annually (Riksstroke a).

Stroke affects all population groups, but it is well-known that people with low socioeconomic status have an increased risk of suffering a stroke as well as having a fatal outcome (Addo et al. 2012). In Sweden, Sjölander et al. (2013) and Sjölander et al. (2015), have shown that socially underprivileged patients have poorer access to secondary prevention after stroke. Lindmark et al. (2014) show that stroke patients with high income have a higher probability of survival than patients in lower income groups. It is of interest to further investigate this inequality by studying the association between socioeconomic status and death after stroke using mediation analysis.

Mediation analysis is useful when it is believed that a third variable, called mediator, is responsible for a part of the effect of an exposure on an outcome. Thus, mediation analysis seeks to decompose this effect into two effects, a direct and indirect effect (VanderWeele 2015, 8). The effects are visualized in the directed acyclic graph (DAG) in Figure 1. The curved arrow represents the direct effect and the straight arrows represent the indirect effect. As shown, the indirect effect operates through an intermediate variable, the mediator.

![Figure 1: The relationship between the exposure, mediator and outcome.](image)

The estimation of direct and indirect effects relies on strong assumptions about no unmeasured confounding. Violations of these assumptions result in biased estimates. The assumptions cannot be evaluated using observed data and it is therefore necessary to use statistical methods for sensitivity analysis to evaluate how robust the estimates are to violations (VanderWeele 2015, 66).

1.1 Purpose and aims

The purpose of this thesis is to study the causal mechanisms behind the association between income and death after stroke. More specifically, it is of interest to investigate to what extent the effect of low income on death 29 days to 1 year after stroke is mediated through treatment according to guidelines. This will be done using mediation analysis. Furthermore, the aim also includes using sensitivity analysis to investigate how sensitive the results are to unobserved confounding.
2 Background and data

This section begins with an introduction to stroke. Then follows a description of the data material, the included variables and how the data has been modified.

2.1 Stroke

Stroke is a collective term for brain damages that are caused by either a blood clot or a brain hemorrhage, which means that there is a bleeding in the brain. The most common reason for a stroke is that a blood clot blocks the circulation in a specific part of the brain. This type is called ischemic stroke (Healthcare Guide 1177 2016). There are different types of blood clots that can cause a stroke. Some of them are developed within a blood vessel in the brain (thrombotic stroke) and others are formed somewhere else, for example in the heart, and are then transported to the brain through the bloodstream (embolic stroke) (The Swedish Heart-Lung Foundation 2018a). A stroke leads to a lack of oxygen in the brain and the symptoms vary depending on which part of the brain that is affected. However, common symptoms are numbness in the face, arm or leg, usually on one side of the body, confusion or difficulties speaking and understanding (Healthcare Guide 1177 2016).

2.1.1 Risk factors

There are a number of factors that are associated with the risk of having a stroke. Some of them are possible to treat or control, but others are not. Examples of significant factors are high blood pressure, smoking, diabetes, atrial fibrillation, high age or a sedentary lifestyle. A person that fulfills many of the risk factors has a higher probability to suffer a stroke and it is therefore important to investigate the total risk profile (The Swedish Heart-Lung Foundation 2018b). It is possible to adjust most of the above mentioned risk factors and thus lower the risk of having a stroke, but some of them cannot be controlled. An example of such a factor is high age. In Sweden 2017, the average age of having a stroke was 73 for men and 78 for women for patients registered in Riksstroke, the Swedish Stroke Register. The total average age was 75. The gender distribution of those who suffered a stroke were approximately equal; 53 % men and 47 % women (Riksstroke 2018a).

2.1.2 Treatment

When a stroke occurs, it is important for the patient to receive treatment at a hospital as soon as possible in order to decrease the risk of permanent brain damage. Patients that have suffered an acute ischemic stroke and arrive at the hospital in an early stage can be treated with medicine that dissolves blood clots. The effect of such medicines decreases with time and it is recommended that it should be given to a patient within 4.5 hours after their stroke. There is an increased risk of having a stroke for patients that have suffered one before and it is therefore important with follow-up care. A patient can lower his or her risk by certain lifestyle changes, such as quitting
smoking or exercising more, but it is also necessary to consider if treatment is needed. Possible treatments are antithrombotic drugs (reduces the formation of blood clots), antihypertensive drugs (treats high blood pressure) and statins (lowers cholesterol levels) (The National Board of Health and Welfare 2018a). If a patient suffers from atrial fibrillation, he or she can also be treated with anticoagulants (blood thinners) to reduce the risk for another stroke (The National Board of Health and Welfare 2018b).

2.2  Data

The data material is from Riksstroke, the Swedish stroke register. Riksstroke was established in 1994 and covers all Swedish hospitals that admit acute stroke patients. The registry contains information that is collected during the acute stage of a stroke and at follow-up 3 and 12 months after stroke. Each year, around 25 000–26 000 admissions for stroke is registered. The purpose of the register is to support quality improvement of the stroke care in Sweden (Riksstroke b).

The data used in this thesis is from 2009–2011 and consists of 40879 observations. Patients included have suffered a stroke for the first time and are followed up at least a year after the stroke. The data material only includes patients who have suffered an ischemic stroke. They were registered as living at home at the time of the stroke and being independent in activities of daily living (ADL). Independence in ADL is considered fulfilled if the patient is able to walk, go to the toilet and get dressed without assistance (Riksstroke 2018b). All patients in the data set are older than 44 years.

2.2.1 Variable Definitions

The exposure variable is low income. Income is defined as the individual’s share of the family disposable income. The variable for income is divided into two categories, low and mid to high income, where low income is classified as the bottom third of the income scale. Information about income is retrieved from the LISA database (Longitudinal integration database for health insurance and labor market studies), administered by Sweden Statistics. The mediator variable is treatment according to guidelines (TAG). Treatment according to guidelines is considered fulfilled for patients who suffered a thrombotic stroke if they received antihypertensive drugs, statins and antithrombotic drugs after their stroke. This is registered in Riksstroke. If a patient instead suffered an embolic stroke, they should receive the above mentioned medicines as well as anticoagulant drugs. The mediator is an indicator variable, coded yes if the patient received treatment according to guidelines and no otherwise. The outcome variable is death 29 days to 1 year after stroke. The date of death is retrieved from the Swedish Cause of Death Register, administered by the National Board of Health and Welfare. Note that the exposure, mediator and outcome are binary variables.
A number of covariates are included in the analysis to adjust for confounding. These are:

- Age
- Atrial fibrillation
- Conscious
- Diabetes
- Education level
- Living alone
- Sex
- Smoker

The variable conscious is the level of consciousness when the patient arrived at the hospital. It is based on the Reaction Level Scale and has two levels; conscious and unconscious (Starmark, Stålhammar, Holmgren 1988). Age is a continuous variable that measures age at the time of stroke. The others variables are categorical with either two or three groups. The binary variables are living alone, conscious, sex, atrial fibrillation and diabetes. Education level and smoker has three categories. Education level is divided into primary school, secondary school and university and the categories of smoker is yes, no or unknown.

2.2.2 Modification

The original data has been somewhat modified. To begin with, an unrealistic value of the variable age was removed (167). Patients that did not survive at least 29 days after the stroke were not included in the analysis due to the definition of the outcome variable. Thus, 2956 observations were deleted. The variables concerning treatment contained information about whether or not a patient received a specific medicine after the stroke and if he or she was deceased upon discharge. The observations where the patient was deceased, 302 cases, were removed since it is not possible for them to receive secondary prevention. Observations with missing values on the mediator TAG were also deleted (81 cases) and observations with missing values on any of the covariates (59-920 cases) or the exposure (315 cases) were not included in the analyses (a total of 1395 cases). The remaining data set consisted of 36 144 observations.
3 Theory

This section begins with an introduction to notation and the potential outcome framework. Then follows a description of effects, assumptions and identification of direct and indirect effects. Lastly, this section ends with an explanation of parametric modeling and estimation as well as the method used for sensitivity analysis.

3.1 Notation

The following notation will be used in this thesis. Let $Z$ denote the exposure, where $Z_i = 1$ if individual $i$ is exposed and $Z_i = 0$ if not. Let $M_i$ be the mediator and $Y_i$ the outcome. A set of observed covariates, i.e. a vector, are denoted by $X_i$. Unobserved confounders are denoted by $U_i$.

3.2 Potential outcome framework

In order to investigate the effect of an exposure on some outcome of interest, we would like to observe the outcome of an individual under different treatment assignments and compare the results. However, it is not possible to observe all potential outcomes for a unit since it only can receive one treatment at the same time (Rosenbaum and Rubin 1983). The potential outcome framework is used in causal inference to conceptualize what the outcome might have been if the treatment had been something other than it was (VanderWeele 2015, 4).

For an individual $i$, where $i=1,\ldots,N$, we can define two potential outcomes for a binary exposure; $Y_i(0)$ and $Y_i(1)$. $Y_i(0)$ is the outcome that would be realized for individual $i$ if he or she had not been exposed to the treatment and $Y_i(1)$ is the outcome that would be realized if he or she had been exposed (Imbens, Wooldridge 2009). The treatment effect for unit $i$ is $Y_i(1) - Y_i(0)$, but since only one of these outcomes can be observed, it is often of interest to estimate the average causal effect for the population instead. The average treatment effect (ATE) is defined as (Imbens and Wooldridge 2009)

$$ATE = E[Y_i(1) - Y_i(0)].$$

The approach for mediation analysis in this thesis is based on the potential outcome framework. In order to include the mediator, we can denote the potential value of $M$ for an individual $i$ under the exposure level $z$ as $M_i(z)$. Thereafter, let $Y_i(z, m)$ denote the potential outcome under exposure level $z$ and mediator level $m$. Note that $Y$ is a function of $Z$ and $M$ (Lindmark, de Luna and Eriksson 2018a).

3.3 Definitions of effects

By using the potential outcome framework, we can define three effects that are of interest in mediation analysis; controlled direct effect (CDE), natural direct effect (NDE) and natural indirect
effect (NIE). We are also interested in the total effect. The definition of the total effect is equal to the definition of the ATE (VanderWeele 2015, 57).

3.3.1 Controlled direct effect

The CDE measures the effect of the treatment Z on the outcome Y that does not take the pathway through the mediator M. Thus, it measures the effect of Z on Y when M is set to one specific value \( m \). It is defined as \( Y_i(1, m) - Y_i(0, m) \). However, it is difficult to obtain the effect for an individual and it is therefore more common to estimate the average effect for a population. The effects in the theory section will henceforth be presented as average effects. The average CDE is defined by

\[
CDE = E[Y_i(1, m) - Y_i(0, m)].
\]

It is also possible to condition on certain covariates, that is fixing the value of \( X_i \) so that \( X_i = x \). The definition then is \( E[Y_i(1, m) - Y_i(0, m) | x] \) (VanderWeele 2015, 57-58).

The CDE is commonly used in practical settings when it is of interest to intervene on the mediator M. By intervening, we want to change the effect of the exposure on the outcome. This might for example be the case when working with policies (VanderWeele 2015, 50).

3.3.2 Natural direct and indirect effect

The NDE has similarities with the CDE, but there is a difference in how the level of M is fixed. When estimating the NDE, M is fixed for every individual to the level it would have been if the exposure had been zero (VanderWeele 2015, 58). This means that the mediator can vary as it naturally would in the absence of the exposure (Lindmark, de Luna and Eriksson 2018a). The NDE is defined by (VanderWeele 2015, 58)

\[
NDE = E[Y_i(1, M_i(0)) - Y_i(0, M_i(0))].
\]

When estimating the NIE it is assumed that the exposure Z is fixed so that Z=1. The mediator is changed from the value it would have been if Z=1 to the value it would have been if Z=0 and the outcomes are thereafter compared. The NIE is defined by

\[
NIE = E[Y_i(1, M_i(1)) - Y_i(1, M_i(0))].
\]

Note that the indirect effect would be zero if \( M_i(1) = M_i(0) \). The exposure has to affect the mediator and this change has to in turn change the outcome in order for it to be nonzero. The NDE and NIE can also be defined conditional on covariates in the same way as the CDE (VanderWeele 2015, 58).
The NDE and NIE are used as estimates when we are interested in evaluating pathways and causal effects. It is possible to relate the natural direct and indirect effect to the total effect (TE) by using the definitions based on the potential outcome framework. The sum of NDE and NIE equals the total effect (TE), that is $TE = NDE + NIE$ (Pearl 2014).

### 3.3.3 Proportion mediated

The NIE and TE can be used in order to evaluate how much of the total effect of $Z$ on $Y$ that operates through $M$, i.e. the importance of the pathway through the intermediate variable. This is done by a measure called proportion mediated (PM). When effects are on the difference scale, it is defined as

$$PM = \frac{NIE}{TE}.$$

The PM can be a useful summary, but it has certain disadvantages. For example, it should not be used when the NDE and NIE have different directions, e.g. the NDE is negative and the NIE is positive. The reason for this is that the proportion value can be negative or greater than one and thus not be interpreted. It is also a very variable measure and the associated confidence intervals are generally wide (VanderWeele 2015, 47-48).

### 3.4 Assumptions

Certain assumptions need to be fulfilled in order to estimate direct and indirect effects using observed data. To begin with, an assumption about consistency is made. This assumption concerns the fact that we are considering interventions on the exposure and mediator when estimating direct and indirect effects. The consistency assumption states that interventions to set $Z=z$ and $M=m$ does not have an effect for people where these values were naturally observed. This means that $Y(z, m) = Y$ if $Z=z$ and $M=m$ (Vansteelandt 2012). An assumption about no-interference is also made. We assume that the exposure value for one individual does not effect another individuals mediator or outcome (De Stavola et al. 2015).

#### 3.4.1 Confounding assumptions

Apart from the assumptions described above, we also need to make assumptions about confounding in order to give mediation effects a causal interpretation. There are three types of confounding in mediation analysis; exposure-mediator confounders, mediator-outcome confounders and exposure-outcome confounders. These are visualized in Figure 2 as $U_1$, $U_2$ and $U_3$, respectively (Lindmark, de Luna and Eriksson 2018a).
Figure 2: A DAG with Z, M, Y and the unobserved confounders U₁, U₂ and U₃.

The confounding assumptions can be written in various ways. In this thesis, the sequential ignorability assumption introduced by Imai, Keele and Yamamoto (2010) is used. Let \( X_i \) be a set of observed pre-exposure covariates for individual \( i \) and let \( \mathcal{X} \) denote the range of values \( X_i \) can take (\( \mathcal{X} \) is the support of \( X_i \)). Pre-exposure means that the exposure does not affect the covariates. Then, the assumption consists of the following two statements:

\[
\begin{align*}
\{Y_i(z', m), M_i(z)\} & \perp \perp Z_i | X_i = x, \\
Y_i(z', m) & \perp \perp M_i(z) | Z_i = z, X_i = x,
\end{align*}
\tag{1}
\]

where \( 0 < P(Z_i = z | X_i = x) \) and \( 0 < P(M_i(z) = m | Z_i = z, X_i = x) \) for \( z = 0, 1 \), and all \( x \in \mathcal{X} \) and \( m \in \mathcal{M} \) (\( \mathcal{M} \) is the support of M).

Equation (1) states that the exposure assignment, \( Z_i \), is independent of potential outcomes and mediators, given the observed covariates. This means that there is no unobserved confounding of the exposure–outcome relationship or the exposure–mediator relationship. Equation (2) states that the mediator is independent of the potential outcome, given the observed treatment and pre-exposure covariates. Thus, it says that there is no unmeasured confounding of the mediator–outcome relationship (Imai, Keele and Tingley 2010). Note that it is also assumed that unobserved confounders, \( U_i \), are pre-exposure (Imai, Keele and Yamamoto 2010).

### 3.5 Identification of direct and indirect effects

The natural direct and indirect effect are identified when the assumptions about consistency, no-interference and sequential ignorability are fulfilled. The marginal NDE and NIE, i.e. averaged for the population, are then given by (Pearl 2014)

\[
\begin{align*}
NDE &= \sum_m \sum_x [E(Y_i | Z_i = 1, M_i = m, X_i = x) - E(Y_i | Z_i = 0, M_i = m, X_i = x)] \\
&\quad \times P(M_i = m | Z_i = 0, X_i = x)P(X_i = x) \\
NIE &= \sum_m \sum_x [P(M_i = m | Z_i = 1, X_i = x) - P(M_i = m | Z_i = 0, X_i = x)] \\
&\quad \times E(Y_i | Z_i = 1, M_i = m, X_i = x).
\end{align*}
\tag{3}
\]

\[
\begin{align*}
NDE &= \sum_m \sum_x [E(Y_i | Z_i = 1, M_i = m, X_i = x) - E(Y_i | Z_i = 0, M_i = m, X_i = x)] \\
&\quad \times P(M_i = m | Z_i = 0, X_i = x)P(X_i = x) \\
NIE &= \sum_m \sum_x [P(M_i = m | Z_i = 1, X_i = x) - P(M_i = m | Z_i = 0, X_i = x)] \\
&\quad \times E(Y_i | Z_i = 1, M_i = m, X_i = x).
\end{align*}
\tag{4}
\]
By using the result of (3) and (4), we can identify the NDE and NIE conditional on covariates. To do this, we do not sum over all \( x \). This gives the following expressions:

\[
NDE(x) = \sum_{m} \left[ E(Y_i | Z_i = 1, M_i = m, X_i = x) - E(Y_i | Z_i = 0, M_i = m, X_i = x) \right] \times P(M_i = m | Z_i = 0, X_i = x)
\] (5)

\[
NIE(x) = \sum_{m} \left[ P(M_i = m | Z_i = 1, X_i = x) - P(M_i = m | Z_i = 0, X_i = x) \right] \times E(Y_i | Z_i = 1, M_i = m, X_i = x).
\] (6)

The expressions in (3)-(6) are used when the mediator is binary. If the mediator is continuous, there are densities instead of probabilities and integrals instead of sums (Lindmark, de Luna and Eriksson 2018a).

3.6 Parametric estimation

In this thesis, it is of interest to estimate the NDE and the NIE using an approach based on parametric estimation. This means that we specify models that are used as the basis for the NDE and NIE estimates. Three models are specified; an exposure, a mediator and an outcome model, where the response variable is the exposure, the mediator and the outcome, respectively. It is the mediator and outcome model that are included in the estimation of direct and indirect effects. The exposure model is used in the sensitivity analysis. When the mediator and outcome variable are binary, it is possible to use e.g. logistic regression or probit regression to model them. The sensmediation package in R (Lindmark 2018) uses probit regression and the estimated effects are given on the risk difference scale (Lindmark, de Luna and Eriksson 2018a). Probit regression are used to model the inverse of the cumulative distribution function of the standard normal distribution (Liao 1994, 21).

Let \( M_i \) and \( Y_i \) be binary variables. Note that \( Z_i \) is also binary. Assume that \( M_i \) and \( Y_i \) can be modeled by \( M_i = I(M_i^* > 0) \) and \( Y_i = I(Y_i^* > 0) \), where

\[
M_i^* = \beta_0 + \beta_1 Z_i + \beta_2^T X_i + \beta_3^T Z_i X_i + \eta_i
\] (7)

and

\[
Y_i^* = \theta_0 + \theta_1 Z_i + \theta_2 M_i + \theta_3 M_i Z_i + \theta_4^T X_i + \theta_5^T Z_i X_i + \theta_6^T M_i X_i + \epsilon_i.
\] (8)

\( I(A > 0) \) is an indicator variable that equals 1 if \( A > 0 \) and 0 if \( A < 0 \). A is a general term. It is assumed that the error terms, \( \eta_i \) and \( \epsilon_i \), are i.i.d. standard normal random variables. The models can then be expressed by

\[
E(M_i | Z_i = z, X_i = x) = P(M_i = 1 | Z_i = z, X_i = x) = \Phi(\beta_0 + \beta_1 z + \beta_2^T x + \beta_3^T z x),
\] (9)

\[
E(Y_i | Z_i = z, M_i = m, X_i = x) = \Phi(\theta_0 + \theta_1 z + \theta_2 m + \theta_3 z m + \theta_4^T x + \theta_5^T z x + \theta_6^T m x + \theta_7^T z m x).
\] (10)
Φ(·) is the standard normal cumulative distribution function, i.e. the link function. Equation (9) and (10) can be substituted into (5) and (6) in order to receive expressions for the conditional NDE and NIE. This gives:

\[
\begin{align*}
NDE(x) &= \{\Phi(\theta_0 + \theta_1 + (\theta_4^T + \theta_5^T)x) - \Phi(\theta_0 + (\theta_4^T x))\}(1 - \Phi(\beta_0 + \beta_2^T x)) \\
&\quad + \{\Phi(\theta_0 + \theta_1 + \theta_2 + \theta_3 + (\theta_4^T + \theta_5^T + \theta_6^T + \theta_7^T)x) - \Phi(\theta_0 + \theta_1 + (\theta_4^T + \theta_5^T)x)\}\Phi(\beta_0 + \beta_2^T x) \\
nIE(x) &= \{\Phi(\theta_0 + \theta_1 + \theta_2 + \theta_3 + \theta_4^T + \theta_5^T + \theta_6^T + \theta_7^T)x) - \Phi(\theta_0 + \theta_1 + \theta_2 + \theta_3 + \theta_4^T + \theta_5^T)x)\} \\
&\quad \times \{\Phi(\beta_0 + \beta_1 + (\beta_2^T + \beta_3^T)x) - \Phi(\beta_0 + \beta_2^T x)\}
\end{align*}
\]

By fitting (7) and (8) with maximum likelihood (ML), it is possible to estimate the conditional direct and indirect effect. The marginal NDE can be estimated by

\[
\hat{NDE} = \frac{1}{n} \sum_{i=1}^{n} NDE(x_i),
\]

where \(n\) is the sample size and \(x_i\) is a vector of observed covariates for unit \(i\). The marginal NIE can be estimated in the same way (Lindmark, de Luna and Eriksson 2018a).

### 3.6.1 Interactions

There are interaction terms in both models in (7) and (8). In the mediator model (7), it is possible to include interactions between the exposure and the observed covariates \((Z_i X_i)\). In the outcome model (8), we can include interactions between the exposure and the mediator, the exposure and covariates and the mediator and covariates (the variables related to the coefficients \(\theta_3, \theta_5^T, \theta_6^T\), respectively).

It is of interest to include interactions for different reasons. The interaction between the exposure and mediator, in (8), is considered important because it can allow us to better capture the dynamics of mediation. Also, it makes the model more flexible, which can improve our understanding of the mediated effect. Interactions including the covariates might help to further control for confounding (VanderWeele 2015, 47). They can also be added to the models in order to evaluate if the effect of a cause on an outcome differs for different types of individuals (VanderWeele 2015, 9). For example, an interaction between low income and sex in the mediator model can be used to assess if the effect of having low income on receiving treatment according to guidelines differs for men versus women.

### 3.7 Sensitivity analysis

The results of estimating the direct and indirect effects rely on the assumptions mentioned in Section 3.4. Unobserved confounding is common and it is therefore necessary to quantify the effect of violations. This is done by a sensitivity analysis (VanderWeele 2015, 66).
The sensitivity analysis in the sensmediation package (Lindmark 2018) evaluates mediator-outcome, exposure-mediator and exposure-outcome confounding. The analysis is based on the error terms of the exposure, mediator and outcome models. More specifically, on the correlations between them. The correlations are made part of the estimation of the regression parameters, which are the basis for the estimates of the direct and indirect effects. The correlations thus allows us to perceive the effect of unobserved confounding on direct and indirect effects (Lindmark, de Luna and Eriksson 2018a). The method is illustrated using mediator-outcome confounding and the estimated conditional NIE in Section 3.7.1 below.

3.7.1 Point estimates and confidence intervals for unmeasured confounding

Assume that the mediator and exposure can be modeled as in (7) and (8). The error terms of the mediator and outcome model, \( \eta_i \) and \( \epsilon_i \), are uncorrelated if there are not any unobserved mediator-outcome confounding and correlated if there is. Assume that \( \eta_i \) and \( \epsilon_i \) are bivariate standard normal distributed and that their correlation is denoted by \( \rho_{\eta \epsilon} \). Then, \( \rho_{\eta \epsilon} = 0 \) if there is no unobserved confounding of the mediator-outcome relationship and \( \rho_{\eta \epsilon} \neq 0 \) otherwise (Lindmark, de Luna and Eriksson 2018a).

In order to examine the effect of unmeasured mediator-outcome confounding on the estimated NIE(\( x \)), we use a modified ML method introduced by Lindmark, de Luna and Eriksson (2018a). Let \( \beta \) and \( \theta \) denote the vectors of regression parameters in (7) and (8). Given the observed data, we can derive the log-likelihood of these regression parameters and \( \rho_{\eta \epsilon} \) as

\[
\ell(\beta, \theta, \rho_{\eta \epsilon}) = \sum_i (1 - m_i) \ln \left\{ \Phi_2(w_{2i} - \beta^T c_i; -\rho_{2i}^*) \right\} + \sum_i m_i \ln \left\{ \Phi_2(w_{2i}, \beta^T c_i; \rho_{2i}^*) \right\},
\]

where \( \Phi_2(\cdot, \cdot, \cdot) \) is the standard bivariate normal cumulative distribution function with three arguments. The first two are the means of the two random variables and the third is the correlation between them. And where \( w_{2i} \), \( c_i \) and \( \rho_{2i}^* \) are

\[
w_{2i} = (2y_i - 1)(\theta_0 + \theta_1 z_i + \theta_2 m_i + \theta_3 z_i m_i + \theta_4^T x_i + \theta_5^T z_i x_i + \theta_6^T m_i x_i + \theta_7^T z_i m_i x_i),
\]

\[
c_i = (z_i, x_i^T, z_i, x_i^T)^T,
\]

\[
\rho_{2i}^* = (2y_i - 1)\rho_{\eta \epsilon}.
\]

The modified ML procedure means that we maximize (13) with regards to \( \beta \) and \( \theta \) for a fixed \( \rho_{\eta \epsilon} = \tilde{\rho}_{\eta \epsilon} \). This gives the estimated regression parameters in (7) and (8), \( \hat{\theta}(\tilde{\rho}_{\eta \epsilon}) \) and \( \hat{\beta}(\tilde{\rho}_{\eta \epsilon}) \), under correlation \( \tilde{\rho}_{\eta \epsilon} \). Estimates of NIE(\( x \)) for a given level of mediator-outcome confounding can be obtained by inserting \( \hat{\theta}(\tilde{\rho}_{\eta \epsilon}) \) and \( \hat{\beta}(\tilde{\rho}_{\eta \epsilon}) \) in (11) and (12).
(1 - \alpha) \times 100\% \text{ CIs for NIE}(x) \text{ are constructed using the standard errors for } \hat{NIE}(x, \tilde{\rho}_{\eta \epsilon}). \text{ The delta method based on the estimated covariance matrices are used when calculating the standard errors. See Lindmark, de Luna and Eriksson (2018a) for a detailed description.}

A sensitivity analysis can also be performed for the marginal NIE. In order to study the effect of unobserved mediator-outcome confounding on the estimated marginal NIE, we can average the \( \hat{NIE}(x_i, \tilde{\rho}_{\eta \epsilon}) \) over the sample size. This gives \( \hat{NIE}(\tilde{\rho}_{\eta \epsilon}) \). Note that the standard errors used in the CIs are different when studying the marginal effect. We can also perform sensitivity analyses for the conditional and marginal NDE in the same way as shown for the NIE (Lindmark, de Luna and Eriksson 2018a).

The method is illustrated using mediator-outcome confounding, but the same steps apply for exposure-mediator and exposure-outcome confounding as well. The difference is which regression models that are being used. For example, the exposure and mediator model is used when investigating unmeasured exposure-mediator confounding. Note that we assume that the exposure can be modeled in a similar way as \( M_i \) and \( Y_i \) in (7) and (8). That is, \( Z_i = I(Z_i^* > 0) \) where

\[
Z_i^* = \alpha_0 + \alpha_1^T X_i + \xi_i
\]

and \( \xi_i \) are i.i.d. standard normal variables. The sensitivity analysis is performed for each type of unmeasured confounding separately under the assumptions that the other two does not exist (Lindmark, de Luna and Eriksson 2018a).

### 3.7.2 Choosing correlations

The sensitivity analysis can be performed for different intervals of correlation values. They are not the same in all mediation analyses because the choice depends on the performed study. An approach for choosing the range of correlations is explained below using mediator-outcome confounding, but the same approach can also be applied for unobserved exposure-mediator and exposure-outcome confounding as well.

An excluded confounder can have different effects on the mediator and outcome and the correlation induced can thus have a positive or negative effect. It has a positive effect when the excluded confounder affects the mediator and outcome in the same way, i.e. both positive or both negative. The correlation is negative when the effect goes in opposite directions, e.g. the excluded confounder has a positive effect on the mediator and a negative effect on the outcome. It is useful to have subject-matter knowledge when choosing the range of correlations. This makes it possible to consider variables that might be omitted from the analysis and their effect on the mediator and outcome (Lindmark, de Luna and Eriksson 2018b).
4 Method

This section presents the method for specifying probit regression models and performing mediation- and sensitivity analysis. All analyses were performed in R version 3.5.2 (R Core Team, 2018).

4.1 Models

To begin with, three probit regression models were built as the basis for further analyses; an exposure, a mediator and outcome model, where the response variable is the exposure, the mediator and the outcome, respectively. The first models included all available covariates and the variable $age^2$. $Age$ and $age^2$ were included because the squared variable captures a stronger effect for higher ages. The preliminary models were built in order to investigate which of the covariates that were significant. The significance level 0.05 was used for all statistical methods. In order for a covariate to be included in the final models, it should be significant in at least two of three models. A covariate might not have a significant relationship with all three response variables, but if it was significant in two models, it was considered important in order to adjust for confounding. Covariates with more than two categories, education level and smoker, were considered significant in a model if at least one category was significantly different from the reference category.

Interactions between the exposure and covariates were thereafter included in the mediator model. In the outcome model, interactions between the exposure and mediator, exposure and covariates and mediator and covariates were added. It was of interest to include significant interaction effects and non-significant interaction variables were therefore removed. Interactions with education level or smoker were considered significant if at least one category was significant. Non-significant variables were removed using backward stepwise selection, where the least significant interaction was removed until only significant interactions remained. The models with covariates that were significant in at least two models and significant interactions were used in the mediation and sensitivity analysis.

4.2 Mediation and sensitivity analysis

The mediation and sensitivity analysis was performed using the sensmediation package in R (Lindmark 2018). The prespecified models were used in order to obtain estimates of the marginal and conditional NDE and NIE, as well as the associated 95 % confidence intervals and p-values.

When estimating conditional natural direct and indirect effects, it is possible to condition on a set of covariates. In this thesis, it was of interest to estimate the effects for a high-risk patient and compare them with the effects for a low-risk patient. A high-risk patient is defined as a patient that has higher probability of dying 29 days to 1 year after stroke compared to a low-risk patient. All available covariates were included and different values was specified for high versus low risk patients. The signs of the estimated coefficients for the outcome model was used in order to evaluate which covariate values that were associated with higher versus lower probability of
dying. Covariates with a negative estimate indicated a lower probability of dying while covariates with a positive estimate indicated a higher probability.

A high risk patient was an old male who lives alone. Old is defined as the average age plus one standard deviation (85 years). His education level is primary school. He has diabetes, atrial fibrillation and it is unknown if he is a smoker. He was not conscious when he arrived to the hospital after stroke. A low-risk patient was a young female with a university education that does not live alone. Young is defined as the average age minus one standard deviation (63 years). She does not have diabetes or atrial fibrillation and she is not a smoker. She was conscious when arriving to the hospital after having a stroke.

A sensitivity analysis to the three different types of confounding, mediator-outcome, exposure-mediator and exposure-outcome, was also obtained by using the sensmediation package. The used method requires a specification of the sensitivity parameters that will be used. In this case, these were ranging from $-0.9$ to $0.9$ with $0.1$ as the steps. The reason for this is that it is a broad set of values that includes both positive and negative correlations.
5 Results

This section begins with descriptive statistics and the results from the estimated probit regression models. Then follows the mediation analysis for marginal and conditional direct and indirect effects and the sensitivity analysis for the marginal NIE and NDE.

5.1 Descriptive statistics

The included patients were on average 74.4 years old (standard deviation 11.1). The youngest patient was 45 years and the oldest was 104 years. There were 19877 men (53%) and 17662 women (47%). The number of patients with low income were 12408 (33%) and 36% of them received treatment according to guidelines. 40% of the patients with mid to high income received treatment according to guidelines. A total of 3690 patients died 29 days to 1 year after their stroke (10%). Patients with low income were more often dead 29 days to 1 year after stroke than patients with high income (12% compared to 9%).

5.2 Probit regression models

The estimated probit regression models are shown in Table 1 to 3. All available covariates are included, which means that they are significant in at least two models.

The exposure model is shown in Table 1. All covariates have a significant relationship with the response variable except atrial fibrillation. Variables that increase the probability for low income (positive estimates) are age$^2$, diabetes and the reference categories for smoker and education level, i.e. unknown and primary school. The other variables have negative estimates, which means that they decrease the probability of having low income.
Table 1: Estimated coefficients and standard errors for the exposure model. Low income is the response variable.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate (Standard error)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.9376*** (0.2665)</td>
</tr>
<tr>
<td>Age</td>
<td>-0.0284*** (0.0074)</td>
</tr>
<tr>
<td>Age^2</td>
<td>0.0003*** (0.0001)</td>
</tr>
<tr>
<td>Male</td>
<td>-0.6799*** (0.0149)</td>
</tr>
<tr>
<td><strong>Education level</strong></td>
<td></td>
</tr>
<tr>
<td>Primary school</td>
<td>Reference</td>
</tr>
<tr>
<td>Secondary school</td>
<td>-0.2848*** (0.0158)</td>
</tr>
<tr>
<td>University</td>
<td>-0.6802*** (0.0226)</td>
</tr>
<tr>
<td>Living alone</td>
<td>-0.1518*** (0.0155)</td>
</tr>
<tr>
<td>Conscious</td>
<td>-0.0725** (0.0269)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.0850*** (0.0183)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>-0.0170 (0.0170)</td>
</tr>
<tr>
<td><strong>Smoker</strong></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>Reference</td>
</tr>
<tr>
<td>Yes</td>
<td>-0.0030 (0.0351)</td>
</tr>
<tr>
<td>No</td>
<td>-0.0596* (0.0303)</td>
</tr>
</tbody>
</table>

***P < .001. **P < .01. *P < .05.

In the estimated mediator model (Table 2), it is shown that low income does not have a significant effect on receiving treatment according to guidelines. However, it is difficult to interpret this variable alone because it is included in interactions as well. There are three significant interactions in the model; between low income and living alone, low income and male and low income and atrial fibrillation. The interactions show that the effect of low income differs for different types of patients. For example, the effect is positive, 0.0369, for female patients that are not living alone and does not have atrial fibrillation. For patients who live alone, are male and/or have atrial fibrillation, the effect is instead negative, i.e. there is a decreased probability of receiving treatment according to guidelines. Patients with higher education level have a significantly lower probability of receiving treatment according to guidelines compared to patients that went to primary school. Variables that are related to a increased probability of treatment according to guidelines are age, conscious and diabetes. All variables are significant on the 5% level except smoker.
Table 2: Estimated coefficients and standard errors for the mediator model. TAG is the response variable

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate (Standard error)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-8.2361*** (0.2822)</td>
</tr>
<tr>
<td>Age</td>
<td>0.2344*** (0.0079)</td>
</tr>
<tr>
<td>Age$^2$</td>
<td>-0.0017*** (0.0001)</td>
</tr>
<tr>
<td>Male</td>
<td>0.0797*** (0.0197)</td>
</tr>
</tbody>
</table>

**Education level**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate (Standard error)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary school</td>
<td>Reference</td>
</tr>
<tr>
<td>Secondary school</td>
<td>-0.0403* (0.0169)</td>
</tr>
<tr>
<td>University</td>
<td>-0.0946*** (0.0221)</td>
</tr>
<tr>
<td>Living alone</td>
<td>-0.0453* (0.0196)</td>
</tr>
<tr>
<td>Conscious</td>
<td>0.4678*** (0.0332)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.3038*** (0.0193)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>-1.8581*** (0.0339)</td>
</tr>
</tbody>
</table>

**Smoker**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate (Standard error)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td>Reference</td>
</tr>
<tr>
<td>Yes</td>
<td>0.0391 (0.0379)</td>
</tr>
<tr>
<td>No</td>
<td>0.0651 (0.0338)</td>
</tr>
<tr>
<td>Low income</td>
<td>0.0369 (0.0290)</td>
</tr>
<tr>
<td>Low income×Living alone</td>
<td>-0.0923** (0.0332)</td>
</tr>
<tr>
<td>Low income×Male</td>
<td>-0.0701* (0.0343)</td>
</tr>
<tr>
<td>Low income×Atrial fibrillation</td>
<td>-0.1561* (0.0665)</td>
</tr>
</tbody>
</table>

***P < .001. **P < .01. *P < .05.

In the estimated outcome model (Table 3), there is a significant positive effect of the exposure *low income*. This means that having low income increases the probability of dying 29 days to 1 year after stroke. The mediator, *TAG*, cannot be interpreted alone since it is included in interactions. There are significant interactions between *TAG* and *age*, *TAG* and $age^2$ and *TAG* and the education level university. This means that the effect of treatment according to guidelines differs depending on the patients age and education level. Note that the interaction between *TAG* and the education level secondary school is non-significant and that the interaction between the exposure and mediator is not included in the model.

The category non-smokers are negatively associated with the probability of dying 29 days to 1 year after stroke compared to the category unknown. The other variables that represent risk factors, *diabetes* and *atrial fibrillation*, are positively associated with the probability of dying 29 days to 1 year after stroke. The positive estimate for *male* shows that male patients have a higher probability of dying 29 days to 1 year after stroke compared to female patients. All covariates are significant except *age*. 
Table 3: Estimated coefficients and standard errors for the outcome model. Death 29 days to 1 year after stroke is the response variable.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate (Standard error)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>−2.3509*** (0.5639)</td>
</tr>
<tr>
<td>Age</td>
<td>−0.0004 (0.0148)</td>
</tr>
<tr>
<td>Age²</td>
<td>0.0003** (0.0001)</td>
</tr>
<tr>
<td>Male</td>
<td>0.0997*** (0.0215)</td>
</tr>
<tr>
<td><strong>Education level</strong></td>
<td></td>
</tr>
<tr>
<td>Primary school</td>
<td>Reference</td>
</tr>
<tr>
<td>Secondary school</td>
<td>−0.0323 (0.0256)</td>
</tr>
<tr>
<td>University</td>
<td>−0.1681*** (0.0368)</td>
</tr>
<tr>
<td>Living alone</td>
<td>0.0603** (0.0214)</td>
</tr>
<tr>
<td>Conscious</td>
<td>−0.5190*** (0.0302)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.1813*** (0.0246)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.1690*** (0.0227)</td>
</tr>
<tr>
<td><strong>Smoker</strong></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>Reference</td>
</tr>
<tr>
<td>Yes</td>
<td>−0.0105 (0.0469)</td>
</tr>
<tr>
<td>No</td>
<td>−0.1686*** (0.0377)</td>
</tr>
<tr>
<td>Low income</td>
<td>0.0453* (0.0215)</td>
</tr>
<tr>
<td>TAG</td>
<td>2.6888* (1.0552)</td>
</tr>
<tr>
<td>TAG×Age</td>
<td>−0.0810** (0.0287)</td>
</tr>
<tr>
<td>TAG×Age²</td>
<td>0.0005* (0.0002)</td>
</tr>
<tr>
<td>TAG×Secondary school</td>
<td>0.0028 (0.0495)</td>
</tr>
<tr>
<td>TAG×University</td>
<td>0.1578* (0.0675)</td>
</tr>
</tbody>
</table>

***P < .001. **P < .01. *P < .05.

5.3 Estimated effects

The estimates of the marginal NDE and NIE and total effect (TE) are shown in Table 4. All effects are significant. The TE is positive (0.0075). This indicates that having low income increases the probability of dying 29 days to 1 year after having a stroke by 0.75%. The significant estimate for the NIE provides evidence that a part of the effect is mediated through the variable TAG. This means that low income affects TAG and that this change in turn changes the outcome, death 29 days to 1 year after stroke. The estimate for the NIE shows that the mediated effect is positive. The estimated proportion mediated, i.e. $\hat{NI}_E/\hat{T}E$, is 0.08. Thus, around 8% of the effect of low income on death 29 days to 1 year after stroke is mediated by TAG.
Table 4: Estimated marginal natural direct and indirect effect and total effect. 95 % confidence intervals (CIs) in parenthesis

<table>
<thead>
<tr>
<th>Natural direct effect</th>
<th>Natural indirect effect</th>
<th>Total effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0069*</td>
<td>0.0006**</td>
<td>0.0075*</td>
</tr>
<tr>
<td>(0.0004; 0.013)</td>
<td>(0.0002; 0.001)</td>
<td>(0.0010; 0.014)</td>
</tr>
</tbody>
</table>

***P < .001. **P < .01. *P < .05.

Table 5 shows the conditional effects for a high-risk patient. The NDE, NIE and TE are significant and positive. The effects are greater than the estimated marginal effects in Table 4. For example, the conditional TE for a high risk patient is 1.88% while the marginal TE is 0.75%. This indicates that there is a greater effect of having low income on the probability of dying 29 days to 1 year after stroke for a high-risk patient. The estimated proportion mediated is 0.04. This means that a smaller proportion of the total effect of low income on death 29 days to 1 year after stroke operates through TAG for a high-risk patient.

Table 5: Estimated conditional natural direct and indirect effect and total effect for a high risk patient. 95 % CIs in parenthesis

<table>
<thead>
<tr>
<th>Natural direct effect</th>
<th>Natural indirect effect</th>
<th>Total effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0180*</td>
<td>0.0007***</td>
<td>0.0188*</td>
</tr>
<tr>
<td>(0.0013; 0.035)</td>
<td>(0.0003; 0.001)</td>
<td>(0.0020; 0.036)</td>
</tr>
</tbody>
</table>

***P < .001. **P < .01. *P < .05.

The estimated conditional effect for a low-risk patient is shown in Table 6. The NDE, i.e. the effect of low income on death 29 days to 1 year after stroke not operating through TAG, is positive and significant. There is no evidence of an indirect effect, i.e. the effect operating through TAG, for a low-risk patient. The total effect is not significant. Note that in this case, it is not possible to calculate and interpret the estimated proportion mediated since it would be negative.

Table 6: Estimated conditional natural direct and indirect effect and total effect for a low risk patient. 95 % CIs in parenthesis

<table>
<thead>
<tr>
<th>Natural direct effect</th>
<th>Natural indirect effect</th>
<th>Total effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0016*</td>
<td>-0.0001</td>
<td>0.0015</td>
</tr>
<tr>
<td>(0.0001; 0.003)</td>
<td>(-0.0018; 0.000)</td>
<td>(-0.0000; 0.003)</td>
</tr>
</tbody>
</table>

***P < .001. **P < .01. *P < .05.

5.4 Sensitivity analysis for the natural direct and indirect effect

The sensitivity analysis for the marginal $\hat{NDE}$ and $\hat{NTE}$ (Table 4) are visualized in Figure 3 and 4. The figures show how sensitive the estimates are to unmeasured confounding. The grey areas in the figures represents 95 % confidence intervals. The light blue shaded areas corresponds to CIs
where the effect is reversed and dark blue areas are where the intervals include zero, i.e. where the effect is non-significant. The black line shows point estimates over the range of correlations, $[-0.9, 0.9]$. Note that the y-axis differs between the plots. See Appendix A1 and A2 for the sensitivity analysis plots for the estimated conditional direct and indirect effects in Table 5 and 6, respectively.

Figure 3 shows the sensitivity analysis for the estimated marginal NDE. The plot for mediator-outcome confounding shows that effect is non-significant when $\rho_{\eta\epsilon} = [0.2, 0.9]$. This indicates that the $\widehat{NDE}$ is sensitive to mediator-outcome confounding when unobserved confounders cause a positive correlation between $\eta$ and $\epsilon$. However, the effect is not reversed for any correlation value in the chosen interval. The black line showing the point estimates has a negative slope, which means that the $\widehat{NDE}$ is largest when $\rho_{\eta\epsilon} = -0.9$ and that it decreases for higher values of $\rho_{\eta\epsilon}$. The plot for exposure-mediator confounding shows that the estimated NDE is not sensitive to exposure-mediator confounding. The effect is not reversed or non-significant for any value of $\rho_{\xi\epsilon}$. The exposure-outcome confounding plot shows that the $\widehat{NDE}$ would be reversed if there are unobserved confounders that induce a positive correlation ($\rho_{\xi\epsilon} \geq 0.1$) between the error terms in the exposure- and outcome model. The effect would still be positive and significant in a situation where the induced correlation is negative.

*Figure 3: Sensitivity analysis for the marginal NDE.*
The plot for mediator-outcome confounding in Figure 4 shows that the \( \hat{NIE} \) would be reversed if there are unobserved confounders that induce a negative correlation (\( \rho_{\eta \epsilon} \leq -0.2 \)) between the error terms in the mediator- and outcome model. This indicates that it is quite sensitive to mediator-outcome confounding that induce a negative correlation but not so sensitive for unobserved confounding that induce a positive correlation. The plot for the exposure-mediator confounding shows a similar pattern to the plot with mediator-outcome confounding. The \( \hat{NIE} \) is largest when the correlation is 0.9 and decreases as the correlation goes towards −0.9. The effect is reversed when \( \rho_{\xi \eta} = [-0.9, -0.1] \), which means that the \( \hat{NIE} \) is sensitive to unobserved exposure-mediator confounding that cause a negative correlation between \( \xi \) and \( \eta \). The exposure-outcome confounding plot show that the \( \hat{NIE} \) is not sensitive to exposure-outcome confounding since there are not any areas where the effect is reversed or non-significant. The \( \hat{NIE} \) is largest when \( \rho_{\xi \epsilon} \approx -0.7 \) and decreases for higher values of the correlation.

**Figure 4:** Sensitivity analysis for the marginal NIE.
6 Discussion

In this thesis, the causal mechanisms behind the association between low income and death 29 days to 1 year after stroke have been evaluated by including the intermediate variable treatment according to guidelines. The results from the mediation analysis for the marginal NDE and NIE and total effect show that having low income increases the probability of dying 29 days to 1 year after stroke and that a quite small part of this effect is mediated by treatment according to guidelines. The indirect effect is positive. Since previous studies have shown that people with low socioeconomic status have poorer access to secondary prevention care after stroke, it is possible that having low income decreases the probability of receiving treatment according to guidelines and that this in turn increases the probability of dying 29 days to 1 year after stroke. The estimated proportion mediated was approximately 0.08 (8 %). This estimate needs to be interpreted with caution since the PM is a highly variable measure.

The estimated conditional effects for a high-risk patient was greater than the marginal ones. The total effect was for example more than twice the size compared to the total effect for the marginal estimate (1.88 % vs 0.75 %). Having low income is thus associated with a higher risk of dying 29 days to 1 year after stroke for high-risk patients compared to the study population (marginal effects). The proportion mediated is however smaller for high-risk patients which implies that the effect of treatment according to guidelines is of less importance than for the population. Note that the estimated PM needs to be interpreted with caution.

There was no evidence of an effect of low income on death 29 days to 1 year after stroke for low-risk patients. This might be because ”stronger”, i.e. low-risk, patients might have a higher chance of surviving 29 days to 1 year after stroke regardless of their income level. The NIE was not significant either. Thus, ”stronger” patients differs from the study population when investigating the association between income and death. This suggests that the conclusions for the study population, i.e. that there is an effect of low income on death 29 days to 1 year after stroke and a part of the effect is mediated through treatment according to guidelines, does not apply for this specific group of patients. Patients younger than 45 years old are not included in the study. This means that the conclusions for the study population cannot be made for them either. However, the result applies for the majority of stroke patients since most of them are older than 44 years when suffering a stroke.

The mediator in this thesis was treatment according to guidelines. It would have been possible to use another mediator; for example if the patient received medicine that dissolves blood clots within 4.5 hours after the stroke. It is possible that having low income affects the probability of receiving this medicine and that this change in turn affects the probability of dying. Another example of a mediator is the distance from a patients home to the nearest hospital. These variable was not included in the data material used in this thesis, but it should be possible to measure them and possible include in other studies.
The results from the estimates mentioned above relies on confounding assumptions. It is unlikely that the confounding assumptions are fulfilled since there probably exists unobserved variables that induce mediator-outcome, exposure-mediator and/or exposure-outcome confounding. An example of a unobserved confounding that might cause mediator-outcome confounding is if the patient suffers from another disease prior to the stroke. That might affect their given treatment and the probability of dying after stroke. However, in order to evaluate which variables that should be included to avoid unobserved confounding, a person with subject-matter knowledge should be consulted. It should also be noted that even if the unobserved confounders were identified, it is not certain that they can be measured and included in an analysis.

Furthermore, when stating the confounding assumptions as in this thesis, it is supposed that the observed covariates are pre-exposure. This assumption seems to be fulfilled in this study. The variables that precede the exposure, sex and education level, are guaranteed to be unaffected by low income and age is also unaffected. It is not likely that low income affects whether a patient has diabetes, atrial fibrillation, if he or she is a smoker or whether the patient is conscious when arriving to the hospital. The assumption might not be fulfilled if low income affects a patients living status, i.e. that it affects if a patient lives alone or not. However, it seems reasonable to assume that the assumption is fulfilled. It is also assumed that the unobserved confounders are not affected by the exposure. The potential unobserved confounder mentioned above, a prior disease, might be affected by low income. This could for example be the case if a patient does not afford to visit the hospital, or does not afford to miss work in order to visit the hospital. Then, he or she could develop diseases that increase the risk of dying. It is likely that there exists other unobserved confounders as well and they might also be affected by the exposure. Therefore, this assumption cannot be considered fulfilled.

The results of the sensitivity analysis were that the NDE was sensitive to unobserved confounding that induce positive correlation between the error terms in the mediator- and outcome model or the exposure- and outcome model. The NIE was sensitive to unobserved confounding that induce a negative correlation between the error terms in the mediator- and outcome model or the exposure- and mediator model. The results display the need for a sensitivity analysis when performing a mediation analysis, even when adjustment for observed covariates is made. There is a risk that the estimated marginal NDE and NIE, which were significant and positive, are non-significant or even negative if there are unobserved confounders that induce the type of correlation mentioned above. As previously mentioned, it was not possible to determine what the unobserved confounders might be. It was therefore also not possible to determine their effect on the error terms in the model, i.e. if they induce a positive or negative correlation. To do this, subject-matter knowledge is required.
References


Appendix

A1

Sensitivity analysis for the $\hat{NDE}(x)$ and $\hat{NIE}(x)$ for a high-risk patient.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure5.png}
\caption{Sensitivity analysis for the conditional NDE.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure6.png}
\caption{Sensitivity analysis for the conditional NIE.}
\end{figure}
Sensitivity analysis for the $\hat{NDE}(x)$ and $\hat{NIE}(x)$ for a low-risk patient.

**Figure 7:** Sensitivity analysis for the conditional NDE.

**Figure 8:** Sensitivity analysis for the conditional NIE.