

Spouses' long-term support to midlife stroke survivors

Consequences in a health economic perspective

Josefine Persson

Department of Clinical Neuroscience
Institute of Neuroscience and Physiology
Sahlgrenska Academy at University of Gothenburg



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josefine.persson.2@gu.se

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The most precious jewels you will ever have
around your neck are the arms of your children
-Author unknown-

To Melvin

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ABSTRACT

Spouses of midlife stroke survivors often experience demands on family roles and professional life due to the impact of stroke, however knowledge concerning spouses' support and the long-term consequences for their own health is limited. Hence, the overall aim of this thesis was to describe the long-term effects health related quality of life (HRQoL) of spouses of midlife stroke survivors' and the annual cost of the informal support provided. Data were collected from the study population at the seven-year follow-up of the Sahlgrenska Academy Study on Ischemic Stroke (SAHLSIS). Cohabitant dyads of 248 stroke survivors aged <70 at stroke onset and 245 controls were included in this study. HRQoL was assessed by the SF-36 and the time spent on informal support was assessed with a study specific time-diary. Spouses of dependent and independent stroke survivors were categorised according to their scores on the modified Rankin Scale.

Findings showed that spouses of dependent stroke survivors reported poorer physical, general and mental health in comparison to the spouses of independent stroke survivors and spouses of controls. The spouses' physical health was negatively related to their own age and the global disability of the stroke survivor, and the spouses' mental health was negatively related to the partners' global disability, level of depression and cognitive dysfunction as well as if the spouses experienced lack of social support. The dyads of stroke survivors and spouses reported similar role emotional and mental health, but poorer in comparison to the dyads of controls. Spouses of dependent stroke survivors reported nearly 15 hours of informal support per day, which corresponds to an estimated annual cost of €25,000. Spouses of independent stroke survivors reported less than one hour of informal support per day, corresponding to an estimated annual cost of €1,000. In conclusion, spouses of dependent midlife stroke survivors, reported lowered HRQoL and provides more informal support. Thus, to include the spouses' consequences in economic evaluations of healthcare interventions that seeks to reduce the dependency of stroke survivors could capture more of the total effects in dyads of stroke survivors.

Keywords: Stroke, Spouses, Health-related quality of life, Quality-adjusted life-years, Informal support, Time-diary, Cost analysis, Opportunity cost

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SAMMANFATTNING PÅ SVENSKA

Makar till personer som haft stroke ”mitt i livet” upplever ofta svårigheter att förena den stödjande rollen till sin partner med andra roller i familjelivet, samt med fritids- och yrkeslivet. Tidigare forskning har framförallt studerat konsekvenserna av makarnas stödjande roll under de första två åren efter strokeinsjuknande, medan kunskapen om makars stödinsatser och deras självupplevda hälsa är begränsad i ett längre tidsperspektiv. Utifrån detta var det övergripande syftet i denna avhandling att i ett längre tidsperspektiv undersöka sammanboende makars hälsorelaterade livskvalitet och vilket ekonomisk värde deras informella insatser i vård och stöd representerar. Data insamlades vid sjuårsuppföljningen av Sahlgrenska Academy Study on Ischemic Stroke (SAHLISIS). Undersökningsgruppen var 248 sammanboende par där personen med stroke insjuknat före 70 års ålder samt 245 sammanboende kontrollpar. Deltagarnas hälsorelaterade livskvalitet självskattades med frågeformuläret Short-Form 36. Personer som haft stroke indelades i grupper enligt modified Rankin Scale avseende grad av funktionell återhämtning och beroende och oberoende av stöd i vardagen. Uppgifter om den tid som makarna gav stöd till sin partner samlades in genom att makarna förde tiddagbok. Resultatet visade att makar till personer som haft stroke och som var beroende av stöd i vardagen rapporterade lägre självskattad fysisk, generell och mental hälsa i jämförelse med makar till personer som var oberoende av stöd samt makar till kontroller. Makarnas fysiska hälsa var negativt relaterad till egen ålder och partners grad av beroende och makarnas mentala hälsa var negativt relaterad till partners grad av beroende, nedstämdhet och kognitiva svårigheter samt om makarna upplevde av brist på socialt stöd. Paren rapporterade likvärdig emotionell rollfunktion och mental hälsa som var lägre än vad som rapporterats från de sammanboende kontrollparen. Makar med parter som var beroende stöd i vardagen rapporterade knappt 15 timmar informellt stöd per dag, vilket uppskattningsvis motsvarar detta ett årligt värde av 250 000kr. Makar med mer oberoende partner rapporterade att de gav knappt en timma stöd per dag, vilket uppskattningsvis motsvarar ett årligt värde på 10 000kr.

Sammanfattningsvis rapporterar många makar till personer som haft stroke ”mitt i livet” rapporterar lägre hälsorelaterad livskvalitet i ett långtidsperspektiv, framför allt om partnern är i behov av stöd i vardagen. Makar till personer som var beroende av stöd i vardagen rapporterade mer informellt stöd motsvarande ett betydligt högre årligt värde. Att erbjuda riktat stöd till makarna även lång tid efter insjuknandet kan antas öka möjligheten till förbättrad hälsorelaterad livskvalitet. Att även inkludera makarnas konsekvenser i hälsoekonomiska utvärderingar av vårdinsatser kan således fånga mer av den totala effekten för sammanboende par.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

- I. Persson J, Holmegaard L, Karlberg I, Redfors P, Jood K, Jern C, Blomstrand C, Forsberg-Wärleby G. Spouses of stroke survivors report reduced health-related quality of life even in long-term follow-up – Results from Sahlgrenska Academy Study on Ischemic Stroke. *Stroke* 2015;46;2584-2590.
- II. Persson J, Aronsson M, Holmegaard L, Redfors P, Stenlöf K, Jood K, Jern C, Blomstrand C, Forsberg-Wärleby G, Levin L-Å. Long-term QALY-weights among spouses of dependent and independent midlife stroke survivors. *Submitted manuscript.*
- III. Persson J, Levin L-Å, Holmegaard L, Redfors P, Svensson M, Jood K, Jern C, Blomstrand C, Forsberg-Wärleby G. Long-term cost of spouses' informal support for dependent midlife stroke survivors. *Brain and Behavior* 2017, *accepted for publication.*
- IV. Persson J, Levin L-Å, Holmegaard L, Redfors P, Jood K, Jern C, Blomstrand C, Forsberg-Wärleby G. Stroke survivors' long-term QALY-weights in relation to their spouses' QALY-weights and informal support: a cross-sectional study. *Submitted manuscript.*

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CONTENT

ABBREVIATIONS.....	IV
1 INTRODUCTION	1
1.1 A theoretical background of health economics	2
1.1.1 Cost analysis.....	3
1.1.2 Assessing the value of health in economic evaluations	5
1.1.3 Informal caregivers in economic evaluations.....	6
1.2 Stroke.....	7
1.3 Spouses of stroke survivors	9
1.4 Dyads of stroke survivors.....	10
1.5 Rationale for the thesis	11
2 AIM.....	12
3 SUBJECTS AND METHODS	13
3.1 Subjects.....	13
3.2 Assessments	14
3.2.1 Sociodemographic information.....	15
3.2.2 HRQoL and QALY.....	15
3.2.3 Stroke-related variables.....	16
3.2.4 The time-diary	19
3.3 Cost analyses	20
3.3.1 Sensitivity analyses.....	21
3.4 Statistical analyses.....	22
3.5 Ethical considerations	23
4 RESULTS.....	24
4.1 SAHLSIS baseline for the seven-year follow-up	24
4.2 Study population	25
4.2.1 Stroke-related variables.....	26
4.3 HRQoL of dyads of stroke survivors and controls	27
4.3.1 QALY-weights of dyads of stroke survivors and controls.....	29

4.3.2	Determinants of spouses' HRQoL and QALY-weights	29
4.4	Spouses' informal support	31
4.4.1	Validation of the time-diary	32
4.4.2	Informal support in hours per day	32
4.4.3	Annual cost of spousal informal support	35
5	DISCUSSION	37
5.1	HRQoL and QALY-weights.....	37
5.1.1	Spouses' physical health.....	37
5.1.2	Spouses' mental health.....	38
5.1.3	HRQoL of spouses of controls.....	39
5.1.4	HRQoL in a dyadic perspective	39
5.1.5	Determinants of spouses' HRQoL and QALY-weight.....	40
5.1.6	Methodological considerations.....	41
5.2	Spouses' informal support	42
5.2.1	Time spent on informal support	42
5.2.2	Cost of informal support	43
5.2.3	Methodological considerations.....	44
5.3	Spouses' consequences in economic evaluations.....	47
5.4	Overall methodological considerations	48
5.5	Ethical considerations	49
6	CONCLUSION	50
7	FUTURE PERSPECTIVES	51
	ACKNOWLEDGEMENT	53
	REFERENCES.....	55

ABBREVIATIONS

BI	Barthel Index
BNIS	The Barrow Neurological Institute Screen for Higher Cerebral Functions
CEA	Cost-effectiveness analysis
CI	Confidence interval
COI	Cost of illness
CUA	Cost-utility analysis
EQ-5D	EuroQol 5 Dimension
HADS	Hospital anxiety and depression scale
HRQoL	Health-related quality of life
ICD-10	International statistical classification of diseases
ICER	Incremental cost-effectiveness ratio
MMSE	Mini-mental state examination
mRS	modified Rankin Scale
NIHSS	National Institute of Health Stroke Scale
OR	Odds ratio
QALY	Quality-adjusted life-years
SAHLSIS	Sahlgrenska Academy Study on Ischemic Stroke
SD	Standard deviation
SF-36	Short form-36 health survey
SF-6D	Short form 6 domains
SG	Standard Gamble
TTO	Time Trade-Off
WTP	Willingness to pay

1 INTRODUCTION

How to deal with the consequences for informal caregivers in economic evaluations is a field that has been widely debated in the literature during the past decades. Nonetheless, the debate has thus far not reached any consensus or recommendations (1). This means that few economic evaluations with a societal perspective include the cost of informal support and the health effects with regard to the caregivers (2). The impact of not including the caregivers' consequences may lead to policy decisions with undesirable allocation effects (3) and ultimately poorer public health.

One important group to include in economic evaluations are informal caregivers who provide many hours of unpaid support (4). In the literature, different terms are used for persons who are closely related to a person with a disease or disability who are in need of care, such as informal caregivers, family caregivers, caregivers, next of kin and relatives (5). The health economic literature normally defines a person who support a family member, friend or neighbour as an informal caregiver (6-8). Hence, in this thesis the term "informal caregivers" will be used, although the focus in this thesis is on cohabitant partners to the stroke survivors, referred to as spouses.

Spouses of stroke survivors provide support to their partner to an extent that far exceeds what is normally offered by the society (9). Previous studies have mainly focused on spouses of older stroke survivors, whereas less is known about the lives of younger families. The focus in this thesis has been to investigate the long-term impact on health and cost of informal support for spouses of midlife stroke survivors. The rationale for highlighting this subgroup of informal caregivers was two-fold. Firstly, spouses of midlife stroke survivors often also have responsibilities for the family and an own professional life (10). Thus, spouses of younger stroke survivors may experience a greater conflict between the support provided to their partner and their regular daily family and household chores. Secondly, given that younger stroke survivors have longer survival time, also in line with the secular trend of decreasing risk of mortality (11), spouses must provide support to their partner over a longer period of time compared to older stroke survivors.

1.1 A theoretical background of health economics

Economics is the science of scarcity and choice. Resources are always scarce to some extent and choices have to be made between different alternatives. When a choice is made and resources are used on one alternative, they cannot be used for something else. Thus, the value of the best alternative use of that resources is referred to as the *opportunity cost* (6).

Health economics is a branch in economics that concern issues related to efficiency, effectiveness, value, and behaviour in the production and consumption of health and health care. Hence, health economists study the problems of scarcity as it arises with respect to health and health care. Choices have to be made between different alternatives on how to spend the scarce resources within the health care sector to maximise the health and welfare of the population. Thus, the opportunity cost is the value or benefit forgone by the alternative not chosen. Economic evaluations of health care interventions seek to estimate this opportunity cost to compare with the benefits of the alternatives (6, 7). Hence, economic evaluations are useful tools when evaluating cost-effectiveness of health care interventions to provide guidance for decision makers about how allocate the scarce resources to maximise health and welfare.

To evaluate the cost-effectiveness of new health care interventions with a cost-effectiveness analysis (CEA) or cost-utility analysis (CUA), the difference in costs are divided by the difference in effects between the new health care intervention and the comparative alternative. With the analytical techniques, CEA and CUA, health economists can assist decision making on how to prioritise the scarce resources within the health care sector. The difference between the two methods is that effects in a CEA are measured as natural units, for example as life years gained, meanwhile in a CUA the effects are measured as quality-adjusted life-years (QALY). QALY is a generic concept, which is the recommended outcome measure of effects in economic evaluations (7, 12, 13). A QALY combines both health status, often called QALY-weights, and life expectancy into the same outcome measure.

Figure 1 illustrates the incremental cost-effectiveness ratio (ICER) for a new health care intervention (A) in comparison with, for example, usual care (B). To estimate the cost-effectiveness of a new health care intervention, the cost for the new intervention is compared to the costs for usual care, and the QALYs for the new interventions are compared with the QALYs for usual care. The change in costs are divided by the change in QALYs for the new intervention compared to usual care gives a ratio to relate to the societal willingness to pay threshold (WTP) for a QALY gained.

$$ICER = \frac{Cost_A - Cost_B}{QALY_A - QALY_B} = < WTP \text{ per QALY gained}$$

Figure 1. Incremental cost-effectiveness formula.

There are two significant advantages with QALY as an outcome measure. Firstly, QALY is a generic outcome measure; hence, it allows the decision makers to compare a specific ICER to other analyses of various health care interventions in various medical areas. Secondly, health care decision makers can relate the result of an economic evaluation, i.e. cost-per-QALY gained, with a given threshold or WTP for a QALY for the intervention to be considered as cost-effective.

1.1.1 Cost analysis

A cost analysis identifies, quantifies and puts a value on the costs of an illness or a health care intervention. The costs to be considered in a cost analysis depend upon the perspective. A societal perspective should include all costs within the society as a whole, such as, consumption of health care resources, out-of-pocket expenditure for the patient and their family, productivity losses and cost of informal care (14). Resource consumption should ideally be quantified as opportunity costs (7), describing the value for the next best alternative use of the resources. In a perfect competitive market, this value represents the market prices. But when there is no market price available for the opportunity costs the use of a “shadow price” is recommended (15).

Costs are divided into direct costs and indirect costs. Direct costs include the resource use within the hospitals, transportations to hospital, out-of-pocket expenditure for the patient, and care services in other sectors. Indirect cost is the change in resources that does not directly occur in relation to the disease and includes loss of production, i.e. the value forgone to the society when the patient loses the ability to work (16). The opportunity cost for productivity loss is recommended to be quantified by the human capital approach (17), i.e. valuation of production is done under the assumption that production shortfalls can be valued at market price, such as, age- and gender-specific wage estimates (7).

To estimate the cost of informal support, several methods for quantifying and costing the support have been recommended in the literature. To quantify informal support, two methods used in the literature are *the diary* and *the recall method*, where the diary method is considered to be the golden standard (18). Both methods are constructed through written surveys. With the time-diary, the respondents are asked to prospectively report the time of provided support during a specific period. With the recall method, the respondents are asked to retrospectively recall the provided support during a specific period back in time. A dilemma with time measurements of informal support is the *joint production* (19). Joint production is an important issue especially in informal support since informal caregivers provide support to their partners that they often to some extent derive benefits from themselves. Thus, joint production needs to be considered in the cost analysis.

Methods for valuing informal support into monetary terms are the *opportunity cost* and the *replacement cost approach* (20), also called the *proxy good method* or *market cost method*. The replacement cost approach values the informal care as to what it would cost to have a professional health carer providing the same care. The opportunity cost method, on the other hand, values informal support as the person's best alternative use for that time. If the best alternative use of the time is to work, then the time spent on informal caregiving could equal the market wage rate of the informal caregiver (6, 15). However, problems with costing informal support arises when the next best alternative use is to have leisure time, simply because there is no market value for leisure time. Thus, the opinion on how to value leisure time into monetary terms is divided in the literature. Some researchers argue that since there is no market value for leisure time, lost leisure time should be valued as quality of life (QoL), and not in monetary term (21). This is due to the need to avoid the risk of double-counting, i.e. to avoid that the costs and benefits may be included in both the QALYs and in the costs in a CUA (22). However, different approaches for costing informal care are suggested in the literature. According to the recommendations stated in Gold et al. (7), with regard to unpaid services such as family members' home production, the preferred approach should be "*to use the hourly wage of individuals with similar characteristics who do work for pay*". Hence, unpaid services, also during leisure time, should be valued in monetary terms. Koopmanchap et al. (23) state that if a caregiver provides informal care by reducing unpaid work or leisure time, the value of that time needs to be estimated. The suggested approach is to use the reservation wage rate, i.e. the wage rate that the caregiver is willing to supply at least one hour of paid labour, or impute the known wage rate of similar people concerning age, sex, and education. The transport sector has previously valued travel time to 15-35% of the gross wage rate, where Johannesson et al. (24) had used a value of 35% of the gross wage rate to value leisure time into monetary terms. The Dental and

Pharmaceutical Benefits Agency (Tandvårds- och Läkemedelsförmånsverket, TLV), values leisure time at 50 SEK per hour (25), which corresponds to a similar costing approach. However, according to the TLV's recommendations on how to conduct economic evaluations from 2017 (17), it is only stated that relatives' costs and effect should be included without any recommendations regarding which approaches to use.

Other methods for valuing informal support in monetary terms is the *contingent valuation method* (CVM) and *conjoint measurements* (CM) (23). CVM values the informal support by assessing the minimum amount of money the informal caregivers are willing to accept (WTA) for providing an additional hour of informal support, or the maximum amount of money an informal caregiver is willing to pay (WTP) for reducing their support by one hour. CM is also a stated preference method, as the CVM, but is analysing preferences for a set of multi-attribute alternatives. With the CM, the responders are asked to evaluate scenarios that differ according to pre-specified attributes with different levels. By evaluating a set of these scenarios, the responders reveal their preference for the scenarios. There are different CM techniques available for eliciting preferences for scenarios and attributes, such as ranking, rating, discrete choice and best-worse scaling.

1.1.2 Assessing the value of health in economic evaluations

The World Health Organization (WHO) defines health as “*a state of complete physical and mental and social well-being, and not merely the absence of disease or infirmity*” (26). At the first international conference for health promotion in Ottawa in 1986, it was stated that to reach this state “*an individual or group must be able to identify and to realize aspirations, to satisfy needs, and to change or cope with the environment. Health is, therefore, seen as a resource for everyday life, not the objective of living. Health is a positive concept emphasizing social and personal resources, as well as physical capacities.*” (27). Thus, in health economics it has become essential to develop instruments for assessing the value of health interventions embracing mental well-being, capacity for an independent life, as well as physical functioning. The aim of the developmental effort has been to create generally accepted multidimensional scales to be able to quantify the effects of, for example, a health care intervention. Health-related quality of life (HRQoL) consists of such multidimensional scales that focus on the impact health status has on QoL (28, 29), in contrast to QoL that refers to an individual's total wellbeing (30).

In economic evaluations, where calculations of cost and values of interventions are in focus, there is a need for a single digit of HRQoL. This figure should capture states of health ranging from perfect health, or 100% of health to zero health, i.e. death. This single digit of HRQoL is often called utility or QALY-weight. To elicit utilities or QALY-weight, direct and multi-attribute methods of preference-based measures are used.

Direct methods to elicit utilities are the Standard Gamble (SG) (31), Time Trade-Off (TTO) (32), and Rating Scales (RS). The SG aims to measure a cardinal preference for health outcome. The subject is asked to choose between remaining in a state of ill health for a period of time, or choose a medical intervention which has a chance of either returning to perfect health or die immediately. The probability of remaining healthy is varied until the subject is indifferent between the two alternatives. The TTO also aims to measure a cardinal preference for health outcome. The subject is asked to choose between to live for 10 years in the current health state or to give up some years to live for a shorter period in perfect health. The time of perfect health is varied until the subject is indifferent between a shorter period in perfect health and a longer period in the current health state. With the RS, such as the visual analogue scale, the respondents are asked to mark their current perceived health state on a cardinal scale with endpoints such as best to worse possible health state. These direct measures are, however, more commonly used to generate scores for the estimation of multi-attribute utility functions, used to provide the index from the multi-attribute preference instruments, such as the EuroQol EQ-5D (33, 34), Short Form 6 Dimension (SF-6D) (35), and health utility index (HUI) (36). The EQ-5D consists of five dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each health status has been weighted using mostly the TTO method from large population studies conducted in several countries, as well as in Sweden (37). The SF-6D is based the SF-36 or the SF-12 and consists of six attributes; physical functioning, role limitation, social functioning, pain, mental health and vitality. Each health state has been weighted directly or indirectly using the SG on a random sample of the general population in the United Kingdom. HUI3 consists of eight dimensions: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain with 5 to 6 levels per dimensions. Preference scores were collected from a random sample in Canada using the VAS and SG.

1.1.3 Informal caregivers in economic evaluations

The health economic literature is consistent with regard to the notion that an economic evaluation with a societal perspective should include all costs and

effects, regardless of who pays or benefits from them (6, 7). Hence, also the caregivers' consequences should be included, particularly if the relatives are significant (4). However, this is neglected in many analyses due to lack of reliable data (15, 19, 38). One reason for this is probably the lack of applicable methods to value both costs of informal care and capturing health consequences for the caregivers. Knowledge about the cost of informal support is described in more details (39), while the knowledge about the caregiver's QALY-weight is in general limited (40).

Although, the literature is consistent with regard to the need to include caregivers' consequences in economic evaluations with a societal perspective the existing literature is, however, inconsistent as to how to include the consequences. This is due to several methodological problems. One problem that concerns this thesis is the debate as to whether both unpaid caregiver time and caregiver HRQoL or QoLs should be included in economic evaluations due to the risk of double-counting (23). It is argued that by including both the monetary value of caregivers' unpaid time and decrements of caregivers' QALYs in the ICER, there is a risk of double-counting the consequences. Therefore, it has been argued that the consequences for caregivers should only be included in the ICER in terms of caregivers' QoL (21). However, others argue that both cost of informal care and health effects belong in the evaluation, and that new guidance can be expected as the field moves forward (1). A systematic review (2) report that just a small proportion of the applied economic evaluations included the consequences for informal caregivers, and in those that did, the measurement and valuations techniques varied to a great extent.

1.2 Stroke

Stroke is a generic term for damage caused when an artery in the brain is blocked by a blood clot, i.e. ischemic (85%), or when a diseased vessel within the brain bursts, i.e. hemorrhagic (15%) (41). Stroke symptoms are heterogeneous and depend on several factors, such as localisation and extent of the lesion and the brain condition generally. The damage causes sudden loss of functions, such as; speech, movement, touch and sight. Common consequences after a stroke in the right cerebral hemisphere are left hemiparesis, lack of orientation in time and space, problems with interpreting other person's emotions and attitudes, and changes in personality and mood. Neglect is also a common consequence after a stroke in the right hemisphere, and often concerns problems with hemi-spatial attention, such as problems in perceiving one-half of the body or one-half of the visual field. Consequences after a stroke in the left cerebral hemisphere can

include problems such as right hemiparesis, difficulties with speech, writing or calculating. Aphasia refers to problems of speech after a stroke. A stroke in the cerebellum and/or the brain stem may have symptoms such as dizziness, difficulty to coordinate movements, balance problems, and affected consciousness, motor, and sensory functions (42).

Stroke is the global leading cause of long-term disability and death among adults (42-44). The positive trend of declining stroke mortality during the last two decades has resulted in increasing prevalence of stroke survivors with disabilities (11, 45). In Sweden, with 10 million inhabitants, 25,000-30,000 patients are annually diagnosed with stroke (46). The mean age of stroke patients registered in the quality register Riks-Stroke during 2015 was 73 for males and 78 for females. Among younger patients (≤ 65 years), male stroke patients predominate, while for older patients (≥ 85 years), female stroke patients predominate (46). Of the stroke survivors living in their own home prior to the stroke, 90% still live in their own homes after the stroke onset, provided that many receive support from the society and the family (46). The caregiver's role is important in influencing the outcome after stroke within a dyadic relationship. Previous studies have shown that individuals suffering from a stroke who live with their family or spouse arrive earlier to the hospital, receive more thrombolytic therapy, are more likely to return home (47), and receive more anticoagulants as secondary prevention (48), compared to individuals living alone before stroke onset. Further, cohabitant stroke survivors have shorter hospital stay by 1.9 days compared to patients living alone (49). Previous studies show that stroke survivors living alone predicts mortality after stroke (50), which was especially true for male stroke survivors in the long-term perspective (51).

Stroke is the somatic illness that requires most days in Swedish hospitals. In addition, utilisation is also extensive within the municipal care. According to a cost of illness (COI) study of first ever stroke in the Region Västra Götaland during the first year after stroke onset (52), the average annual cost per patient was 193,000 SEK and the estimated life-time cost was 768,000 SEK in year 2008 prices. Of the stroke survivors, 20% were in working age. This younger group has a higher lifetime cost compared to older stroke survivors due to longer expected lifetime and higher cost of loss of production. The average annual cost per patient under the age of 55 was 280,000 SEK, and the lifetime cost was estimated to 2,447,000 SEK. A COI analysis with a national perspective (53) estimated that the total cost of stroke in Sweden during 2009 was 16 billion SEK with a lifetime cost per stroke survivor of 741,000 SEK.

The support provided by informal caregivers constitutes to a significant part of the total health care provided for stroke survivors. Fattore et al. (54), reported

that the informal support accounted for 33.4% of the total societal cost of stroke in Italy. Alvarez-Sabín et al. (55) estimated the cost of informal support to 60% of the total health care costs of stroke in Spain. Similar results were reported for the Canary Islands, Spain (56). Saka et al. (57) report that the cost of informal care accounts for 27% of the total cost of stroke in the UK. According to a systematic literature review of burden of stroke in the US (58), cost of informal support account for the second largest contributor to the overall costs of stroke in the US.

1.3 Spouses of stroke survivors

Spouses of stroke survivor often have to enter the caregiving role without any warning or preparation. The usually sudden event of a stroke contributes to changes in the family, such as new economic and social adjustments as well as providing support to new physical and medical needs of the stroke survivors (59). Supporting a family member is often perceived as natural and important (60), and provide benefits such as being able to appreciate life more (61). However, the caregiving role can also be demanding and can have an impact on the relative's own life and health (62). The situation for the spouses as informal caregivers has been well documented during the first years after stroke onset. Spouses of stroke survivors report lower psychological well-being (63), lower life satisfaction (62), reduced leisure activities and social relationships (64). A recent review article (65) provided a meta-analysis based on 1,756 caregivers of stroke survivors worldwide, which showed that the pooled prevalence of depressive symptoms was 42.2% and anxiety symptoms was 21.4%. The caregiver burden of spouses was shown to be determined by the mental health of the stroke survivor and amount of time and effort of support provided by the caregiver (66). The depressive symptoms of the stroke survivors have been shown to be associated with family caregiver depression (67). Further, studies has also shown that the well-being of the caregiver in the acute phase could predict the outcome later on. Spouses' caregiver burden and anxiety at two months after stroke onset predicts the one-year outcome (68). Caregiver depression at the acute stage predicts caregiver depression at 12 and 18 months after stroke onset (69). A stroke onset has also been shown to have an impact on the caregivers' HRQoL; however, previous studies have all considered this form a short-term perspective (70-73). According to these studies, the most important determinants of the caregivers' HRQoL were their own age and their partner's functional and cognitive impairment.

During the recent decades there has been a significant increase in stroke survivors in working ages (74). A stroke in this age group has often a wide-spread impact on the daily lives of the stroke survivors and their families (75). The informal

caregivers in this age group are often in the middle of life with responsibilities for their family and sometimes their own professional career (10). Consequently, their lives can often be affected in a different way compared to informal caregivers within the older population. This affects the ability to work and to fulfil own goals such as education and professional advancement, especially among women (5), which can result in productivity loss and loss in human capital (76). Knowledge concerning informal caregivers to stroke survivors in their midlife who frequently provide support and care is fragmentary, especially from a long-term perspective (77).

Due to the heterogeneity of the stroke disease, informal caregivers support covers a wide range of support activities. Some of these activities are more task-oriented while some are to provide security by being available, sometimes around the clock. In general, there is no difference between males and females in the time spent on informal support however, males provide more practical and economic support while females provide more supervision and personal care (5). Previous estimates of the time spent on informal support to stroke survivors were 4.6 hour per day after six months, and 3.6 hours per day after 12 months (78). When time for surveillance was also included, the time spent on informal support was estimated to 14.2 hours per day after six months (79). The estimated economic burden of informal caregiving per stroke survivor during the first year ranged from €3,100 to €7,600 (54, 80-82). A recent systematic review of the valuation of informal support in COI studies (39) included nine COI studies regarding stroke showing an average annual cost of informal support at €6,576. The cost of informal support has only been estimated in a short-term perspective and based on activities in daily living (ADL) or instrumental activities of daily living (iADL) (80, 81) or based on questions regarding help with self-care, mobility, or household activities (82). These studies concern an older population of caregivers of stroke survivors (80-82), while there is a lack of knowledge concerning the time of support and cost of informal support provided by spouses of midlife stroke survivors.

1.4 Dyads of stroke survivors

In the previous two paragraphs, it has been mentioned that the caregivers' role is important in influencing outcome after stroke, but also that this caregiving role could have a negative impact on the caregivers' own well-being and health. The caregiving role for younger spouses of stroke survivors may be experienced differently due to responsibilities for the family and an own professional life (10), compared to older spouses. Hence, younger spouses may experience a greater

conflict between the support provided to their partner and their regular daily family and household chores.

Within a mutual dyadic relationship, the characteristics of both the stroke survivor and the caregiver could influence the other partner's outcome. Mental illness, such as depression and anxiety, are characteristics that have been shown to influence the dyads in both directions, both from stroke survivor to caregiver and from caregiver to stroke survivor. Caregivers' depression has been shown to be associated with lower scores of stroke survivors' physical function, communication, social participation, and mood (83). At the same time, the stroke survivor's anxiety, depression and cognitive impairment predicted the caregivers' anxiety, and the stroke survivor's anxiety and depression, predicted the caregivers' depression (84). Further, spouses with lower levels of self-esteem and optimism tend to be spouses to a stroke survivor with higher levels of depressive symptoms, and stroke survivors having lower levels of self-esteem tend to have a spouse with higher levels of depressive symptoms (85).

Previous research has also investigated the association between HRQoL for dyads of stroke survivors. A Swedish study (70) showed that there were no significant differences in the domains bodily pain, emotional role, and mental health between the dyads after four months. After 16 months, there were no differences in the domains bodily pain and mental health between the dyads. The scores for the domain bodily pain were more or less in line with the normal population; however, the scores in the domain emotional role and mental health were lower compared to the Swedish norms (86). An Israeli study (87) showed similar results for a small sample of stroke survivors and their primary caregivers (88% spouses) for more than one year after stroke onset. There were no significant differences between the stroke survivor and their primary caregiver in the four SF-36 mental domains, and the scores were considerably lower compared to Israeli norms.

1.5 Rationale for the thesis

Throughout this introduction, it has been shown that previous studies have investigated the spouses' HRQoL, cost of informal support, and the dyadic relationship concerning health outcome in a short-term perspective. However, it remains to investigate these consequences in a long-term perspective.

2 AIM

The overall aim of this thesis was to describe the long-term HRQoL of spouses of midlife stroke survivors and controls and to investigate if the stroke-related variables and HRQoL of the stroke survivors were associated with their spouses' HRQoL and cost of informal support. The aims of the studies included in this thesis were:

- To explore the HRQoL of spouses of midlife stroke survivors seven years after stroke onset and to identify predictors of HRQoL of spouses based on demographic features and stroke-related variables (Paper I).
- To investigate whether the dependency of the midlife stroke survivors had any impact on their spouses' QALY weights value in a long-term perspective (Paper II).
- To estimate the resource use and cost of the support provided by spouses to their stroke surviving partner in a long-term perspective (Paper III).
- To describe the HRQoL and QALY-weight in dyads of stroke survivors in comparison to dyads of controls and to study the relationship between stroke survivors' QALY-weights and spouses' consequences in a long-term perspective (Paper IV).

3 SUBJECTS AND METHODS

3.1 Subjects

Data on the 248 dyads of stroke survivors and 245 dyads of controls were collected from the Sahlgrenska Academy Study on Ischemic Stroke (SAHLSIS) (88). Data on the cohabitant spouses were collected as cross-sectional data, seven years after stroke onset. Data for the stroke survivors were collected as longitudinal data from stroke onset to seven years after stroke onset.

The SAHLSIS database covers 600 consecutively recruited white patients diagnosed with ischemic stroke before the age of 70 during 1998 and 2003. The inclusion criteria were that the clinical symptoms at stroke onset suggested stroke and that the CT scan or MRI of the brain indicated an ischemic stroke. The exclusion criteria were if the patient was younger than 18 or older than 69, had other etiology than ischemic stroke and was diagnosed with an advanced stage of cancer, infectious hepatitis, or HIV. The patients were recruited at stroke units within four hospitals in western Sweden (Västra Götalandsregionen): Sahlgrenska university hospital (Sahlgrenska hospital and Östra hospital), Södra Älvsborg hospital and Skaraborg hospital. The stroke survivors were examined in the acute stage (day 1-10 after stroke onset), with follow-ups at three months, two years, and seven years after stroke onset.

At baseline, the stroke survivors were age-, sex- and geographically matched with 600 healthy white controls. The controls were recruited randomly from a group of participants in a population-based health-survey (89). Residents from Skövde and Borås, as well as controls younger than 30 years, were collected from the Swedish Population Register. The exclusion criteria for the controls were history of stroke, coronary heart disease, or peripheral artery disease.

Data for the seven-year follow-up of the stroke survivors and controls were collected with a questionnaire sent to the subjects' homes with questions regarding background variables and self-rating instruments concerning health issues. Stroke survivors recruited at the Sahlgrenska hospital were invited to a visit to the research nurse and research physician. If the stroke survivors had difficulties in travelling to the hospital, the research nurse and physician made home visits.

For the seven-year follow-up, the researchers asked the stroke survivors or the controls for permission to contact the spouses regarding participation in the study. After approval by the stroke survivors and the controls, the researcher asked the spouse to participate in the study. The recruited spouse participated through responding to a questionnaire concerning sociodemographic measures and completing a self-rating instrument for HRQoL.

The distribution of participants from each stroke unit was; Sahlgrenska University hospital/Sahlgrenska hospital 71%, the Södra Älvsborg hospital 14%, the Skaraborg hospital 13% and the Sahlgrenska University hospital/Östra hospital 2%.

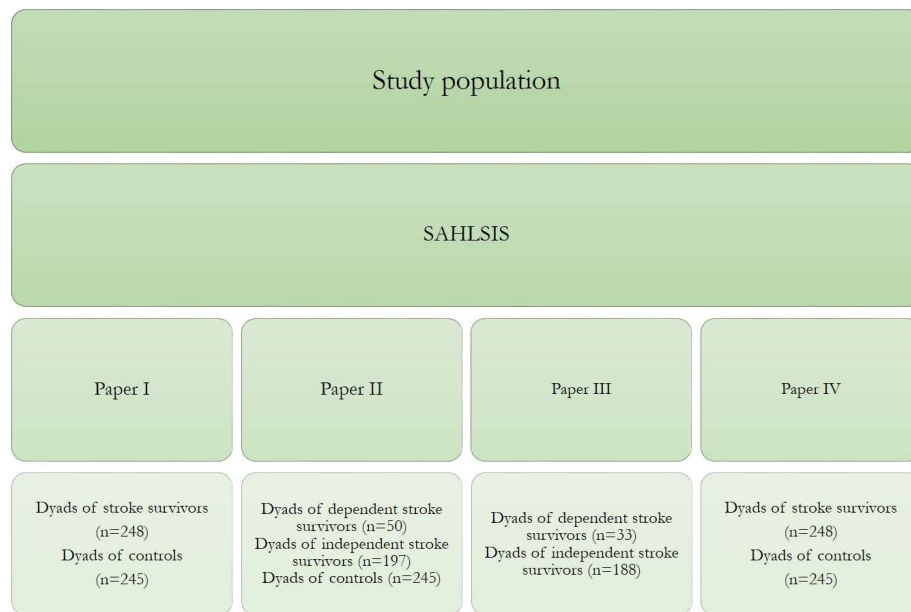


Figure 2. The study population.

3.2 Assessments

The SAHLSIS database covers a broad range of assessments for the spouses, such as life satisfaction, sense of coherence, level of depression and anxiety, and instrumental activities of daily activities. However, the focus in this thesis is on the assessment of spouses HRQoL and time and annual cost of informal support, in relationship to the stroke-related outcome.

3.2.1 Sociodemographic information

Questionnaires administered by the research nurse were used to collect information concerning socio-demographic data about the stroke survivors, controls, and their spouses. The socio-demographic data contained questions regarding age, sex, level of education, occupations status, and information about children in the household. The questionnaires to the spouses also contained questions about the spouses' support concerning housework tasks, practical support, and contact with health care, and for how long the spouses perceived that the stroke survivor or control could be alone.

3.2.2 HRQoL and QALY

The HRQoL for the spouses was assessed using the Short Form-36 (SF-36) questionnaire (version 1) in a Swedish version (86). The SF-36 consists of eight domains covering the subjective evaluation of physical functioning (PF), physical role (PR), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), emotional role (ER), and mental health (MH). Each domain has a score from 0-100, and a higher score indicates better HRQoL. The validity and reliability of the questionnaire for Swedish norms was demonstrated by Sullivan et al. (90). For the study population in this thesis, the internal consistency (reliability) of the questionnaire was calculated using Cronbach's alpha (Table 1). The Cronbach alpha ranged from 0.85 to 0.90; all exceeded the criteria for acceptable instrument internal reliability (Cronbach alpha $\alpha > 0.70$) (91).

Table 1. Internal consistency of study population based on the SF-36 scores.

	Spouses of stroke survivors	Stroke survivors	Spouses of controls	Controls
Cronbach's alpha	0.90	0.85	0.88	0.86

To derive a preference-based measure of health, often called QALY-weights, from the SF-36, an algorithm developed by Brazier et al. 2002 was used (35). The algorithm revised the SF-36 questionnaire into the six-dimensional health state classification, called SF-6D. The SF-6D consists of the following attributes: physical functioning, role participation (combined role-physical and role-emotional), social functioning, bodily pain, mental health, and vitality. The classification system consists of four to six levels on each of the six response

levels, resulting in 18 000 different health states. The scoring model of the SF-6D was developed based on standard gamble utility measurement on a random sample of the general population of the United Kingdom.

3.2.3 Stroke-related variables

Stroke survivor's neurological impairment was assessed using the National Institutes of Health stroke scale (NIHSS) (92). NIHSS is primarily a tool used by stroke health care professionals to objectively quantify the impairment caused by an acute stroke. The NIHSS is composed of 11 items that assess the level of consciousness, extraocular movements, visual fields, facial muscle function, extremity strength, sensory function, coordination, language, speech, and neglect. A score of 0 indicates no stroke symptoms, a score of 1-4 indicates a minor stroke, a score of 5-15 indicates a moderate stroke, a score of 16-20 indicates a moderate to severe stroke, and a score of 21-42 indicates a severe stroke.

Stroke survivor's global disability was assessed using the modified Rankin Scale (mRS) (93, 94) and assessments were collected at three months, two years, and seven years after stroke onset. Stroke survivors included at the Sahlgrenska hospital were interviewed face-to-face by the research nurse trained in stroke medicine. Stroke survivors unable to answer the research nurse interviewed a relative as proxy. Stroke survivors included at stroke units within Östra hospital, Södra Älvsborg Hospital, and Skaraborg Hospital were interviewed by the research nurse over the phone. To avoid that the subjective view of the interviewer might influence the results, the research nurse was trained to use key issues to distinguish different categories in a similar approach used in clinical trials (95). The mRS is defined categorically with seven different scores (Figure 3). A score of 0-2 indicates independence, while a score of 3-5 indicates dependence (96).

Modified Rankin Scale						
mRS 0	mRS 1	mRS 2	mRS 3	mRS 4	mRS 5	mRS 6
No symptoms at all	No significant disability despite symptoms (able to carry out all usual duties and activities)	Slight disability (unable to carry out all previous activities, but able to look after own affairs without assistance)	Moderate disability (requiring some help, but able to walk without assistance)	Moderately severe disability (unable to walk without assistance and unable to attend to own bodily needs without assistance)	Severe disability (bedridden, incontinent, and requiring constant nursing care and attention)	Dead

Figure 3. Description of the modified Rankin Scale.

Stroke survivor's basic ability to perform activities in daily life (ADL) was assessed with the Barthel Index (BI) (97, 98). The BI is a scale that measures basic aspects of activity related to daily living. Stroke survivors included at the Sahlgrenska hospital were interviewed face-to-face by the research nurse trained in stroke medicine. For stroke survivors included at stroke units within Östra hospital, Södra Älvsborg Hospital and Skaraborg Hospital, interviews were performed by the nurse over the phone. The BI score ranges from 0 to 100, and a higher score indicates less severe outcome. A cutoff score of 75 indicates dependency (99).

Stroke survivor's cognitive impairment was assessed using the Mini-Mental State Examination (MMSE) (100) and the Barrow Neurological Institute Screen for Higher Cerebral Functions (BNIS) (101, 102). The MMSE is comprised of questions grouped into seven categories, that evaluate specific cognitive functions, such as: orientation in time and space, registration of three words, attention and calculation, recall of three words, language, and constructive visual capacity. The MMSE ranges from 0 to 30; lower score indicates more severe outcome and a MMSE score less than 29 indicates cognitive dysfunction (103).

The BNIS is a more elaborate instrument comprised of questions grouped into eight categories that evaluate specific cognitive functions in a neurological setting: pre-screening, speech and language, repetition, orientation, attention/concentration, visuospatial and visual problem-solving, memory, affect, and awareness. The BNIS ranges from 0 to 50; lower score indicates more severe outcome, and a BNIS score less than 47 indicates cognitive dysfunction (103).

Stroke survivor's depression and anxiety was assessed using the Hospital Anxiety and Depression scale (HADS-A for anxiety and HADS-D for depression) (104). HADS-A and HADS-D is a self-report questionnaire that comprises seven statements relating to anxiety and seven relating to depression. A score of 0-6 indicates no anxiety or depression, a score of 7-10 indicates mild to severe anxiety and depression, and a score higher than 10 indicates presence of anxiety and depression.

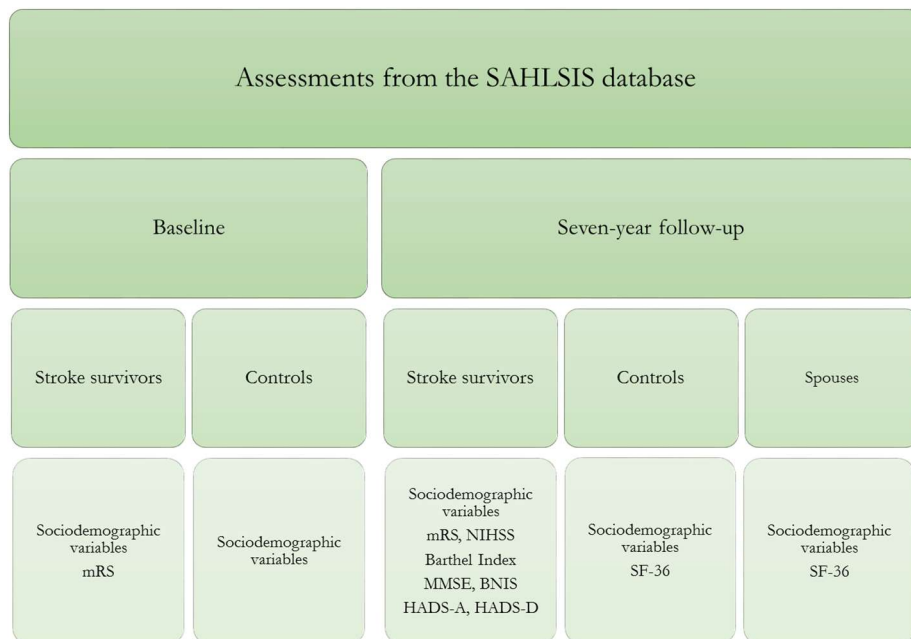


Figure 4. Assessments from the SAHLIS-database used in this thesis.

3.2.4 The time-diary

The time-diary (Figure 5) was designed to identify and quantify spousal informal support. The spouses completed the time-diary during for them a normal 7-day week. The time-diary was divided into four blocks of six hours in each block. Within each time block there were four categories: "Practical support", "Housework", "Support in contacts", and "Being available", where spouses could state the type of care that was provided. The category "Practical support" included the support the spouse experienced that the partner needed in their daily life. "Housework" included cleaning, cooking and shopping for groceries. The category "Support in contacts" included support in contacts with other individuals and with different authorities. Finally, the category "Being available" was the time that the spouses perceived that they needed to be available for their partner, beyond what was provided in the other categories. The categories "Practical support", "Housework", and "Support in contacts" were based on the suggested categories by van den Berg et al. (19). The fourth category used in the time-diary, "Being available", was included to capture an overall estimation of the spouses' time of support. This was based on clinical experiences and previous research in which caregivers expressed a feeling of being bounded and unfree (105). In the analyses, the categories "Practical support", "Housework", and "Support in contacts", were aggregated into one category, i.e. "Practical support".

Together with the time-diary, a detailed information package on how to quantify the support in the time-diary was sent to the spouses. The spouses were also asked to provide background information concerning occupational status and hours of home care provided by the municipality. The spouses were asked to state the "excess" time of informal support, i.e. support that was specifically provided for the stroke survivors that the spouses did not provide prior to the stroke.

Before the time-diary was used in the study, it was discussed with people in various ages to test the feasibility of completing the diary.

To validate that the data from the time-diaries were consistent with data from the questionnaire from the seven-year follow-up concerning support of housework tasks, contact with health care, and perceptions concerning the length of time during which the stroke survivors could be left alone, the amount of time in each time-diary category was compared with equivalent questions from the questionnaire.

Monday

	What did I do?	Time in minutes	Description
Night 00.00 – 06.00	Practical support		
	Housework		
	Support in contacts		
	Being available		
Morning 06.00 – 12.00	Practical support		
	Housework		
	Support in contacts		
	Being available		
Afternoon 12.00 – 18.00	Practical support		
	Housework		
	Support in contacts		
	Being available		
Evening 18.00 – 00.00	Practical support		
	Housework		
	Support in contacts		
	Being available		

Figure 5. The time-diary.

3.3 Cost analyses

The informal support was valued according to the opportunity cost method (6), where the informal support is valued as the person's best alternative use of time, i.e. spent on work or leisure. The loss of production was valued by the human capital approach (106) assuming that production loss is valued at market price, i.e. gross salaries and payroll taxes. Due to lack of data concerning whether the spouses reduced their working time to provide informal support, we valued the informal support as leisure time. The hourly estimation of informal support is presented in Table 2. In the cost analysis, joint production was considered for the category "Being available", i.e. when the spouses provided support to their partner that they themselves to some extent benefited from. Hence, support as

being available was valued at 50% of the leisure time. The annual cost of informal support was estimated by an extrapolation from the weekly reported support in the time-diaries.

Table 2. Hourly estimation of informal support.

	SEK	EUR	Reference
Hourly estimation of loss of production	200	20	(107)
Hourly estimation of leisure time	70	7	(24)
Being available (50% of rate for economically inactive)	35	3.5	Assumption

Exchange rate 0.10 from € to SEK

3.3.1 Sensitivity analyses

To analyse the robustness of the results, four one-way sensitivity analyses were conducted:

1. The hourly rate for the category “Being available” were varied between €1 and €6, i.e. 20% and 80% of full hourly rate (€7).
2. Limiting the maximum possible time of support per day to 16 hours.
3. Valuing the hourly rate of all the informal support when set at €20, i.e. loss of gross salaries and payroll taxes.
4. Valuing the hourly rate with the replacement cost approach, i.e. estimating the cost of the informal support at the wage rate, including payroll taxes, of a market substitute (6).
 - a. The category “Housework” was estimated at the hourly wage rate for housemaids, i.e. €15.
 - b. The categories “Practical support” and “Support in contacts” were estimated at the hourly wage rate for nursing aids, i.e. €16.4.
 - c. The category “Being available”, was estimated at the hourly wage rate for personal assistance, i.e. €16.5.

3.4 Statistical analyses

The statistical method used in this thesis is presented in Table 3. The distribution of the variables is presented as mean and SD or 95% CI, or median and first (Q1) and third (Q3) quartiles for continuous variables, and as number and percentages for categorical variables. All significance tests were two-sided and conducted at the five percent significance level. Non-parametric tests were used due to skewed data. However, the SF-36 domains were also presented as means to be comparable to other studies. SF-6D, on the other hand, was normally distributed and hence parametric statistics were used.

To test differences between groups, the Mann-Whitney U test or Wilcoxon signed rank test was used for continuous variables. To study the strength of associations between two variables, Spearman rank order correlation was used.

In paper I, a logistic regression was performed to evaluate predictors of HRQoL of the spouses. Stroke-related variables and spouses' demographic features displaying correlation with P -values of ≤ 0.10 were included in a stepwise logistic regression of each SF-36 domain of the spouses.

In paper II, an ordinary least squared (OLS) regression was performed to investigate the relationship between the spouse's QALY-weight and the stroke survivor's dependency (mRS 3-5).

In paper III, a two-part econometric model was performed. The first part of jointly estimated two-part model was a binary choice model for estimating the probability of observing a positive outcome (informal support). The second part was a regression model based on the observations with positive outcomes (informal support). The chosen approach for the first part was a logit and for the second part was an OLS with the natural logarithm of the outcome variable.

In paper IV, an OLS regression was performed to analyse the relationship within the dyads between stroke survivors' and spouses' QALY-weights. To investigate the relationship between the stroke survivors' QALY-weight and the cost of informal support, a two-part model was performed. The chosen approach for the first part was a logit and for the second part was an OLS with the natural logarithm of the outcome variable.

The analysis in paper I and II was carried out in SPSS software (version 20, SPSS, Inc., Chicago, IL, USA). The analyses in paper III and IV was carried out in STATA (version 14, STATA, College Station, TX, USA). The statistical methods are presented in details in each paper.

Table 3. *Statistical methods used in Paper I-IV.*

		Paper I	Paper II	Paper III	Paper IV
Descriptive statistics	Mean, SD	X	X		X
	Mean, 95% CI		X	X	X
	Median, quartiles	X	X		
Group comparison	Mann-Whitney U test	X	X	X	X
	Wilcoxon signed rank test				X
Correlations	Spearman rank order correlation	X	X		
Regression analyses	Logistic regression	X			
	Ordinary least square regression		X		X
	Two-part model			X	X
Other methods	Area under the ROC-curves	X			

3.5 Ethical considerations

The Regional Ethical Review Board in Gothenburg approved the studies (reference number 413-04, 622-06, T715-10). All respondents gave informed consent and approved merging data with their partners' data.

4 RESULTS

4.1 SAHLSIS baseline for the seven-year follow-up

At SAHLSIS baseline, 422 stroke patients and 437 controls were cohabitant. During baseline to the seven-year follow-up, 48 stroke survivors and 38 controls became single, 63 stroke survivors and 19 controls deceased, and 20 stroke survivors and 51 controls were excluded from the study. Of the 178 stroke survivors and 163 controls who were single at SAHLSIS baseline, 8 stroke survivors and 15 controls became cohabitant from baseline to the seven-year follow-up. Hence, at the seven-year follow-up, 299 cohabitant dyads of stroke survivors and 344 dyads of cohabitant controls were available (Figure 6).

The stroke survivors who were lost between baseline and the seven-year follow-up had worse global disability at 3 months after stroke onset than those who were available at the seven-year follow-up (mRS: $P < 0.001$). However, the dropout analysis showed that there were no differences concerning age but more males than female were lost to follow-up. Concerning the controls, the dropout analysis showed that there were no differences in age, sex, or occupational status between the controls who were lost and those available at the seven-year follow-up.

Of the 299 cohabitant dyads of stroke survivors who were available at the seven year follow-up, 20 stroke survivors did not give permission for the researcher to contact their spouse, and 31 spouses declined participation. Corresponding figures for the 344 dyads of cohabitant controls were 46 controls not giving permission to contact their spouse and 53 spouses who declined participation (Figure 6). The dropout analysis showed that there were no differences in age or sex between the dropouts compared to the included spouses, both concerning stroke survivors and controls, nor were there any differences in the stroke-related variables between stroke survivors included in the study and those who declined.

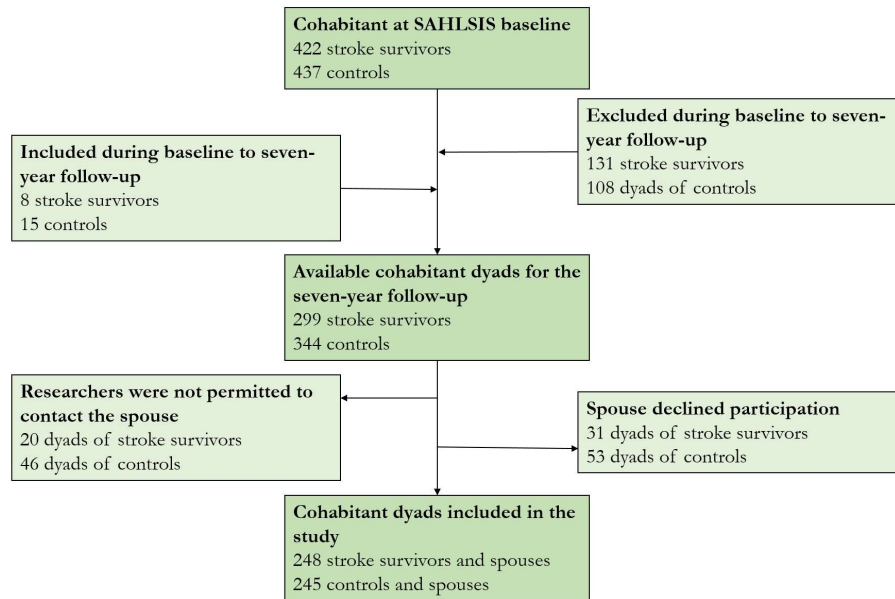


Figure 6. Flowchart of the cohabitant study population in SAHLISIS.

4.2 Study population

The population of this thesis consisted of 248 cohabitant dyads of stroke survivors and 245 cohabitant dyads of controls. As assessed by the mRS data at the seven-year follow-up, 50 were dyads of dependent (mRS 3-5) stroke survivors, and 197 were dyads of independent (mRS 0-2) stroke survivors.

The mean ages (SD) of the spouses and the stroke survivors were 63 (11) and 64 (11), respectively, and 65% and 34% were females. The demographic features of the dyads of dependent and independent stroke survivors are presented in Table 4. The mean ages (SD) of the spouses of controls and the controls were 64 (9) and 65 (9), respectively, and 66% and 34% were females. Of the spouses of controls, 38% were employed and 52% were retired, and 35% had completed university and 36% had completed high school. Of the controls, 40% were employed and 56% were retired, and 30% had completed university and 36% had completed high school.

Table 4. Demographic features of the dyads of dependent and independent stroke survivors.

	Spouses of dependent stroke survivors (%) (n=50)	Spouses of independent stroke survivors (%) (n=197)	Dependent stroke survivors (%) (n=50)	Independent stroke survivors (%) (n=197)
Mean age, y (SD)	67 (8)	62 (11)	68 (8)	63 (11)
Female sex	31 (63)	131 (67)	19 (38)	65 (33)
Education				
Secondary or less	24 (48)	72 (37)	21 (42)	70 (36)
High school	11 (22)	65 (33)	17 (34)	70 (36)
University	15 (30)	60 (30)	11 (22)	57 (28)
Occupation ¹				
Employed	13 (26)	92 (47)	0 (0)	64 (32)
Retired	35 (70)	91 (46)	38 (76)	110 (56)
Other ²	7 (14)	25 (13)	13 (26)	57 (29)
Household				
Children <18	2 (4)	25 (13)		
Support in home				
Informal support ³	48 (96)	31 (16)		
Formal support ⁴			20 (40)	4 (0.02)

¹Sum not equal to 100% because of multiple response alternatives.

²Other: Unemployed, sick leave, student.

³Self-reported information from the spouse concerning whether they provided informal support to their partner.

⁴Home care, personal assistant, or living at nursing home.

4.2.1 Stroke-related variables

The scores in the different stroke-related measures are presented in Table 5. Of the stroke survivors, 62% had no stroke symptoms, 25% had minor stroke symptoms, 12% moderate stroke symptoms, 1% had moderate to severe stroke symptoms, and 1% had severe stroke symptoms according to the NIHSS. According to the Barthel Index, 11% of the stroke survivors had a score ≤ 75 , indicating dependency in performing activities in daily life (ADL). Concerning the cognitive dysfunction (BNIS), 88% of the stroke survivors had a score less than 47, which indicates cognitive dysfunction. Further, 15% reported mild depression and 9% severe depression (HADS-D), and 15% reported mild anxiety and 8% severe anxiety (HADS-A).

Concerning the global disability assessed by mRS, 16% of the stroke survivors had no symptoms at all (mRS 0), 21% had no significant disability despite symptoms (mRS 1), 43% had slight disability (mRS 2), 10% had moderate disability (mRS 3), and 10% moderately severe (mRS 4) and severe (mRS 5)

disability. Hence, 80% were independent (mRS 0-2) and 20% were dependent (mRS 3-5). When the stroke survivors were categorised into dependent and independent stroke survivors, the dependent stroke survivors scored significantly lower in all the stroke-related variables ($P<0.001$), except for anxiety ($P=0.145$).

Table 5. Stroke-related measures (Paper II).

	Stroke survivors (N=248)	Dependent stroke survivors (mRS ≥ 3) (n=50)	Independent stroke survivors (mRS ≤ 2) (n=197)
	Median (Q ₁ -Q ₃)	Median (Q ₁ -Q ₃)	Median (Q ₁ -Q ₃)
Neurological impairment (NIHSS) ¹	0 (0-2)	6 (2-12)	0 (0-0)
Cognitive function (BNIS) ¹	40 (37-44)	32 (27-37)	41 (38-45)
Depression (HADS-D) ²	3 (1-6)	6 (2-11)	3 (1-6)
Anxiety (HADS-A) ²	3 (1-6)	4 (1-8)	3 (1-6)
Barthel Index ²	100 (95-100)	75 (49-90)	100 (100-100)
Global disability (mRS) ²	2 (1-2)		

¹Subgroup from the Sahlgrenska hospital (n=170).

²Total study population (n=248).

4.3 HRQoL of dyads of stroke survivors and controls

Compared to the spouses of controls, spouses of stroke survivors scored lower in the four SF-36 mental domains and in the domains physical role and general health. There were no significant differences between male and female spouses of stroke survivors regarding the scores of the separate SF-36 domains. However, female spouses of controls scored significantly lower than male spouses on physical role ($P=0.017$), bodily pain ($P=0.036$), and mental health ($P=0.033$).

The ages of the spouses of stroke survivors were correlated with their HRQoL, such that older spouses had significantly lower scores in all the SF-36 domains compared to the younger spouses. Further, older spouses of controls scored lower in the domains physical functioning ($P<0.001$) and general health ($P<0.001$), compared to the younger spouses.

Since previous research in a short-term perspective has shown that the functional status of the stroke survivors was an important determinant of spouses' HRQoL, we compared the HRQoL of spouses of dependent (mRS 3-5) and independent (mRS 0-2) stroke survivors. Spouses of dependent stroke survivors scored significantly lower in all the SF-36 domains compared to spouses of independent stroke survivors (Figure 7).

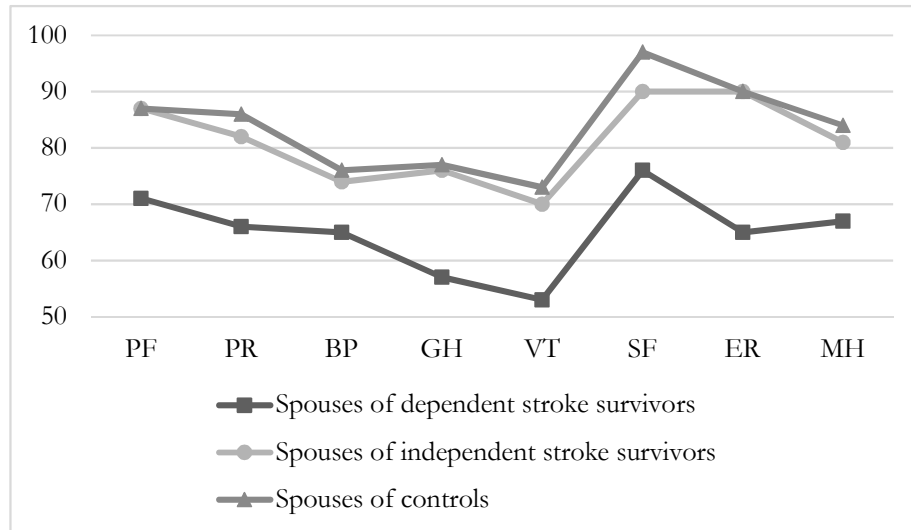


Figure 7. Spouses of dependent and independent stroke survivors and spouses of controls HRQoL in each SF-36 domain.

The stroke survivors and their spouses reported significant differences in the SF-36 domains physical functioning, general health, vitality, and social functioning. While there were no significant differences in their scores in the domains emotional role and mental health, both were lower compared to the scores of the dyads of controls. Also, there were no significant differences between their scores in the domain bodily pain. Further, there were no significant differences in any of the scores in the eight SF-36 domains between the controls and their spouses. Figure 8 illustrates the SF-36 scores of the dyads of stroke survivors and dyads of controls.

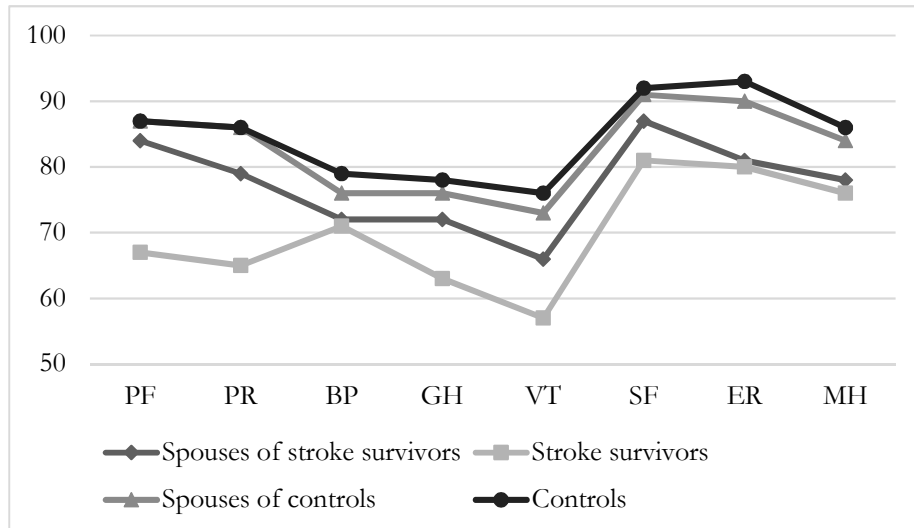


Figure 8. Dyads of stroke survivors and dyads of controls HRQoL in each SF-36 domain.

4.3.1 QALY-weights of dyads of stroke survivors and controls

Spouses of stroke survivors reported a mean (SD) QALY-weight of 0.75 (0.12), and stroke survivors reported a mean QALY-weight of 0.70 (0.12) ($P < 0.001$).

Spouses of controls reported a mean QALY-weight of 0.77 (0.11), and the controls reported a mean QALY-weight of 0.78 (0.10). There was no significant difference between the dyads' mean QALY-weight.

Spouses of dependent stroke survivors reported a mean QALY-weight of 0.69 (0.12) in comparison to spouses of independent stroke survivors, whose mean QALY-weight was 0.77 (0.11) ($P < 0.001$).

4.3.2 Determinants of spouses' HRQoL and QALY-weights

The determinants of the spouses' physical health (SF-36 domains: physical functioning, physical role and general health) were their own age and the level of global disability of the stroke survivor. The determinants of the spouses' mental

health (SF-36 domains; vitality, social functioning, emotional role, and mental health) were the stroke survivors' level of depression, cognitive dysfunction (MMSE), global disability, and if the spouses perceived lack of social support.

The global disability of the stroke survivors was also significantly associated with their spouses' QALY-weight. Figure 9 shows the mean QALY-weight of the spouses for each mRS score for the stroke survivors. Spouses of stroke survivors with a score of mRS 3 reported lowest QALY-weights. In the ordinary least squared regression, solely mRS 3 had a significant negative association with the spouses' QALY-weights ($P=0.002$). The dependency (mRS 3-5) of the stroke survivors had a negative association with their spouses' QALY-weight ($P<0.001$, $R^2 0.096$). There was an association within the dyads' QALY-weights, such that lower QALY-weight of the stroke survivor was significantly associated with lower spousal QALY-weight ($P<0.001$, $R^2 0.142$).

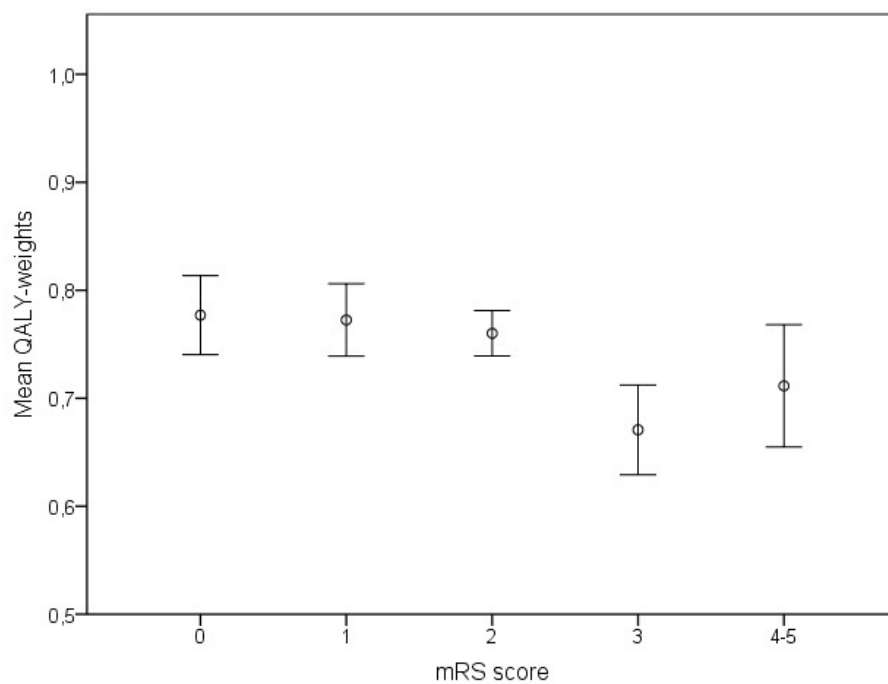


Figure 9. Spouses' mean QALY-weights according to the stroke survivor's mRS score, including 95% CI error bars (Paper II).

4.4 Spouses' informal support

The time measurements concerning spouses' informal support were based on 53 spouses who completed the time-diaries and 168 spouses who reported that they provided no informal support, illustrated by the flowchart in Figure 10. In the SAHLSIS questionnaire, 80 spouses reported that they provided support to their partner, whereof 53 completed the time-diary. The spouses who completed the time-diary study did not differ concerning spouses' age, sex, occupational status, level of education, or the global disability of the included stroke survivors compared to the drop-outs (n=27).

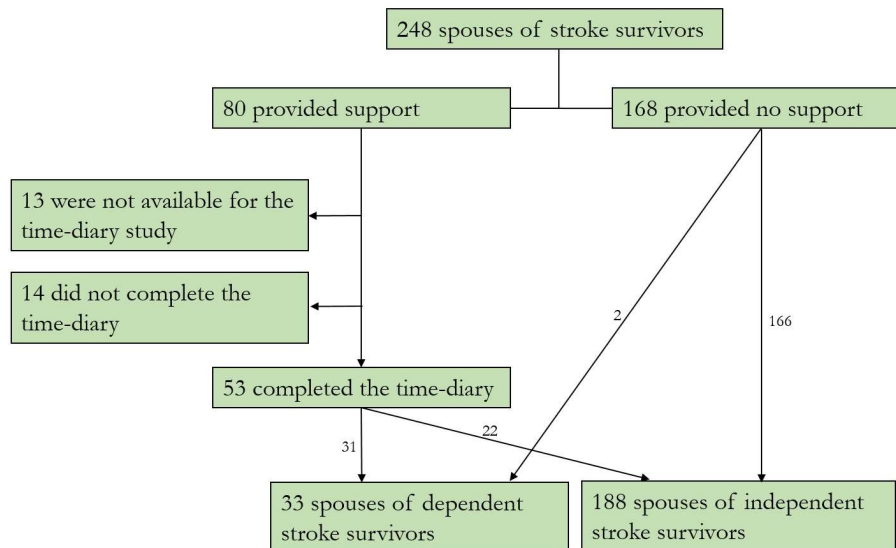


Figure 10. Flowchart of study population in Paper III.

The analyses of time and annual cost of informal support were based on 33 spouses to dependent stroke survivors and 188 spouses to independent stroke survivors. There were 22 spouses who completed the time-diary whose partners were independent (mRS 0-2), where the majority (n=20) had a score of mRS 2. This group of stroke survivors had less severe outcome compared to the stroke survivors with mRS score 3 and 4 (Table 4). The stroke survivors with mRS 2 had a minor stroke (NIHSS), were independent according to the BI and had no depression or anxiety. However, the BNIS score indicated cognitive dysfunction, although not as severe as for the stroke survivors with mRS 3 and 4.

Table 6. Stroke-related measures for stroke survivors in the time-diary study.

	mRS score 2 (n=20)	mRS score 3 (n=15)	mRS score 4-5 (n=16)
	Median (Q ₁ -Q ₃)	Median (Q ₁ -Q ₃)	Median (Q ₁ -Q ₃)
Neurological impairment (NIHSS) ¹	1 (0-2)	6 (3-8)	9 (4-15)
Cognitive function (BNIS) ¹	42 (39-46)	35 (25-42)	29 (27-34)
Depression (HADS-D) ²	3 (2-8)	4 (1-8)	7 (3-11)
Anxiety (HADS-A) ²	4 (1-7)	5 (1-9)	5 (1-7)
Barthel Index ²	100 (95-100)	85 (75-90)	45 (25-75)

¹Subgroup from the Sahlgrenska hospital (n=33).

²Total study population (n=51).

4.4.1 Validation of the time-diary

For the validation of the time-diary, the time spent in each category in the time-diary (practical support, housework, support in contacts and being available) was compared to similar questions in the seven-year questionnaire. The spouses who reported in the questionnaires that they provided support with dressing, toileting, moving indoors and outdoors, rehabilitation activities, and support in contacts also reported significantly more time of support in each corresponding category in the time-diaries.

For the category “Being available”, there was no corresponding question in the seven-year questionnaire to compare with. Hence, we compared time of being available reported in the time-diaries with a question in the seven-year questionnaire concerning for how long the spouses perceived that their partner could be alone. The spouses who reported that their partner could be alone for less than half a day also reported that they were available for more hours per week compared to the spouses reporting that their partner could be alone for more than half a day.

4.4.2 Informal support in hours per day

In the analyses, the data from time-diaries (n=53) were merged with the spouses who reported in the seven-year questionnaire that they did not provide any informal support (n=168). Further, the categories “Practical support”, “Housework”, and “Support in contacts” were merged into one category; “Practical support”.

Spouses of independent stroke survivors provided on average (95% CI) 0.15 (0.01-0.30) hours per day of practical support and 0.48 (0.14-1.09) hours per day of being available. Corresponding figures for spouses of dependent stroke survivors were 5.00 (2.76-7.24) regarding practical support and 9.51 (1.35-17.68) regarding being available. As illustrated by Figure 11, spouses of stroke survivors with mRS score 3-5 (dependent stroke survivors) provided informal support to a greater extent compared to spouses of stroke survivors with mRS score 0-2 (independent stroke survivors).

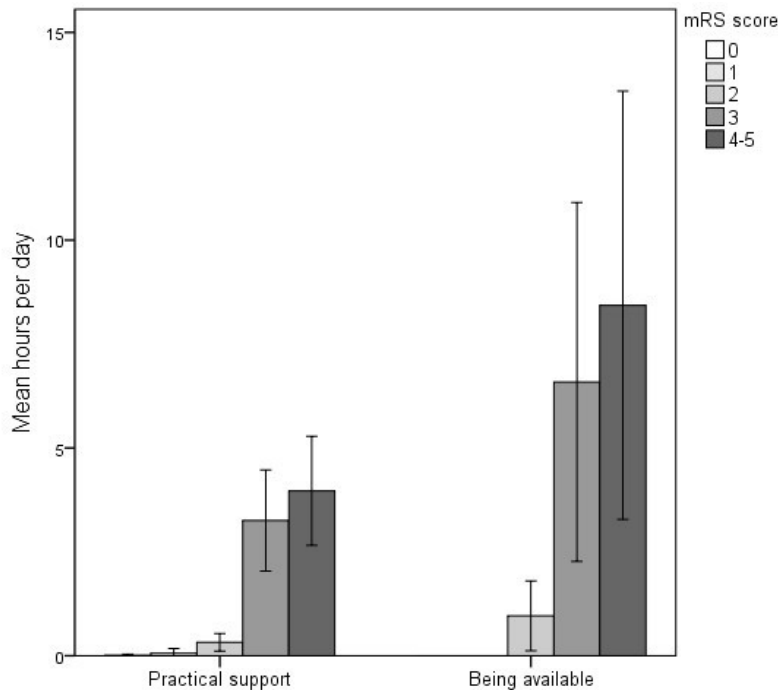


Figure 11. Mean hours of informal support according to mRS score (Paper III).

The spousal informal support in hours per day was also estimated as a function of the stroke survivor's QALY-weight with a two-part econometric model. Figure 12 illustrates the predicted estimates of hours of practical support and being available according to the stroke survivors QALY-weight. Lower QALY-weight of the stroke survivor predicted more time spent on practical support and support by being available. For QALY-weight of 0.8, the associations with the time spent on practical support and support by being available were no longer significant.

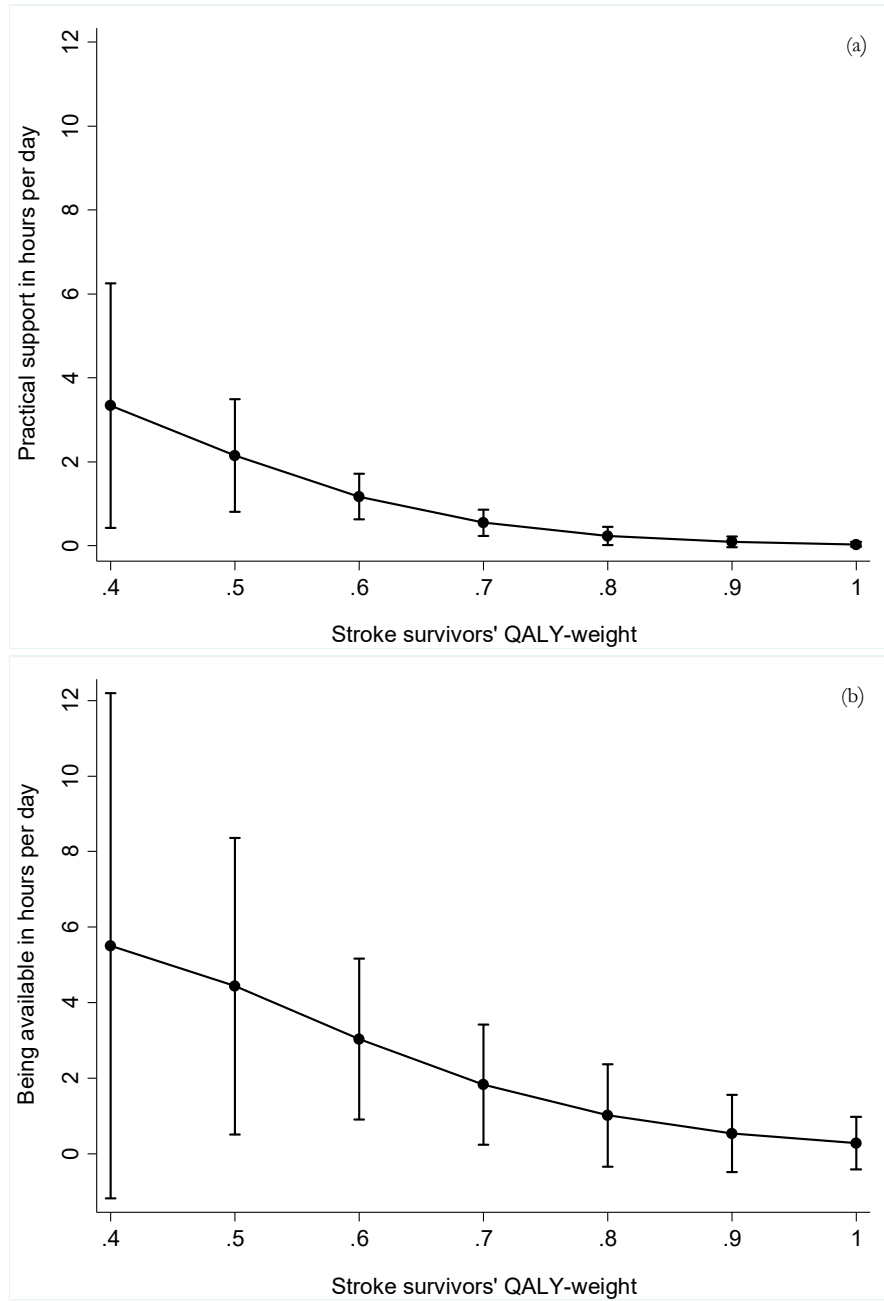


Figure 12. Spouses' informal support in practical support (a) and being available (b) in mean hours per day per stroke survivors QALY-weight, adjusted for spouses' occupational status and including 95% CI bars with percentile bootstrap with 1,000 replicates (Paper IV).

4.4.3 Annual cost of spousal informal support

The mean (95% CI) annual cost of informal support provided for independent stroke survivors was estimated at €412 (€-14.4-€838) for practical support and €579 (€-200-€1,358) for support by being available. Corresponding figures for spouses of dependent stroke survivors were €13,539 (€7,030-€20,049) regarding practical support and €11,588 (€1,897-€21,278) regarding support by being available.

The sensitivity analyses showed that the results were most sensitive to how the support was valued, i.e. if it was valued as loss of gross salaries and payroll taxes and, the replacement cost approach instead of loss of leisure time (Table 7).

Table 7. Sensitivity analyses. Annual costs are presented in € (2015). (Paper III).

	Independent stroke survivors	Dependent stroke survivors
Being available, valued at €1	652 (32-1,273)**	18,156 (9,830-26,483)***
Being available, valued at €6	1,219 (2-2,441)**	35,871 (15,183-56,558)***
Limit of 16 support hours per day	819 (51-1,589)**	23,788 (11,633-35,952)***
Informal support valued at €20	1,862 (50-3,773)**	41,164 (15,578-66,751)***
Replacement cost approach	1,720 (61-3,378)**	57,215 (31,002-83,428)***

95% confidence interval estimated with percentile bootstrap with 1000 replications in parentheses.

Level of significance: ***1%, **5%, *10%.

Costs was adjusted for spouses' sex and occupational status.

The results from the two-part econometric model regarding annual cost of informal support as a function of the stroke survivors' QALY-weight are shown in Table 8. From a QALY-weight of 0.8, the annual cost of informal support increased gradually with lower QALY-weight of the stroke survivor.

As shown in Figure 12b and in Table 8, the post-estimates were not significant for time spent on support and annual cost of informal support for stroke survivors with QALY-weight of 0.4. This were probably due to few observations (n=6) with QALY-weight 0.4 and wide distribution in the category "being available".

Table 8. Annual cost of spouses' practical support and being available per stroke survivors' QALY-weight. Costs are presented in € (2015). (Paper IV)

Stroke survivors QALY-weight	Practical support	P-value	Being available	P-value
0.40	9,009 (1,339-16,680)	0.021	6,697 (-1,581-14,976)	0.113
0.50	5,787 (2,233-9,341)	<0.001	5,398 (574-10,221)	0.028
0.60	3,134 (1,673-4,594)	<0.001	3,697 (1,091-6,305)	0.005
0.70	1,460 (602-2,318)	<0.001	2,225 (293-4,156)	0.024
0.80	609 (12-1,205)	0.046	1,230 (-340-2,859)	0.139
0.90	233 (-112-578)	0.185	648 (-578-1,874)	0.300
1.00	85 (-85-254)	0.328	334 (-498-1,165)	0.432

Costs are adjusted for formal support and spouses' occupational status, with 95% confidence intervals estimated by percentile bootstrap with 1,000 replications.

5 DISCUSSION

The focus in this thesis has been to highlight the long-term consequences of stroke among spouses of stroke survivors in terms of HRQoL and time and annual cost of the informal support provided. It is important to gain knowledge of these consequences, both with regard to the clinical perspective and with regard to the field of health economics.

It is known that a stroke has a wide impact also on the health of stroke survivors' families in a short-term perspective. However, knowledge is limited about the consequences of a caregiving role in a long-term perspective. Thus, the results in this thesis provide long-term knowledge about a well-defined study population, showing that the spouses of stroke survivors reported poor HRQoL and extensive time spent on informal support, both of which were primarily related to the dependency of the stroke survivors.

The consequences selected for study in this thesis were specifically chosen to provide long-term knowledge concerning measures usually used in the field of health economics. However, the debate is still on going concerning how to assess health effects of caregivers and how to measure time spent on care and which monetary value to use when costing the informal care. Thus, several issues concerning our results and the underlying theoretical framework need to be discussed. The discussion in this thesis is divided into the two main study areas, including discussions of both the results and the methodological considerations.

5.1 HRQoL and QALY-weights

5.1.1 Spouses' physical health

It has previously been shown in a short-term perspective that the evidence for a relationship between the caregiving role and poor physical health is limited (108). It has, however, been shown that high strain on caregivers increases the risk of coronary heart disease, stroke (109), and premature death (110). The spouses of stroke survivors in this thesis reported poorer general health in comparison with the spouses of controls. Poorer general health was primarily found among spouses of dependent stroke survivors, while spouses of independent stroke survivors reported similar scores of general health as the spouses of controls. Further studies are needed to investigate the determinants of spouses' poorer general health. One possible determinant could be that the long-lasting caregiver

role has a negative impact on spouses' general health due to anxiety, depression, stress, and caregiver strain (59). Another explanation might be that the dyads share the same life style factors such as smoking habits, sedentary life, overweight, and risk factors such as high blood pressure and level blood lipids including cholesterol (111). High caregiving strain among caregivers of stroke survivors has been shown to be associated with higher estimated stroke risk (109). Hence, interventions to reduce cardiovascular risk factors could be addressed to both the patients and their spouses.

Further, the spouses of stroke survivors reported impaired ability to perform physical activities (SF-36 domain physical role), represented foremost by the spouses of dependent stroke survivors. This may have consequences for the spouses' ability to provide informal support to their partner, which in turn might have consequences for the support needed from the municipalities.

5.1.2 Spouses' mental health

Previous studies have shown that supporting a stroke survivor was often related to poorer mental health and social functioning in the caregiver (73, 108). A review by Camak (59) reported that lack of preparedness for the caregiver role and increased caregiver burden were related to caregiver depression and anxiety in a short-term perspective. Further, an American longitudinal study by Haley et al. (64) showed that the family caregivers reported poorer mental health and life satisfaction as well as depression and affected leisure activities nine months after stroke onset, compared to non-caregivers. However, three years after stroke onset, only leisure satisfaction was poorer among the caregivers compared to the non-caregivers. One possible explanation for this different long-term outcome in comparison to our results is that we solely included spouses, whereas the study by Haley et al. (64) included family members in various ages and with various relationships to the stroke survivors. The long-term impact is expected to be different for cohabiting spouses compared with other non-cohabiting family members. In this thesis, we showed that stroke-related outcome, such as functional status or cognitive impairment of the stroke survivors, predicts poorer mental and physical health of their spouses, whereas the study by Haley et al. (64) does not provide such information. Further, a study by Carod-Artal et al. (112) showed that in the short-term perspective, the caregiver burden increased with the dependency of the stroke survivors, measured with the mRS. Higher mRS score of the stroke survivor was also shown to have an impact on the spouses' HRQoL in this thesis.

5.1.3 HRQoL of spouses of controls

The spouses of controls in this thesis scored 2-5 units higher in each SF-36 domain compared to the Swedish normative population in ages 45-64 (86). This difference might be due to the fact that the controls were healthy as regards cardiovascular disease at inclusion in SAHLSIS, and therefore their spouses might be healthier compared to the normative population. According to a Dutch study (113), a large cohort of almost 12,000 couples showed that responders whose partner reported poor health were three times more likely to report poor health, compared to responders whose partner reported good health.

In contrast, the mean QALY-weight of the spouses of controls was somewhat lower compared to the Swedish norm measured with EQ-5D (37). It has previously been shown that the EQ-5D and SF-6D provide different indices, where the EQ-5D gives more weight to the physical functioning and the SF-6D focuses more on the social functioning (114). Thus, the SF-6D provides other perspectives concerning HRQoL that might be more appropriate when capturing the impact on QALY-weights among individuals who do not experience physical impairment, such as the general population, and also caregivers (4).

5.1.4 HRQoL in a dyadic perspective

Few studies have investigated the dyadic relationship between spouse and patient HRQoL. A study by Ågren et al. (115) of dyads of patients with chronic heart failure (CHF) showed that the patients reported lower HRQoL in all the SF-36 domains, except in the mental health domain. This study also reports significant differences in QALY-weights (SF-6D) in the dyads, 0.63 for the patients and 0.79 for their spouses. Further, our findings show that dyads of stroke survivors report similar bodily pain, emotional role, and mental health, in line with the results reported by Jönsson et al. (70). Previous studies have indicated that depression seems to have a negative impact on the dyads, in both directions (83, 84, 116). However, further longitudinal studies are needed to better understand the dyadic perspective of the determinants for mental poor health of stroke survivors and their spouses. However, our results indicate that there could be a need of targeting interventions to improve both the stroke survivors' and their spouses' mental health in a long-term perspective.

A previous study by Dixon et al (117) has investigated the relationship between patient and spouse QALY-weights in dyads of patients with Alzheimer's. In contrast to their findings, we report an association between the QALY-weight of the stroke survivors and their spouses. One explanation for this difference could be that we solely included cohabitant spouses, while Dixon et al included primary

caregivers (53% spouses). The impact on HRQoL would be expected to be different for cohabiting spouses compared with other non-cohabiting family members and friends (118).

5.1.5 Determinants of spouses' HRQoL and QALY-weight

According to previous research, the functional status of the stroke survivors and the spouses' own age were the most important determinants of poorer HRQoL among the caregivers (119). Our findings support that these determinants also can be applied in a long-term perspective and support as well the notion that the stroke survivors' level of depression and cognitive impairment has a negative impact on the spouses' mental health.

Further, the amount of available social support has previously been shown to have a positive impact on the caregivers' psychological distress (120), depressive symptoms, and life satisfaction (121) in a short-term perspective. The results in this thesis support that this also can be applied in a long-term perspective, and perceived lack of social support was particularly related to poorer mental health and emotional role. The review by Camak (59) showed that the caregiving role can cause caregivers to sacrifice opportunities for social participation. These results could explain why the spouses in this thesis experienced poor emotional role.

The time spent on informal support has also been shown to have a negative impact on the caregivers' well-being (5, 120). However, in this thesis, the aim was to investigate whether the dependency of the stroke survivors had any impact on their spouses' HRQoL. The rationale for this study design was that as shown in Paper I, mRS was an important determinant of poor health among the spouses. The importance of this perspective is two-fold. Firstly, in economic evaluations of stroke interventions with a societal perspective, the mRS is often used as the most important driver in the models, and secondly, the mRS is also used in decision making by clinicians and rehabilitation stakeholders with regard to targeted family interventions. Our findings showed that spouses of dependent stroke survivors reported significantly poorer HRQoL in all the SF-36 domains, and lower mean QALY-weight, compared to spouses of independent stroke survivors. It is, however, interesting to note that it was only the mRS score of 3 that had a significant association with their spouses' QALY-weight, whereas a mRS score of 4-5 did not have a significant association. One possible explanation for this might be that the stroke survivors with mRS score 4-5 had access to formal support to a greater extent compared to stroke survivors with mRS score 3. However, further studies with larger study populations are needed to investigate the mechanisms behind this possible discrepancy in mRS scores.

5.1.6 Methodological considerations

The generic measurement of HRQoL has been criticised, since the instrument may be more responsive or sensitive than disease specific outcome measures (122). However, measuring HRQoL with a generic instrument provides the advantage of comparing HRQoL across various medical areas. The EQ-5D, commonly used to gain QALY estimates, was developed to measure the patient-related health effect, rather than that of the caregivers. Hence, to use a preference based health measurement, such as the EQ-5D, may neglect important aspects of carer-related QoL (123). Measures designed for caregivers include aspects such as relationship and fulfilment from caring, rather than bodily pain and physical functioning included in the EQ-5D and the SF-6D (124, 125). Happiness is also an aspect that is associated with the time spent on informal support (126). It has been suggested that preference-based health measures may be insensitive to the psychological health of the caregiver (127). An explanation may be that when the general population weights the health states in the EQ-5D and the SF-6D, they tend to give higher weight to the physical dimensions. However, it has been shown that persons with mental health issues give comparatively higher weight to the mental health dimensions (128). The use of carer-related QoL, measured with the CarerQoL-7D (125), may be a useful measure when evaluating interventions directed towards the caregivers. However, when evaluating a patient intervention, the carer-related QoL cannot be added to the patients' QALY in a CUA (129). Hence, the preference-based health measurement is more suitable. However, it could also be essential to include other outcome measures to detect changes in a broader perspective as a complement to the preference based measure (130). In this thesis, the focus has been on measures usually used in the field of health economics. However, broader measures of the spouses' well-being such as caregiver burden, life satisfaction, sense of coherence, and levels of depression and anxiety are important to gain a more complete picture of the consequences of the caregiving role.

Further, the consequences for caregivers' health could also be referred to as the health spill-over effect (131-133). The concept of health spill-over effect concerns the effect the patients' health can have on the health of their family members. Hence, to measure the health spill-over effect on the family, direct measurements with questions regarding direct spill-over effects of a disease on the family could be used. However, the aim of our study was not to capture the direct spill-over effects of the stroke disease, but rather to capture the secondary effects related to the dependency of the stroke survivor. Since the dependency of the stroke survivor was highly associated with both formal and informal support, it would be difficult to disentangle the spill-over effects of the dependency from the provided formal and informal support. Further, the data used in our studies were cross-sectional, and hence a limitation of our studies is that we have no information about the HRQoL of the spouses prior the stroke or in the acute

phase. Thus, we cannot show that the significant difference between the spouses of dependent and independent stroke survivors is due to a spill-over effect from the health of the stroke survivors. Neither can we show whether other factors, such as the dyad having shared risk and life style factors, had a negative impact on the HRQoL of the spouses of dependent stroke survivors. Hence, further longitudinal studies are needed to investigate what mechanisms are responsible for the negative impact on the HRQoL of spouses of dependent stroke survivors.

5.2 Spouses' informal support

Caregivers of stroke survivors spend extensive time on informal support, and the opportunity cost for their informal support contributes to a large part of the total cost of the stroke disease (39). The time spent on informal support has an impact on the caregivers' experienced burden and reported HRQoL. However, the methodology used to measure the time spent on informal support and to value that time into monetary terms is widely discussed in the scientific literature. The choice of method to measure the time spent on informal support and how the time is valued into monetary terms could have a widespread impact on the results.

5.2.1 Time spent on informal support

In previous studies, the time spent on informal support for stroke survivors was based on activities of daily living (ADL) or instrumental activities of daily living (iADL) (78, 80-82, 134). According to our results, these activities that we have categorised as "Practical support" represent only a minor proportion of the time spent on informal support. The majority of the reported informal support consisted of time being available. Our results are in line with a Dutch study (79) conducted in a short-term perspective of six months after stroke onset, showing that caregivers (59% spouses) spend 3.4 hours per day on caregiving tasks and 10.48 hours per day on surveillance. The study concluded that caregivers with own health problems caring for a stroke survivor with disability in ADL, measured with BI, experienced the most caregiving burden. In our study, we found that the dependency, measured with mRS, of the stroke survivors had a major impact on the time spent on informal support. Further, Hickenbottom et al. (81) reported time spent in ADL-based informal support to elderly stroke patients (≥ 70 years) with and without self-reported stroke-related health problems. This study also indicated a major difference in caregiver time provided to patients with and without stroke-related health problems (8.6 vs 18.6 hours per

week). This study population was older in comparison to the participants in SAHLSIS, and the caregiver time was self-reported by the patients, while the spouses in our study reported their informal support in a study-specific time-diary. Still, both our results and the results by Hickenbottom et al. (81) indicate major differences in time spent on informal support when grouping by health problems or dependency vs. independency was performed, in comparison to studies reporting overall time spent on informal support.

Further, Dixon et al. (117) showed that the EQ-5D index for a large cohort of patients with various diseases was associated with increased carer time. The results in this thesis also showed an association between the stroke survivors' QALY-weight and time spent on spousal informal support, on practical support, and support by being available. This association were significant up to a QALY-weight of 0.8 for the stroke survivors, which is expected, considering that the Swedish norm is 0.8 (measured with EQ-5D) (37).

5.2.2 Cost of informal support

The estimated cost of spousal informal support for dependent stroke survivors in our study exceeded the previous estimates that ranged from €3,100 to €7,600 during the first year after stroke onset (54, 80-82). The main reasons for the discrepancy between the previous estimates and the estimated annual cost provided in this thesis were two-fold. Firstly, our estimate is based on the annual cost of both practical support and support by being available, instead of solely ADL-based informal support. Secondly, we solely included cohabitant spouses. Spouses who are cohabitant with the stroke survivors could be expected to provide more time of support that otherwise would have been provided by formal care, such as home care to stroke survivors living alone.

According to a recent systematic review (39), the highest average annual cost of informal care was for patients with dementia, i.e. €21,065, followed by mental illnesses, i.e. €15,416 and multiple sclerosis, i.e. €12,709. The average annual cost for stroke patients was reported to be €6,576. One possible reason for this difference could be that in the annual cost of informal support to stroke patients, it is more common to estimate the annual cost based solely on ADL and iADL support, while for dementia, it is common to also include cost of time of surveillance. However, the results in this thesis show that the majority of the spousal support consists of being available. Hence, future studies that aim to estimate the cost of informal support for stroke survivors should also include the cost of support by being available or surveillance.

5.2.3 Methodological considerations

Methods for measuring time spent on informal support

The diary method is stated to be the golden standard for time measurement (18), and it was the method used to measure the spousal informal support in this thesis. However, the methodology used and the results from the time-diaries need to be discussed due to several issues.

Firstly, we designed a study-specific time-diary since no previous time-diaries in the literature were appropriate for this study. When designing the time-diary, we weighed a time-diary with more categories and shorter time-slots, similar to the diary suggested by van den Berg et al. (18), against a time-diary more feasible to complete. Because of our simpler time-diary, we did not schedule the time-diary so that the responders could report only one activity at a time. This would have needed a much more detailed time-diary with shorter time-slots, such as 15 minutes in each time-slot per category. With our time-diary, with four hours in each time-slot, we were not able to control for spouses performing several activities at the same time, i.e. joint production. This is mainly a problem for the category "Being available", where 25% of the spouses reported that they were available 20-24 hours per day. Of course, these spouses had other activities except being available during that time. Hence, we valued the support by being available as half of the time being joint production, to account for time for sleeping and other activities that the spouses themselves benefited from. To avoid some of the joint production, we could have added categories as sleeping, paid work, and shorter time-slots in each time block. However, we chose not to include these categories due to our preference for a time-diary that would be more feasible to complete.

Secondly, the data collection of time spent on informal support was cross-sectional. Hence, we could not test the reliability of the reported time in the diaries with another data collection during a different period. However, we performed a validation of the reported time in the diaries in comparison with the data in the seven-year questionnaire. The time reported in the diary categories "practical support", "housework", and "support in contacts" was comparable to the answers in the seven-year questionnaire. However, the category "being available" was not directly comparable with any of the questions in the seven-year questionnaire. In the time-diary, the spouses reported the time they were available for support, whereas in the seven-year questionnaire, the spouses were asked to report the length of time during which the stroke survivor could be alone without supervision. Hence, there might be a discrepancy between these measures. Other methods to validate the results in the time-diaries could have been to ask the spouses to complete the time-diary a second time or to use a recall method. Previous studies using both the recall method and the time-diary report significant

differences in time spent on informal support. Van den Berg et al. (18) showed that caregivers to patients with various diseases (circulatory, musculoskeletal, neurological and psychological, etc.) reported that they provided on average 5.8 hours of informal support per day, corrected for joint production, measured with a time-diary. However, when the authors used a recall method on the same study population, the spouses reported almost an hour of support less per day. Flyckt et al. (135), also used the time-diary and the recall method to estimate time for relatives' informal support for patients with psychosis. The weekly time spent on informal support was 22.5 hours, including stand-by time (50%). Compared with the recall method, the time-diary resulted in higher values, with greatest difference in the stand-by time.

Thirdly, there is a discrepancy between how the spouses perceive the need of support by their partner and the actual support that is asked for by their partner. This was shown in the seven-year questionnaire, where 22 spouses of the independent stroke survivors reported that they provided support, while 27 independent stroke survivors reported that they received support. However, when costing informal support, it is the informal caregivers' best alternative use of the time spent on support that should be valued.

Methods for valuing informal support into monetary terms

The method chosen for valuing informal support into monetary terms has a large impact on the cost of informal support. According to a recent review (39), the opportunity cost method is the most common when costing informal care, i.e. 59%, compared to the replacement method, 27%. However, the major problem with costing informal support is when the next best alternative use of the time spent on informal support is to have leisure time. There is no natural market value for leisure time, which makes the informal support problematic to value in monetary terms. In this thesis, leisure time was valued as 35% of the gross wage rate, a method which has also been used by many others (52, 136-138). However, others have argued that informal support should be valued as society's willingness to pay, i.e. expressed as the cost of the professional care and services that would be needed if the informal caregiver was absent (139). This replacement cost approach has been presented in our sensitivity analysis in Paper III. However, the replacement cost approach can lead to overvaluation, due to the fact that informal support and professional care are not perfect substitutes and are therefore not directly comparable (6). Nevertheless, the replacement cost approach may not overvalue the valuation of informal support *per se*, but rather the time spent on providing informal support. Professional carers may perform the care and support in a shorter time, and professional cleaners may clean the house in a

shorter time, compared to a spouse. However, as already mentioned, the characteristics of the spouses may influence the perceived need of support, which is a dilemma with the replacement cost method that assumes that all time should be replaced with the cost that would have occurred if professionals had provided the same care and support.

According to the review by Oliva-Moreno et al. (39), the average unit cost was €10.63 with the opportunity cost method and €21.77 with the replacement cost approach in the Nordic countries. Hence, both these unit costs were somewhat higher compared to the unit costs used in this thesis.

Further, according to the labour theory (15), the marginal value of leisure time corresponds to an individual's wage rate. Hence, a monthly salary of 29,000 SEK, which was used in this thesis, gives a net hourly wage of 135 SEK or €13.5.

To value the informal care into monetary terms, the WTP and WTA values could be assessed using a CVM. Van den Berg et al. (140) estimated the WTP and WTA for caregivers of patients with rheumatoid arthritis (RA) and for a heterogeneous sample. WTA was assessed by the minimum amount of money the informal caregivers were willing to accept for providing an additional hour of informal support, and WTP was assessed by the maximum amount of money informal caregivers were willing to pay for reducing their support by one hour. The informal caregivers of patients with RA estimated their WTP to €7.80 and WTA to €9.52. The informal caregivers of the heterogeneous group of patients estimated their WTP to €8.61 and WTA to €10.52. Gervès et al. (141) estimated the WTP value for caregivers of persons with Alzheimer's disease with the question *'Imagine you could be replaced for 1 hour of care to your care recipient. What would be your willingness to pay for this forgone hour of informal care?'* The results of the study indicated that 19% of the caregivers reported a WTP value of \leq €13, 23% a WTP value between $>$ €13 and \leq €18, 13% a WTP value of $>$ €18, and 44% could not estimate their WTP value. The caregivers' WTP value was negatively associated with the caregivers' decreased possibilities of social relationships and positively associated with the feeling of being valued. Studies have also used the CM to assess the monetary value of informal support. Van den Berg et al. (142) reported that caregivers for patients with RA required an extra compensation of €1 per hour for providing one more hour of the same informal care task. Hence, from the seventh to the eighth hour of provided informal support they required €8. Van den Berg et al. (143) performed a similar study on caregivers of a heterogeneous group of patients. Their results indicated that the caregivers required a compensation of €12.35 per hour of informal support. It has been shown that the WTP and WTA are positively associated with the responders' income (23). Since

stroke is overrepresented among individuals with low socioeconomic status (144), these types of values might be lower among caregivers of stroke survivors.

The findings mentioned in this methodological consideration indicate that regardless of chosen method, the value per hour of informal support is within the range of €7 to €15. However, some argue that since there is no market value for leisure time, lost leisure time should be valued as decrements of QoL (21). Nevertheless, the results in this study indicate that the more time spent on informal support does not necessarily result in lower QALY-weight. Spouses of stroke survivors with a mRS score 4-5 provide more informal support compared to the spouses of stroke survivors with a mRS score of 3, although only spouses of stroke survivors with mRS score of 3 have significantly lower QALY-weights. Further research is needed to investigate the mechanisms behind the spouses' perceived need of providing support, including their own characteristics, such as coping strategies and locus of control, and the decrements on their HRQoL.

5.3 Spouses' consequences in economic evaluations

With the increased evidence of spill-over time costs and quality of life effects for caregivers, it is argued that the caregivers' consequences should be included in economic evaluations that have a societal perspective. However, how the consequences should be included seems still to be open for debate, and guidelines are requested (1). Several theoretical frameworks have been presented on how to include cost of informal support and the health of informal caregivers (1).

Davidson et al. (145) presented a measure they call R-QALY, i.e. the effect on the QALY-weight due to being an informal caregiver. The R-QALY weights were generated by comparing the caregivers' QALY-weight with the population-based QALY-weights. Hence, the R-QALY weight is negative if the relatives' QALY-weight is negatively affected by providing support, and positive if the relatives' QALY-weight is positively affected by providing support. If the caregiving has no effect on the relatives' QALY-weight, the R-QALY is zero. To interpret our results in terms of the measure introduced by Davidson et al. (145), the R-QALY would be -0.08 for spouses of dependent stroke survivors in comparison to both spouses of independent stroke survivors and spouses of controls. Further, Al-Janabi et al. (131) present a conceptual framework for including health of informal caregivers in extra-welfarist economic evaluations, i.e. focusing on maximising health benefits from a fixed health care budget. The framework includes two multiplier effects to internalise the caregivers' spill-over health effects, which expresses the ratio of total health effects including the patient and their family

network to patient health effects. The authors argue that these multiplier effects could change the optimal funding decision and generate additional health to society.

5.4 Overall methodological considerations

The results in this thesis concern midlife dyads of stroke survivors and spouses in a long-term perspective of seven years after stroke onset. Hence, the results should not be generalised to either a short-term perspective or to other groups, such as elderly dyads of stroke survivors, due to two reasons. Firstly, the drop-out analysis showed that more stroke survivors with higher mRS scores at three months after stroke onset were lost to follow-up. Hence, the composition of stroke survivors in the seven-year follow-up are different concerning level of global disability. Therefore, the consequences for their spouses may be different in terms of time spent on informal support and decrements of HRQoL. Further, the spouses may have adapted differently to the caregiving role in a long-term perspective compared to during the first year, which may have an impact on how they perceive the consequences in the long-term compared to the first months. Secondly, the long-term perspective for elderly stroke survivors may be different compared to our study population in terms of higher risk of mortality and other morbidities, including recurrent stroke and cognitive deterioration to dementia.

Further, the sample that reported the time spent on informal support in the time-diaries was small, which limits the generalisability of the results due to possible type II error. Moreover, the reported time had a relatively wide distribution, especially in the category “being available”. This might be a reason why the stroke survivors' QALY-weights and dependency (mRS 3-5) were not significantly associated with the time spent on being available. Instead, the fact that the support was provided by the spouses was the driving factor for the post-estimates from the two-part model.

The reported time of practical support and support by being available was skewed due to a minority reporting high frequencies of daily support. The data also consisted of a large proportion of zeroes, i.e. a large proportion of the spouses reported that they did not provide any informal support (zero-costs). The statistical model used when evaluating cost data with skewedness and presence of zero-costs has previously been shown to provide different estimated costs (146). The use of a two-part model is an appropriate method for the analysis of data with a large number of zeroes (147). The first equation predicts the probability of spouses providing informal support, and the second equation estimates the association between the time or cost of informal support and dependency (Paper III) or QALY-weight of the stroke survivors (Paper IV). The time/cost of informal support is then calculated by multiplying these two estimates together.

5.5 Ethical considerations

The studies included in this thesis involved no medical risks. The positive aspects are that the studies provide a better understanding of the challenges faced by spouses in terms of HRQoL and time spent in informal support and that the spouses' experiences are highlighted also in a long-term perspective. The possible negative aspects were that spouses may have experienced that the studies intruded on their privacy a long period after the stroke onset or brought up negative emotions. To diminish this risk, especially with the time-diary study, we included a detailed information letter with the time-diary. We also informed the participants that they could contact the research nurse for advice on where they could turn for professional support. A large part of the spouses expressed that they appreciated taking part in the study, and we believe that the benefits of the studies clearly exceeded the risk.

An ethical consideration that arises when we advocate that the spouses' consequences should be included in an economic evaluation with a societal perspective may be that cohabitant patients would have greater benefits from health care interventions and hence lower ICER values in comparison to patients living alone (132).

6 CONCLUSION

- Spouses of stroke survivors experienced impaired HRQoL seven years after stroke onset. The spouses' own age and the global disability level of the stroke survivors had a negative effect on the spouses' physical health. The stroke survivors' level of depression, cognitive dysfunction, global disability, and if the spouses perceived lack of social support had a negative effect on the spouses' mental health. Further longitudinal studies are needed to better understand the effect of the stroke survivors' disability on the HRQoL of their spouses.
- The QALY-weights for spouses of dependent midlife stroke survivors were significantly decreased compared to spouses of independent midlife stroke survivors. This indicates that reduced dependency through early treatments and effective rehabilitation might have the potential to increase the spouses' QALY-weights to levels comparable to spouses of healthy controls. The inclusion of spouses' QALYs in economic evaluations of treatments for stroke patients would capture more of the total effect in dyads of stroke survivors.
- The informal support provided by the spouses was associated with the dependency of the stroke survivors. Consequently, the opportunity cost of informal support provided to dependent mid-aged stroke survivors is of a major magnitude many years after stroke onset and should be considered in economic evaluations of health care. An implication of the study results is that if early treatment and effective rehabilitation could reduce dependency, society might be able to avoid extensive opportunity costs of informal support.
- The QALY-weight for stroke survivors was associated with the spousal QALY-weight and the cost of informal support. Hence, economic evaluations of interventions that improve the HRQoL of the stroke survivors, but fail to include the consequences for their spouses may underestimate the value of the intervention. Thus, the inclusion of spouses' consequences in economic evaluations could have an impact on the cost-per-QALY estimates.

7 FUTURE PERSPECTIVES

Several interesting aspects remain to be investigated in a longitudinal perspective. Both the spouses' HRQoL and their time spent on support could be assumed to change over time, depending upon changes in the stroke survivor's functional or cognitive impairment, or depending upon changes in the spouses' own health status. Further, the spouses could also adapt to the caregiving role and develop coping strategies over a long period of time, which may influence how the caregiving role is perceived. The impact of societal support for the spouses to counteract their risk of poorer HRQoL also needs to be investigated further. An investigation of potential mechanisms that may contribute to these changes in midlife dyads of stroke survivors and spouses over time would provide answers to many of the questions raised in this thesis. Mixed methods with an addition of qualitative analyses would probably further increase our understanding. Increased knowledge could be helpful for the health care and municipalities to align long-lasting support to the spouses and to prevent or reduce the perceived stress and strain which might contribute to health benefits and, strengths to fulfil goals in work and education.

A further interesting question is whether and to what extent the spouses in working age reduce their paid work to provide more unpaid work. In addition, it would be interesting to investigate whether the spouses' demographic and socioeconomic characteristics, such as age, gender, level of income and education, have any impact on a potential reduction of paid work time to provide unpaid work such as informal support during leisure time.

Another important issue of further research is to investigate mechanisms that influence the poorer general health for spouses in a long-term. It is probable that shared life style and risk factors within the dyad may have impact on the HRQoL of spouses of dependent stroke survivors, but this needs to be investigated in a long-term perspective, as well as possible effects on health care consumption. Large-scaled register-based studies describing the spouses' long-term health care consumption might provide additional knowledge regarding the impact on their general health from a long-lasting caregiving role.

Moreover, further research is needed for several methodological issues. One of these issues is whether loss of leisure time should be valued into monetary terms or is best captured in the caregivers' QoL in an economic evaluation with a societal perspective. The caregiving role includes many aspects, both positive and negative, and the health effects on the caregivers could be assumed to depend on several aspects, whereof loss of leisure time and leisure activities is one of them.

However, other aspects, such as the caregivers own coping ability could be assumed to have an important influence on how they perceive their situation as caregivers, and thereby how they perceive the reduction of leisure time and leisure activities. Another methodological issue concerns how to best capture the HRQoL for caregivers in terms that are compatible to the patients' QALYs as incorporated inputs in an economic evaluation. With the commonly used instruments, EQ-5D and SF-6D (converted from SF-36 or SF-12), important aspects of the caregiver role are not included, and hence the EQ-5D and SF-6D may not capture the health effects to the same extent as other caregiver specific instruments and hence needs to be investigated. It would also be interesting to compare EQ-5D and SF-6D as regarding their ability to capture spill-over health effects. It is possible that SF-6D has an advantage through its inclusion of the domains role participation, social functioning and vitality unlike EQ-5D, but this remains to be investigated.

More knowledge in these important fields would be helpful for the authorities to provide more detailed guidelines concerning if and how to incorporate family spill-over health effects and cost of informal support for more complete economic evaluations of future interventions studies. More knowledge would also be helpful for implementing better social support to dyads of stroke survivors and spouses.

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