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Quality of Life Impacts from Type 1 Diabetes

Evidence from Two Studies in Northern Sweden

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Abstract

Purpose

To estimate the impact upon Health-Related Quality of Life (HRQOL) associated with Type 1 Diabetes Mellitus (T1DM), both with and without associated diabetic complications, for enabling calculation of utility values – Quality of Life Weights (QLW) – for populations with T1DM.

Method

Two cohorts from Northern Sweden, one of T1DM patients and one of a general population, were given surveys measuring their health quality, using the EQ-5D tool. In total, a combined 1,825 persons replied to the surveys. Controlling for both personal characteristics and cardiovascular disease (CVD), the differences in HRQOL were estimated using different regression models. HRQOL was analyzed through both EQ-5D-3L – using three different value sets to ensure the sensitivity of the results – and EQ-VAS.

Results

T1DM was significantly correlated with lower HRQOL. This decrease was estimated to range between -3.2 and -2.1 percentage points (depending on which value set was used) when controlling for CVD, and between -3.8 and -2.4 percentage points, when only controlling for background characteristics. The drop in HRQOL in life amongst the T1DM patients could partly be explained through their increased prevalence of associated diabetic complications. Since T1DM is also associated with an elevated risk of microvascular complications, and these complications were found to lower HRQOL, it is likely these are another cause of the lower HRQOL among T1DM patients. No evidence was found that cardiovascular complications have a different impact upon HRQOL of T1DM patients than upon a general population.

Conclusions

This study has estimated QLWs for both a T1DM and general population, and the decrease in HRQOL that is associated with T1DM, both when the prevalence of cardiovascular complications is known and not. Associated complications can explain part of the drop in HRQOL amongst T1DM patients, but T1DM also appears to have a direct negative effect on HRQOL besides through increasing the risk of associated complications.

Keywords:

Health-Related Quality of Life, Type 1 Diabetes Mellitus, EQ-5D, MONICA, Quality of Life Weights

Table of Content

1. Introduction 1
2. Purpose 3
2.1 Specific aims 3
2.2 Contribution 3
2.3 Paper structure 3
3. Background 4
3.1 Type 1 Diabetes Mellitus 4
3.2 Previous studies on quality of life weights for Type 1 diabetes mellitus 4
4. Theory 7
4.1 The concept of utility valuation 7
4.2 How should Health-related Quality of Life be quantified 8
4.2.1 Direct valuation methods 9
4.2.2 Indirect valuation methods 10
4.3 Who is to value Health-Related Quality of Life 10
4.4 Negative utility values 11
5. Method 12
5.1 EQ-5D 12
5.2 The choice of value set 13
5.3 Statistical methodology 15
5.3.1 Overall health 15
5.3.2 Individual dimensions of health 15
5.3.3 Statistical specifications 15
6. Data 17
6.1 The population surveys 17
6.2 Definitions and descriptive statistics 17
7. Results 21
8. Discussion 26
9. Conclusions 30
References 31
Appendix 35

Table of Tables

Table 1 - Previous studies on Health-Related Quality of Life in T1DM 6
Table 2 – Comparison of value sets 14
Table 3 – Characteristics and complications 19
Table 4 - Distribution of EQ-5D-3L answers 20
Table 5 - Quality of Life Weights: average sub-group values 21
Table 6 - Effects upon HRQOL without controlling for associated complications 22
Table 7 - Effects upon HRQOL, controlling for associated complications 22
Table 8 - Summary of effects to Health-Related Quality of Life from T1DM 23
Table 9 - Microvascular complications and Health-Related Quality of Life 24
Table 10 - T1DM-specific impacts from cardiovascular complications 24
Table 11 - Effects upon HRQOL when measured through EQ-VAS 25
Table 12 - Determinants of problems with 'Mobility' 35
Table 13 - Determinants of problems with 'Self-care' 35
Table 14 - Determinants of problems with 'Usual activities' 36
Table 15 - Determinants of problems with 'Pain & discomfort' 36
Table 16 - Determinants of problems with 'Anxiety & depression' 36

Table of Figures

Figure 1 – Age distribution in the two groups 18
Figure 2 (A) & (B) - Distribution of EQ-VAS score 20

1. Introduction

Increased attention in medical evaluation is given to the Health-Related Quality of Life (HRQOL) of patients. Along with preservation of life, ensuring the highest quality of life is the basic objective of medicine (Williams 1998). The maximization of HRQOL has even been suggested as the ultimate goal of health intervention (Rubin and Peyrot 1999). Although a generally agreed upon definition is missing, HRQOL is usually understood as referring to a person's overall health and physical, emotional as well as social well-being, when it is directly affected by a medical treatments or conditions (Khanna and Tsevat 2007).

To facilitate comparison of different health-states and interventions it is practical to quantify HRQOL. In its simplest form, such quantification expresses the utility value of the health for someone living in a certain health-state as a single index number on a scale. Such numbers quantify all the aspects of health into a weight for quality of life. These utility values, hereafter called Quality of Life Weights (QLW), are often expressed between 0 (health equivalent to being dead) and 1 (the best health imaginable. They underlie the calculation of Quality-Adjusted Life Years (QALYs) and form the basis for different types of cost-utility analysis (Brauer et al. 2006). To ensure an effective allocation of health care resources, it is therefore important that the QLWs of different health-states are known as accurately as possible. The traditional approach to assessing QLWs for health-states has been through consultation of patients and medical practitioners. However, it is not feasible to conduct such an assessment every time an intervention is being considered. Further, such an approach risks yielding different values from time to time, even for the exact same condition. The latter is a problem for health care decision bodies that need to ensure that all cases of the same merits would receive the same treatment. For these reasons, medical practitioners and experts have called for the assembling of a catalogue of life quality weights for different diseases (Brauer et al. 2006; Tengs and Wallace 2000).

This study will estimate QLWs for Type 1 Diabetes Mellitus (T1DM), and use these to assess the impact from the disease upon HRQOL. T1DM is a common disease found all over the world, associated with higher degree of both mortality and morbidity. Together with the more common T2DM, around 422 million people are diagnosed with diabetes and the number suffering from T1DM has been reported to grow steadily by around 3 percentages annually in high-income countries (World Health Organization 2016). T1DM has severe repercussions – both clinically and for HRQOL – for patients (Jacobson et al. 2013), as well as caregivers (Braga de Souza et al. 2015; Awadalla et al. 2006). Treatment costs are significant and, given its prevalence, it is a source of major public expenditures (Baxter et al. 2016; World Health Organization 2016). Compared to a general population, T1DM patients also suffer elevated risk of several associated complications, both macrovascular (e.g. cardiovascular diseases, such as Ischemic Heart Disease [IHD] and stroke) and microvascular (e.g. renal problems and amputation) (Solli 2010; World Health Organization 2016).

Despite the prevalence and severity of the disease, only few studies have attempted to estimate QLWs for T1DM. Most of these have failed to also calculate QLWs for a general population, meaning that the exact drop in HRQOL that is associated with T1DM is impossible to deduct. Whether a single QLW for T1DM is sufficient, or more is needed for capturing the effect of the disease's associated complications is another question that have been left largely unattended. The need for more studies on how T1DM affects HRQOL is apparent.

This study uses data from two different health surveys, both set in Northern Sweden, to estimate the drop in HRQOL associated with T1DM. One survey was sent specifically to patients with T1DM, the other to a representative sample of the general population. Given that they both measured HRQOL using the EuroQol Five Dimension (EQ-5D) framework, it is possible to compare the HRQOL of the two

groups. To the best of knowledge, this is the first study to capture differences in HRQOL as a single index value, using a geographically and demographically appropriate population sample for comparison.

T1DM is a highly complex disease and the exact way in which it affects HRQOL is still not fully established. Does T1DM have a direct effect on HRQOL, or does the association solely stem from the elevated risk of associated complications compared to non-diabetic populations? Does the severity of these associated complications differ from the impacts the same complications would have had on non-diabetics? These questions are important to address as they determine whether it makes sense for medical decision-makers to use a single QLW for T1DM or if multiple, situation-specific QLWs are required.

This study will calculate the difference in HRQOL between populations with and without T1DM, based upon data from Northern Sweden, both when cardiovascular diseases are controlled for and not. Through this, the study hopes to aid medical policymakers in estimating utility weights, to facilitate efficient allocation of health care resources.

2. Purpose

The purpose of this study is to estimate the effect of Type 1 Diabetes Mellitus (T1DM) upon Health-Related Quality of Life (HRQOL) compared to a general population, both when associated diabetic complications are considered and not.

2.1 Specific aims

- **Estimate Quality of Life Weights (QLW) for T1DM and non-T1DM populations**
  - QLWs for T1DM are useful for health-practitioners undertaking different types of cost-utility analysis for the disease
- **Is loss of HRQOL a direct effect of T1DM or an indirect effect of its associated complications?**
  - This question is important to answer since, if T1DM only affects HRQOL indirectly through its increased risk of complications, no T1DM-specific Quality of Life Weights (QLW) are needed.
- **Do macrovascular complications (Ischemic Heart Disease and stroke) affect HRQOL equally for T1DM patients as for non-diabetics?**
  - If macrovascular complications have different impact upon HRQOL for T1DM patient, separate QLWs for T1DM with and without complications must be used, even when the prevalence of complications are known. If the impact is the same, QLWs for a general population with complications can be combined with QLWs for T1DM to obtain QLWs for T1DM patients with complications.

2.2 Contribution

This study estimates the differences in HRQOL between T1DM patients and a general population, and adds a new QLW for the disease to the field of HRQOL in T1DM. It does so using new and relevant data from Northern Sweden. This value distinguishes between T1DM with and without complications, thereby offering a more accurate valuation of the disease for different patient groups. To the best of knowledge, this is the first study to investigate the effect from T1DM upon HRQOL using a geographically and demographically appropriate reference group.

2.3 Paper structure

This paper is structured a follows. “Background” will provide a short introduction to T1DM and some of the previous attempt to quantify HRQOL for the disease. After this, “Theory” will outline the basic concepts and challenges to health valuation that underlies the methodological choices of this study. “Method” will explain how HRQOL was measured and the statistical methods used for estimating QLWs. “Data” will give a short summary of the data used in this study, as well as a provide summary statistics. The outcome of the study is presented under “Results” and further analyzed in “Discussion”. Finally, the main findings of the study will be summarized under “Conclusion”.

3. Background

3.1 Type 1 Diabetes Mellitus

Type 1 Diabetes Mellitus (T1DM) is a widespread disease with substantial impact on both lifestyle and health among those who develop it (World Health Organization 2016). It is a chronic, incurable disease which follows those affected for the remainder of their lives and is associated with a drop in life-expectancy among those affected. T1DM has been associated with a decrease in HRQOL in many studies (Solli 2010; Imayama et al. 2011; Braga de Souza et al. 2015; Hart et al. 2003), and the rate of HRQOL decrease is greater for T1DM patients than the general population (Hart et al. 2005).

T1DM is a complex disease, with elevated risk of both mortality and co-morbidity. Associated complications include both macrovascular complications like cardiovascular disease (CVD), and microvascular complications such as retinopathy (eye problems), neuropathy (nerve damage) and nephropathy (kidney disease). Microvascular complications are also a common reason for lower extremity amputation. Although these associated complications appear in general populations too, the risk of suffering them is higher among T1DM patients. On top of this, given that T1DM patients are continuously treated with insulin injections, the risk of hypoglycemia, an urgent condition of dangerously low blood glucose levels which can lead to unconsciousness or death, increases dramatically (World Health Organization 2016). Besides through the increased risk of associated complications, T1DM may also have direct negative impact on HRQOL for many patients. Through e.g. requirements on diet, self-medication, exercise and monitoring of blood glucose, T1DM often has a limiting effect on lifestyle (Garratt, Schmidt, and Fitzpatrick 2002). A survey in Northern Sweden found prominent direct effects to include lifestyle limitations and the fear of associated complications or hypoglycemia (Gåfvels, Lithner, and Börjeson 1993). The exact factors which links T1DM to lower HRQOL differs between individuals and have been the field of much research.

T1DM is a disease characterized by a high degree of self-management. This management, primarily targeting low blood glucose values, plays an important role in the progression of the disease (World Health Organization 2016). How disease management affects HRQOL is subject to much debate. Diabetes duration, treatment regime and lifestyle choices have all been linked to worsening HRQOL, although some studies have found contradicting results (Reddy et al. 2016; The Diabetes Control and Complications Trial Research Group 1996; van Dijk et al. 2014; Hopkins et al. 2012). Interested readers are referred to Rubin and Peyrot (1999). What is, however, important to understand, is that both clinical and perceived impacts of the disease are likely to vary widely between T1DM patients, partly due to differences in disease management (Gåfvels, Lithner, and Börjeson 1993).

Unlike the much more common Type 2 Diabetes Mellitus (T2DM), there is no proven correlation between lifestyle and diagnosis with T1DM (World Health Organization 2016). Also, although genetics may play a part in obtaining the disease, at least for some people, this component appear to only explain a modest part of why people develop the disease. This makes T1DM attractive from a statistical point of view, as its seemingly random occurrence makes it easier to deduct causality.

3.2 Previous studies on quality of life weights for Type 1 diabetes mellitus

Despite the prevalence of the disease, research comparing HRQOL among adult T1DM patients to those of a general population have been very sparse. Much more research has been conducted for the more common T2DM, sometimes referred to as lifestyle-dependent diabetes. Although they both are types of diabetes, T1DM and T2DM differ considerably, both in treatment, impact and reason for development. Assumptions that Quality of Life Weights (QLW) and determinants for health are the same for the two are unlikely to hold (Imayama et al. 2011) and HRQOL has been shown to differ between the two types of diabetes (Solli 2010). For this reason, diabetes-specific QLWs may be

insufficient; T1DM-specific values are needed to accurately capture the impact of the disease. However, only few studies have attempted to calculate such values. These studies have also differed vastly in methodology, as well as study populations, making meaningful comparisons hard.

To provide a brief background to previous research on the topic of QLWs for T1DM, such values presented from some similar studies are shown in Table 1. Most of these studies have captured the HRQOL of the disease as a single value, although only few have compared them to QLWs for a general population to assess the HRQOL impact of T1DM. Indeed, these values could be compared to corresponding values of a general population post hoc, but methodological differences make such comparisons unreliable. The only studies that have explicitly dealt with this problem is Burström et al. (2001b), who used a regression framework to capture the overall negative impact of diabetes upon HRQOL as a dummy variable, and Hart et al. (2003), who provided a comparison of the results for T1DM patients to those of a non-diabetic population. However, the former study targeted both types of diabetes, and in the latter data from a British cohort from another study was used as a reference group for the Dutch T1DM patients that the authors studied. Although the authors made sure that the two cohorts matched each other well in some regards (e.g. age), whether it is reasonable to only attribute utility differences between the groups to T1DM is questionable. In conclusion, credible estimation of the T1DM-related drop in HRQOL has been sparse.

If studies presenting QLWs for T1DM is uncommon, studies also analyzing the impact of associated complications is rarer yet. The only study of those presented in Table 1 which has done so is that by Solli et al. (2010). The authors found the QLW, on a scale from 0 to 1, to be 0.90 for T1DM patients without any associated complications and 0.68 for those with complications. As expected, a higher number of complications was associated with a lower HRQOL-value. This study indicates that the presence and severity of associated complications largely drive overall HRQOL, something that has also been confirmed by, amongst others, Burström et al. (2001a), Coffey et al. (2002), Hart et al. (2005) and Jacobson et al. (2013). However, Solli et al. (2010) solely counted the number of associated complications, they made no attempt to differentiate between the impacts from different types of complications.

Table 1 - Previous studies on Health-Related Quality of Life in T1DM

Study	Country	Method	QLW for T1DM	Difference to general population
Braga de Souza et al.	Brazil	EQ-VAS	72.5	
Burström (2001b)¤	Sweden	EQ-5D-3L, Dolan	0.74	-6%
Coffey et al (2002).	U.S.	Quality of Well Being Index (QWB-SA)	0.67 (Male) 0.64 (Female)	
Hart et al. (2003)	Netherlands	EQ-5D-3L, Dolan EQ-VAS	0.88 (EQ-5D-3L) 80.8 (EQ-VAS)	-3% (EQ-5D-3L) -5.8% (EQ-VAS)
Imayama (2011)	Canada	Single item question: "How good is your health" with 5 responses, converted to a scale 0-100	54.8	
Solli et al. (2010)	Norway	EQ-5D-3L, Dolan	0.83	

Table 1: *Table listing quality of life weights (QLW) for patients with T1DM, and their size compared to corresponding QLW for the reference group, reported from previous similar studies. For an explanation of methods, see "Theory" and Method" sections below.*

¤ *Results derived for a general diabetic population, and hence not T1DM-specific.*

4. Theory

This chapter outlines the theoretical background for utility valuation of health-states. It also briefly discusses the key questions behind any such valuation: *what* should be valued, *how* is it to be valued and *who* should value it. The chapter concludes with the introduction of a concept that has long challenged practitioners of health valuation – health-states deemed worse than death.

4.1 The concept of utility valuation

Usage of both the Quality-Adjusted Life Years (QALY) method and other cost-utility valuation are important tools for health care evaluation and comparison of treatments. For them to be useable, utility values, in this study referred to as Quality of Life Weights (QLW), are needed. Ideally, QLWs should be available for every disease (Brauer et al. 2006; Tengs and Wallace 2000). Usage of such values enables fairer comparison of cost-effectiveness across diseases and is important to ensure that interventions are based upon fair merits (Russell et al. 1996). However, despite the simplicity of the concept, quantifying health on a scale (e.g. from 0-1, or 0-100) is a hard task that comes with numerous complicating factors. Preferences are subjective and the perceived consequences of a disease or condition may differ depending on who is asked and the implicit standards they have. Furthermore, there are even deeper philosophical questions to consider, e.g. whether the valuation of a health state should be uniform to everyone, or some states can be deemed more intolerable for some people than others (Williams 1997). The answers to such questions have a direct impact upon health care prioritization (Månsdotter, Lindholm, and Öhman 2004).

It has been suggested that there are three main questions to assess when attempting to value a health state: *what* should be valued, *how* is it to be valued and *who* should value it. Each of these creates a challenge for health economists. (Dolan 2011)

The *what* concerns what should be included in the valuation. Exact, uniformly used definitions of what constitutes HRQOL and utility are lacking (Richardson 1994; Watkins and Connell 2004). Should HRQOL only encompass clinical, biological health, or should mental and social health be included too? Should health be measured against a uniform benchmark or against each individual's own health potential? Another important aspect is that for persisting states, such as T1DM, the burden of disease may change over time (Attema et al. 2013). For some chronic health-states, e.g. ones of diminished mobility, the perceived burden appears to diminish over time, due to adaptation to the condition. However, for severe states, in particular conditions of chronic pain, the burden may also rise when the duration of the state is increasing (Dolan 2011, 1996). At which point in time should the overall utility of the health-state be assessed?

Unfortunately there are no generally agreed upon definitions of what should and should not be included (Watkins and Connell 2004). It has been suggested that the great heterogeneity in the conceptualization of HRQOL has ailed the health community's understanding of the connections between T1DM and HRQOL (Coffey et al. 2002; Tengs and Wallace 2000). The uncertainties regarding what should be valued is a concern as this may cause different respondents to value health-states differently, even should they, objectively speaking, be identically impacted.

The traditional approach to health measurements has been to measure health clinically. This is good in that it allows for straightforward comparison of health across individuals. However, for more complex questions on health, clinical measurements may be insufficient. In these cases, patient-assessed measures of health is an option, and its usage has been increasing (Garratt, Schmidt, and Fitzpatrick 2002). Surveys and interviews are ways to learn the HRQOL of the individual. Many different tools have been developed for this purpose, capturing different aspect of health. A distinction between

tools assessing health status and health utility has been proposed (Khanna and Tsevat 2007). Health status tools only measure health in different domains, e.g. physical, mental and social. Measures assessing health utility may also be decomposed into different domains, but these methods allow overall utility for a health-state or condition to be expressed as a single index value. The health utility measures are the main focus of this study.

Many different measurement tools are available. These can be both *generic* tools which can compare health and well-being across multiple disease categories, or *disease specific* which allow for more detailed health assessment within particular diseases (Ferguson and Keown 1995). The theoretical underpinnings of the tools also differ considerably, assessing health in different ways and through different aspects (Watkins and Connell 2004). Generic tools have an advantage in that they can easily be compared across populations and disease groups, allowing for straightforward calculation of QLWs (and thereby QALYs).

The complex nature of diabetes has seen a wide array of diabetes specific measurement tools being developed. Some of these are even T1DM specific, such as the Diabetes Specific Quality of Life Scale (DSQOLS) and, to some extent, the Diabetes Quality of Life Measure (DQOL). These tools are developed to capture more specific aspects of diabetes, e.g. lifestyle limitations and dealings with clinical practitioners. (Garratt, Schmidt, and Fitzpatrick 2002) Among the drawbacks with these more specific measures are the smaller sample size used in their development and their limited usefulness in non-diabetic populations. For this reason, many health economists recommend usage of generic and widely established measurement tools, designated for generating QALYs, e.g. EQ-5D (Dolan 2011; Brauer et al. 2006).

An important aspect of health measurement tools is how responsive they are to changes in health. Some tools may be unable to pick up on the finer differences in health, if problems can only be stated in specific domains and coarse degrees. On the other hand, too much responsiveness may be excessive. A common concept is that of the *Minimum Clinically Important Difference*, i.e. the finest degree of responsiveness where differences in outcome can still mandate a change in treatment (Khanna and Tsevat 2007). For natural reasons this is not a problem for the Rating Scale method if a continuous scale is used for responses.

4.2 How should Health-related Quality of Life be quantified

Another challenge is how to quantify HRQOL. What level of well-being or disutility should correspond to what values on a 0-1 scale? Although it has been suggested that health stock can be viewed as a common good and priced accordingly (Grossman 1972), quantification of the value of something as abstract as health is far from straightforward. Different methods for quantifying health are available, but the choice of method unfortunately appears to have a large impact on the results (Attema et al. 2013). For this reason, direct comparison of results between studies using different methods must be undertaken with great caution.

A common distinction is between direct and indirect utility measures. The first category attempts to directly elicit a QLW for health-states by asking people to value their own health. The most common methods for this are the Standard gamble (SG), Time Trade-Off (TTO) and the Rating Scale (RS) (Morimoto and Fukui 2002). The second category is indirect measures. Here, the health stated by patients is valued by other respondents, often using the techniques mentioned above (Khanna and Tsevat 2007). Below the three valuation techniques are briefly outlined.

4.2.1 Direct valuation methods

The Standard Gamble (SG) has its roots in classic utility and risk theory. Different versions of the method are available, but the principle is roughly the same. The respondent is asked to imagine living in the health-state to be valued, and given the opportunity to choose between two different states of the world. In the first, life will continue like normal in the current health-state. In the second, a gamble occurs, so that the respondent will either be "healed" and continue life in perfect health (i.e. utility equal to 1), or die instantly (utility equal to 0). The gamble results in the best state with probability p and the worst with probability 1-p. The respondent is then asked to value p such that he or she is indifferent between the two states of the world. A high value of p is synonymous with a higher QLW for the health-state as it indicates an unwillingness to risk the gamble to achieve better health unless chances of doing so are favorable. If the utility of the health-state was lower, the respondent would be willing to undertake a riskier gamble to alleviate the condition, which would be reflected by a lower value of p. (Morimoto and Fukui 2002; Khanna and Tsevat 2007)

Time Trade-Off (TTO) uses a similar reasoning. The basic idea is that the respondent is asked to imagine living in a given health state for a set time-frame, commonly 10 years, after which death follows. The opportunity is then given to swap that life for one lived in perfect health but shorter time. Respondents are asked to state the time spent in perfect health for which they would be indifferent between the life in the given health state or the life at full health. As the time spent in perfect health required to achieve indifference decreases, the given health state is considered worse. For example, if health-state A is equivalent of spending 9 years in perfect health and B is equivalent to only 5 years, then health-state A is preferred to B. The respondent is obviously willing to trade away more time in perfect health to alleviate health-state B than is the case for state A. (Dolan et al. 1996; Morimoto and Fukui 2002)

In this way, a trade-off between health quality and time is imagined. If respondents on average deem 10 years spent in a particular health-state equally attractive to spending 5 years in perfect health, the health-state receives a QLW of 0.5. Naturally, the higher the value, the better the health-state. The best imaginable health-state would be given the value of 1, in this case the respondents would not trade off any life-time to obtain a better health. (Attema et al. 2013)

The Rating Scale (RS) is an even more direct and intuitive utility valuation method. The respondent is simply asked to mark where the health-state in question belongs on a utility scale, commonly ranging from e.g. 0-100 and/or death to perfect health (Morimoto and Fukui 2002). It has been shown that the RS method has a strong tendency to yield lower QLWs than both the SG and TTO methods (Morimoto and Fukui 2002; Ferguson and Keown 1995).

The RS method provides explicit preference values by the respondent. By contrast, the SG and TTO methods obtain QLWs through situation-based decisions by the respondents (Morimoto and Fukui 2002). The three techniques each have their strength and drawbacks. The SG and TTO methods require a deeper conceptual understanding which may be difficult for some respondents. They further depend crucially on the patient's approach towards risk and time. With risk behavior differing considerably among people, and the valuation of time being subject to age (Dolan et al. 1996), these shortcomings may be substantial, although there is evidence that TTO is somewhat easier to use and yields more consistent estimates (Ferguson and Keown 1995; Dolan et al. 1996). On the other hand, both the SG and TTO methods provide a clear context for the magnitude of differing valuation, unlike the RS method where the difference between steps along the utility scale may seem quite arbitrary. (Khanna and Tsevat 2007)

4.2.2 Indirect valuation methods

Indirect valuation methods calculate QLWs for particular health-states by consulting a wider population than just the individual. The individual is asked to state his or her health as a combination of levels in different domains, but not as an overall score. Instead, the wider population state what QLW they deem fair for each level and domain. These weights can then be applied to individual patients to obtain a utility value for their health. For example, a large group of respondents may be asked to – using the techniques described above – value the utility of a health state with limited mobility. This QLW can then be given to any patient that reports limited mobility. Common indirect valuation methods include the EuroQol EQ-5D and the Medical Outcomes Study 36-Item Short Form (SF-36). One advantage of indirect valuation methods is that each respondent can value more than one health-state, which diminishes problems with respondents not quite understanding the valuation concept (Khanna and Tsevat 2007). Note that indirect valuation methods are simply imputing a value on overall health as deemed appropriate by others, based upon the health stated in each domain by the patient. Hence, the QLW is not necessarily an accurate valuation of the patient's own actual HRQOL.

4.3 Who is to value Health-Related Quality of Life

When indirect valuation methods are used, the question of who should value health-states is of great importance. A division into two different types of health-state valuation is common: hypothetical and experienced-based valuation. Hypothetical valuation refers to valuation carried out by a general population, whereas experienced-based valuation is undertaken by people that have themselves experienced certain health-states. Hypothetical valuation is easier to undertake as every respondent can value a greater number of health-states which means fewer respondents are needed to obtain sufficient valuation, thus decreasing the risk of respondents using different standards. It has been suggested that comparability of results between different studies and conditions would be greater when hypothetical valuation is at hand (Russell et al. 1996), and that this better reflect the will of tax-payers and potential receivers of health care (Braga de Souza et al. 2015; Khanna and Tsevat 2007). Experienced-based valuation on the other hand dwell upon valuation from those with more knowledge of what the health-states are actually like (Burström et al. 2014).

The choice between hypothetical and experienced-based valuation has been shown to matter for utility valuation of diseases and health-states (Russell et al. 1996; Kiadaliri, Eliasson, and Gerdtham 2015). Presence of medical complications affects respondent's valuation of health-states (Essink-Bot et al. 2007). Generally, experienced-based valuation tends to place a higher QLW on health-states than those obtained through hypothetical valuation. For many conditions there appear to be a considerable degree of adjustment, so that, after a while, the perceived disutility from suffering the condition decreases. Such an adjustment effect is not captured by hypothetical valuation. It has been shown that when hypothetical valuation is used, people are sometimes willing to sacrifice much life-expectancy in order to avoid certain conditions, even when the adaptation effect for the conditions is great. (Dolan 2011)

The choice of valuation regime matters considerably for this study, and its importance will be further explored below. One last point should however be made at this stage. The QALY method favors interventions that have the potential of yielding the highest improvement in HRQOL for the longest time. A higher valuation of a health-state hence means relatively favoring interventions that prolong life and disfavoring those increasing its quality. (Kiadaliri, Eliasson, and Gerdtham 2015)

4.4 Negative utility values

One concept that has caused health valuation techniques much problem is that of negative QLWs, i.e. health-states deemed worse than death (Attema et al. 2013). Although valuation is in practice capped at 1 (perfect health), there is nothing preventing respondents from valuing a state below the lower bound of 0 (equivalent of death). Neither does it require much fantasy to imagining health-states for which, if permanent, those affected would prefer death.

Negative QLWs have challenged scientists in several ways. First, the policy-implementations from such states are very harsh: would it be welfare-enhancing if society was to deny life-extending treatment for people who could otherwise be expected to remain in these negative health-states for all foreseeable future? Secondly, they pose methodological challenges to the measuring concept. Since negative life-years is not possible, TTO valuation of health-states with negative QLWs requires that respondents instead face another question, e.g. "how much time in perfect health would be required to compensate for putting up with this condition for ten years?". Third, it appears that values below zero suffer from a high degree of "inflation", creating an asymmetry between positive and negative values. For example, in a commonly quoted paper on health valuation, Dolan (1997), using TTO, found that one respondent deemed a particular health-state to be valued at -39, an incredibly dramatic value in a setup where the full difference between death and perfect health supposedly was covered between 0 and 1. Naturally, this makes straightforward quantification of health – which is the exact reason for the TTO method – hard. Perhaps this asymmetry is caused by the inherent challenge of the thought-experiment that TTO constitutes; that respondents' ability to meaningfully quantify utility derived from health vanes off the further from "normal" health the thought takes them. Regardless of the cause, the problem of these large negative values have caused many scientists to convert negative values to a scale capped at -1, even though this means interfering in the respondents' valuations.

What makes negative values an even greater problem for scientists is that they are not as uncommon in health-state valuation as one might think. In fact, some valuation methods appear to constantly obtain negative QLWs for at least some health-states.

5. Method

This chapter introduces the EQ-5D tool, which is used for valuing HRQOL in this study. After that, it deals with the topic of choosing a suitable value set for analyzing EQ-5D-3L data. It then concludes by presenting the statistical methods and specifications employed in this study.

5.1 EQ-5D

This study uses the EuroQol EQ-5D instrument to measure Health-Related Quality of Life (HRQOL). EuroQol is a network of international researches, aiming at supporting health research by providing instruments for valuation and description of health. The group's main instrument is EQ-5D, a tool developed by multidisciplinary collaboration, initially constructed for 5 Northern European countries but today available worldwide (EuroQol group 2016a). The EQ-5D instrument has been widely used and validated, and is the most common instrument for calculation of QALYs based upon HRQOL (Räsänen et al. 2006).

The EuroQol EQ-5D instrument consists of two parts: the more commonly used EQ-5D tool, and the complementary EuroQol Visual Analogue Scale (EQ-VAS). EQ-5D asks respondents to value their own health in five different dimensions: 'mobility', 'self-care', 'usual activities', 'pain/discomfort' and 'anxiety/depression'. It is an indirect health utility measure as QLWs cannot be directly inferred, instead the dimensions must be separately valued and weighted together. EQ-VAS on the other hand is a Rating Scale (RS) method, and as such more straightforward. The respondent is simply asked to value the overall quality of their health on a scale from 0 (the worst health imaginable) to 100 (the best health imaginable). The EuroQol group views the two tools as complements to one another and strongly discourage analysis of only one of them (van Reenen and Oppe 2015).

Two versions nowadays exist for the EQ-5D tool, the classic one which allows respondents to state three different levels of problems in each dimension, and a newer system which allows for five different levels of severity. The three-level version, hereby referred to as EQ-5D-3L, is far more commonly used: to this day it has been translated into more than 170 languages (EuroQol group 2016b). This is the EQ-5D version used for this study. It classifies problems in every dimension as one of three levels: 'no problems' (1), 'some problems' (2) and 'extreme problems' (3). For every dimension a brief explanation or example of what constitutes each level of problems is presented. The respondent chooses one of the levels for each dimension, so that a complete answer to EQ-5D-3L becomes a five-digit number, e.g. 12233 (no problems with mobility, some problems with self-care and usual activities and extreme problems with pain/discomfort and anxiety/depression). A total of 243 combinations of health-states thus become possible[1].

Where the EQ-5D-3L tool provides examples of what health problems corresponds to each level of severity, EQ-VAS simply asks the respondent to state how his or her health is today. EQ-VAS uses no further anchoring than the endpoints (the best and worst health imaginable, respectively) which raises questions over its interpretability. Since the lower end of the EQ-VAS scale does not necessarily align with the classic point zero of utility valuation (health equivalent to being dead), health-practitioners have tended to prefer QLWs based upon EQ-5D. Further, age has been shown to be a poor independent determinant of EQ-VAS (Braga de Souza et al. 2015).

Although often preferred to EQ-VAS, two concerns, however, exist over the EQ-5D-3L tool. First, its responsiveness has been questioned due to the great differences between levels (no, some and extreme problems, respectively). Whilst e.g. lifestyle restrictions due to T1DM is often pointed out as

[1] Some studies instead claim that there are 245 states. There are 3^5=243 combinations of responses available. On top of this, two more states, one for unconsciousness and one for death are commonly added.

one of the big problems with the disease (Gåfvels, Lithner, and Börjeson 1993), it is not clear that such restrictions would be registered as an increased level of problems in any of the five dimensions. Second, unlike EQ-VAS, EQ-5D-3L only provides health values in five different dimensions. This means that to obtain a value for overall health based upon EQ-5D-3L, the severity level of each dimension must be weighted together[2]. This problem lacks easy solutions: the respondents solely provide information on which severity level they experience in each dimension, not how they think each dimension impacts their overall health. Researchers have to assume a weighting system (e.g. give all dimensions equal weight), but this may poorly reflect the respondents' own valuation. Furthermore, it is also possible that the weight of each dimension shifts with increasing severity, so that one dimension could be of comparatively small importance to overall health when problems are modest but of great relevance when problems are severe.

The practice recommended by the EuroQol group is to weight together EQ-5D-3L answers into one overall value, using predetermined value sets. Such value sets, previously referred to as tariffs, are essentially a weighting index, specifying how the severity in each dimension affects overall health. Value sets were first derived for EQ-5D data by Dolan in the mid-90s (Dolan 1997), and more studies have since followed, using similar methods. A population of respondents are asked to value different EQ-5D-3L health-states. Valuation can be done through different methods, but the Time Trade-Off (TTO) method has been the most common as it yields more consistent answers than the Standard Gamble (SG) (Dolan et al. 1996). For example, respondents could be asked to, through the TTO method, value the health-state 11223 ("How much time in perfect health do you consider equally attractive as spending 10 years in a condition with no problems with mobility and self-care, some problems with usual activities and pain/discomfort, and extreme problems of depression/anxiety?"). In this way, QLWs for any health-states can be derived. For more details on how this is done, interested readers are referred to the pioneering study by Dolan et al. which derived a value set for a British population (Dolan et al. 1996).

In short, the usage of value sets allows imputation of a value for overall health for any respondent who has completed an EQ-5D-3L questionnaire. However, two important things must be kept in mind. First, as previously mentioned, the method with value sets is simply imputing a value on overall health as deemed appropriate by others, based upon the patient's responses to the EQ-5D-3L. The patient's own overall health valuation is still missing and the imputed value is not necessarily an accurate valuation of the his or hers actual HRQOL. Second, value sets can be derived from any population, and every value set gives a different value to each patient's overall health. Multiple value sets are available (Szende 2007), and it has been shown that the choice of value set has a substantial impact on the results of health-state valuation (Kiadaliri, Eliasson, and Gerdtham 2015). A matter of great importance hence becomes the choice of value set.

5.2 The choice of value set

Above, the importance of the choice of value set for weighting together EQ-5D-3L dimensions have been pointed out. There are multiple value sets available for this task (EuroQol group 2016c; Szende 2007). Since the value set method imputes values for patients' health from valuation by respondents, the respondents' preferences should reflect the patients' preferences as accurately as possible. It has been shown that preferences vary between countries and that results are sensitive to the choice of value sets (Kiadaliri, Eliasson, and Gerdtham 2015). This makes it desirable to use as local value sets as possible. The EuroQol-group suggests that any study attempting to value health-states should be

[2] The possible exception is the health-state 11111, which indicates no problem in any of the five dimension and is hence often given the QLW 1, i.e. perfect health.

subject to sensitivity analysis, i.e. checking the robustness of the results using more than one value set (Szende 2007). For this reason, this study uses three different value sets.

The first value set is the one by Dolan (1997), derived from a general population study in the UK in the mid-90s (Dolan et al. 1996). The system is a hypothetical valuation, based upon the Time Trade-Off (TTO) method, using health-state estimations from 3395 participants. This was the first value set of its kind ever developed for EQ-5D-3L and has become somewhat of the industry's informal standard. Since virtually all subsequent studies deriving value sets have referred to this set, Dolan's value set is an obvious choice, facilitating comparisons towards other studies.

In lack of a hypothetical value set for Sweden, this work instead utilizes the Danish set developed by Wittrup-Jensen et al. (2009), in line with recommendation from the EuroQol group. This value set was derived using TTO valuation and first published in 2009. Two different value sets are available based upon this study. Of these, the one without an additional dummy for "extreme problems" being reported in any dimensions were used, following recommendation from the deriving authors.

The final value set was derived by Burström et al. (2014) and first published in 2014. This value set was selected for two strong reasons. First, the index is based upon Swedish data, making it the geographically most appropriate choice of all available value sets. Secondly, it is yet the world's only experienced-based set to be properly validated, thus the only credible option for providing an alternative to hypothetical valuation. The inclusion of this value set not only allows for sensitivity analysis, it also allows for a more in-depth comparison between the results from hypothetical and experienced-based value sets.

The value sets differ in how harshly they penalize problems, depending on dimension and severity levels. This is shown in Table 2. One difference is the range of possible values that the value sets can yield, i.e. the difference between the best health-state (11111) and the worst health-state (33333). For the hypothetical value sets, these are fairly similar, spanning from 1 to -0.594 in the case of Dolan's set, and 1 to -0,624 for the set by Wittrup-Jensen et al. The experienced-based set by Burström at al. however differ considerably, ranging from 0.969 (11111) to 0.340 (33333). Two notable differences are that Burström's value set never yields negative QLWs for any health-state (i.e. any of the 243 health-states are considered better than death) and that the highest possible value is lower than 1 (perfect health), which was the default for respondents without any problems in the two hypothetical value sets; this value sets hence implicitly deems perfect health unattainable.

Table 2 – Comparison of value sets

	Default	MO 2	MO 3	SC 2	SC 3	UA 2	UA 3	PD 2	PD 3	AD 2	AD 3
Dolan	A	C	B	C	B	A	A	C	B	C	B
Wittrup-Jensen	A	A	C	B	A	B	C	B	C	B	C
Burström	C	B	A	A	N/A	C	B	A	A	A	A

Table 2: *Table showing how harshly the three different value sets penalize 2='Some problems' and 3='Extreme problems', respectively, in each dimension of health. A (Green) is least penalizing and C (Red) most penalizing. MO='Mobility', SC='Self-care', UA='Usual activities', PD='Dain & discomfort, and AD='Anxiety & depression'*

Kiadaliri et al. (2015) compared the value sets, using data from patients with type 2 diabetes in the Swedish National Diabetes Registry (NDR), to find out how the choice of value set affected results in practice. They found that the mean QLW differed between the sets. In line with theory, the experienced-based, Swedish set by Burström et al. gave the highest average HRQOL value (0.88), followed by the set by Wittrup-Jensen et al. (0.80). Dolan's value set gave the lowest average value

(0.77). The combined usage of the Swedish experienced-based and non-Swedish hypothetical-based value sets follows recommendations from this study.

5.3 Statistical methodology

5.3.1 Overall health

To estimate the impact upon Health-Related Quality of Life (HRQOL) associated with Type 1 Diabetes Mellitus (T1DM), an Ordinary Least Squares (OLS) framework was used. HRQOL was used as the dependent variable and the difference in HRQOL between the respondents with and without T1DM could be captured by inclusion of a dummy variable for diabetes status. Given that the reason for developing T1DM remains unclear, one could argue that this difference is causal, i.e. that having T1DM is the cause of any HRQOL differences between the groups.

The basic regression framework is given by Equation 1.

$$Y_i = \alpha + \beta_{T1DM} + \gamma_i + X_i + \varepsilon_i \quad [1]$$

where Y_i denotes HRQOL of individual i, α is the intercept in the linear model, β_{T1DM} is a dummy variable for diabetes status, γ_i is a vector for associated complications, X_i is a vector of other control variables of HRQOL and ε_i is an error term. The estimated impact upon HRQOL from T1DM, after controlling for other characteristics, is hence straightforwardly captured by $\hat{\beta}_{T1DM}$.

Distinguishing between direct and indirect effects to HRQOL from T1DM is a more challenging matter. One problem is that direct effects include many things that are typically hard to measure for the individual, such as lifestyle changes and fear of worsening condition. For this reason, it is easier to establish the size of direct effects through establishing the contribution of indirect effects, which consists of complications (both micro- and macrovascular) that are more commonly measured. The relationship between the total effect that T1DM has upon HRQOL and direct and indirect effects is described by equation 2.

$$\hat{\beta}_{T1DM} = Direct\ effects + Indirect\ effects \quad \rightarrow \quad Direct\ effects = \hat{\beta}_{T1DM} - Indirect\ effects \quad [2]$$

Where $\hat{\beta}_{T1DM}$ indicates the total T1DM-related difference in HRQOL. Note that if data on any associated complication is omitted, direct and indirect effects cannot be fully distinguished.

5.3.2 Individual dimensions of health

When analyzing individual dimensions of EQ-5D-3L data, the statistical approach must be somewhat different than for overall health. This is because the dependent variable can only take on three values: 'no problems', 'some problems' or 'extreme problems'. As these are clearly ordered ('no problems' is better than 'some problems, which in turn is better than 'extreme problems'), the theoretically sound approach was to use either ordered probit regression or ordered logistic regression. The former was chosen given that it is based upon normal distribution and since it does not assume that the difference between 'no problems' and 'some problems' are equal in size to the difference between 'some problems' and 'extreme problems'. (Asteriou 2011; Verbeek 2012)

Since the exact magnitude of problems are hard to establish, an approach using binary dependent variables was also used. This required recoding of the data on individual EQ-5D-3L dimensions into dummy variables that indicated either 'no problems' or 'problems'. These were analyzed using probit regression, a conventional choice when estimating dependent binary variables.

5.3.3 Statistical specifications

Whereas most control variables in the regression models were dummy variables, several alternative specifications were possible for age. A quadratic term for age could be used if HRQOL effects would be

increasing (or decreasing) over time. This scenario seemed likely since the risk of developing associated diabetic complications increases over time. However, tests showed no non-linear correlation between age and HRQOL. An alternative approach was to categorize age into groups of different sizes, e.g. 18-28 years, 28-38 years and so on. However, this would have made results subject to the choice of arbitrary cut-off points. In the end, no specification yielded better results than letting age enter the model linearly, which was therefore the only specification used in the regression framework to conserve statistical power.

Given the purpose of this study, there was no explicit need to test how much each associated diabetic complication contributed to overall HRQOL-loss amongst T1DM patients. For this reason, dummy variables for any macrovascular and microvascular complications, respectively, were created, in order to conserve statistical power. To test if T1DM patients are differently affected by associated complications than a general population, an interaction term for HRQOL and T1DM was created.

Respondents who failed to provide complete answers to either EQ-5D-3L or EQ-VAS were excluded from the study. In cases where at least one of these were provided, missing values only led to respondents being excluded from those regressions for which values were missing. For all other statistics and tests, unless otherwise stated, respondents were also excluded only from the analysis where their missing data was directly needed. Unless otherwise stated, α=5% was used to determine statistical significance.

All calculations in this study were performed using STATA, version 14.0 (StataCorp LP, College Station, TX, USA).

6. Data

This study uses two cross-sectional data sets to obtain a Quality of Life Weight (QLW) for Type 1 Diabetes Mellitus (T1DM). This section will explain the sources of the data, the definitions of the variables and also provide descriptive statistics of the two populations.

6.1 The population surveys

A survey was distributed to all T1DM patients registered at the Section of Endocrinology, Department of Medicine, at Sunderby hospital in Northern Sweden. The survey was initiated as part of a study on the effects of T1DM upon fatigue, and the patient population has been described elsewhere (Segerstedt, Lundqvist, and Eliasson 2015). Only patients over 18 years were admitted to the study. Classification of T1DM was determined by treating clinician in the cities of Luleå and Boden. In total, 435 patients received the survey, comprising an estimated 90% of all patients with T1DM in the area.

Data was collected between August 2012 to August 2014. The questionnaire was sent out by mail and was also available at health clinics during routine check-ups for patients with T1DM. At the end of the time-frame, non-responders were contacted by telephone and asked about their intention to participate in the study. Data about diabetes history and associated complications were taken from patients' medical records. (Segerstedt, Lundqvist, and Eliasson 2015)

To find the effect of T1DM upon HRQOL a reference group was used. This consisted of participants in the Northern Sweden MONICA study. The MONICA (multinational MONItoring of trends and determinants in CArdiovascular disease) project was a repeated cross-sectional and cross-country study on the determinants of and trends in cardiovascular disease, initiated by the World Health Organization (WHO) in the 1980s (WHO MONICA Project Principal Investigators 1988). This influential study has been carried out in many waves and countries. In Northern Sweden, several population-based surveys have been carried out since 1986, even after the discontinuation of the MONICA collaboration in 1995 (Eriksson et al. 2011). The latest study to date was completed in 2014. The cohort was chosen independent of the previous waves. Just as previous studies, the 2014 study included 2500 people, aged 25-74 (Eriksson et al. 2016). Since this was a general population study, it is possible that some respondents with T1DM were included.

In total, 268 T1DM patients and 1557 MONICA respondents participated in the study, yielding a total of 1825 respondents. The response rate for both groups were 62%. Older respondents participated to a higher extent than younger ones. (Segerstedt, Lundqvist, and Eliasson 2015)

Access to the data for both populations was granted by the principal investigators for the Northern Sweden MONICA Project.

6.2 Definitions and descriptive statistics

The age profile of the respondents differed slightly between the two populations, as shown in Figure 1. Since the T1DM survey was not restricted to certain age groups, this cohort spanned a wider age gap, 18-84 years, than the MONICA cohort, despite the smaller sample size. The average age of the respondents were 47.97 years for the T1DM patients, and 51.84 years for the MONICA group.

Figure 1 – Age distribution in the two groups

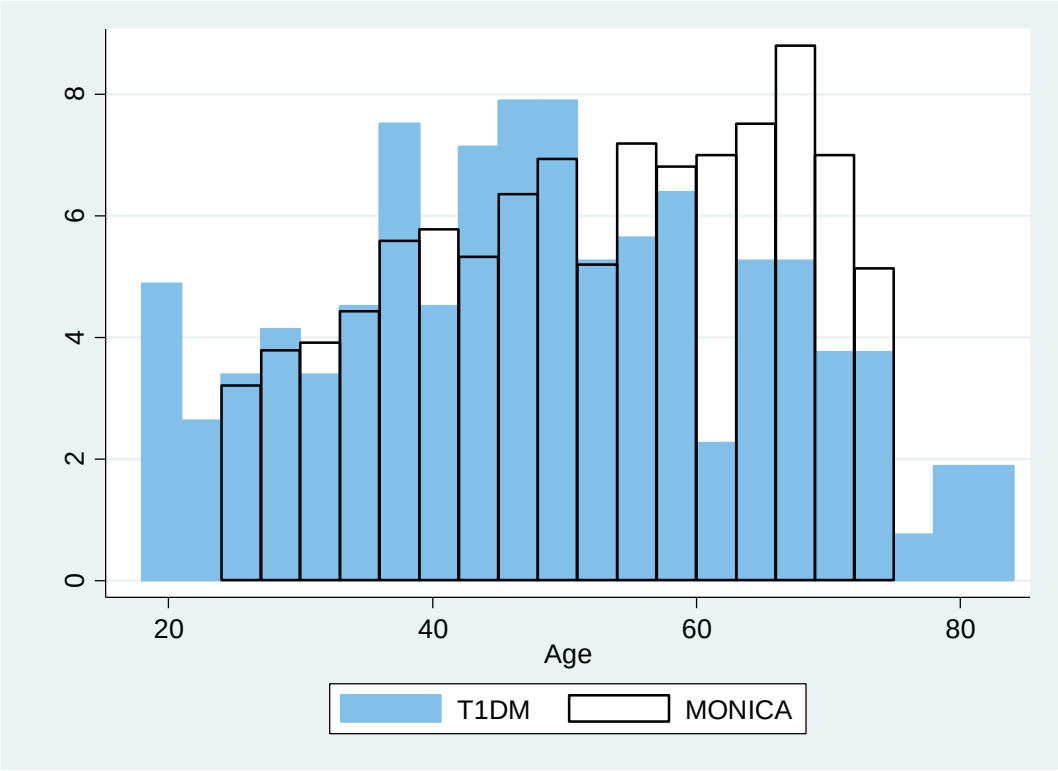

Figure 1: *Age distribution in the two populations. Each bar is 3 years wide. The vertical axis shows the share of respondents in each population that belonged to which age group.*

Data on complications associated with T1DM differed between the groups. Macrovascular complications (Ischemic Heart Disease (IHD) and stroke) were taken from patient journals in the case of the T1DM patients, but stated by the respondents themselves in the MONICA cohort. Data on microvascular complications (retinopathy, neuropathy, nephropathy and lower extremity amputation) were collected for the T1DM patients, but not the MONICA group[3].

Descriptive statistics for each population is shown in Table 3. Given the low prevalence of patients with a history of amputation, a dummy variable for the presence of any microvascular complication was generated. To conserve statistical power, a dummy variable on cardiovascular disease (CVD), comprising both Ischemic Heart Disease (IHD) and stroke was also created.

Information on tobacco usage was collected in both surveys. However, the questions faced by the MONICA group were more elaborate than those for the T1DM patients. To ensure comparable data, smoking was defined in this study as current daily smoking only.

[3] In this study, the following definitions of microvascular complications were used. Retinopathy was defined as either having retinopathy or a history of surgery (with or without laser) due to retinopathy. Neuropathy comprises both neuropathy and/or angiopathy. Nephropathy was defined as the presence of either micro- or macroalbuminuria. Amputation was defined as history of amputation for any reason.

Table 3 – Characteristics and complications

Respondent characteristics and complications			
Characteristics	MONICA n=1557	T1DM n=268	T-value
Age (mean) (n=1823)	47.974	51.843	4.130 ***
Female (n=1825)	804 (51.64)	125 (46.64)	1.51
Smoking (n=1815)	121 (7.81)	16 (6.04)	1.01
Macrovascular			
IHD (n=1805)	70 (4.55)	24 (8.96)	-3.00 **
Stroke (n=1811)	37 (2.4)	10 (3.73)	-1.27
CVD (n=1801)	99 (6.46)	30 (11.19)	-2.78 **
Microvascular			
Retinopathy (n=266)	N/A	146 (54.89)	N/A
Neuropathy (n=264)	N/A	50 (18.94)	N/A
Nephropathy (n=261)	N/A	42 (16.09)	N/A
Amputation (n=264)	N/A	3 (1.14)	N/A
Microvascular (n=260)	N/A	158 (60.77)	N/A

Table 3: *Table showing the characteristics of the respondents for the T1DM and MONICA groups, respectively. Figures show the number (percentage) of respondents for each characteristic. Percentages calculated based upon complete responses only. CVD is defined as history of either Ischemic Heart Disease (IHD) or stroke. T-values show likelihood that the two group averages are statistically different: *=p<0.05, **=p<0.01, and ***=p<0.001*

HRQOL was stated using both EQ-5D-3L and EQ-VAS. The severity and dimension of problems stated using EQ-5D-3L is presented in more detail in Table 4. In total, 31.9% of the respondents who gave complete answers stated the health profile 11111 (i.e. no problems in any dimension), whilst 5.9% stated extreme problems in at least one dimension. Patients with T1DM generally reported more problems than the respondents in the MONICA group.

When HRQOL was stated through EQ-VAS the T1DM patients also stated worse health. The average EQ-VAS value reported by the T1DM patients was 72.74. The corresponding figure for the MONICA group was 73.26. The distribution of the EQ-VAS scores for the two different groups are presented in Figure 2 (A) & (B). From the graphs it is clear that a slightly higher share of the T1DM patients reported low EQ-VAS scores, whereas a higher share of the MONICA group can be found in the higher range of the score.

Table 4 - Distribution of EQ-5D-3L answers

Distribution of EQ-5D-3L answers							
Dimension	Level	T1DM n=268			MONICA n=1557		
		Total %	Men %	Women %	Total %	Men %	Women %
Mobility (n=1805)	1	83.90	86.01	81.45	91.22	90.91	91.52
	2	16.10	13.99	18.55	8.78	9.09	8.48
Self Care (n=1813)	1	94.76	95.80	93.55	99.35	99.73	99.00
	2	5.24	4.20	6.45	0.45	0.13	0.75
	3	0.00	0.00	0.00	0.19	0.13	0.25
Usual Activities (n=1814)	1	83.52	88.81	77.42	92.63	94.65	90.74
	2	15.36	10.49	20.97	7.11	5.21	8.89
	3	1.12	0.70	1.61	0.26	0.13	0.38
Pain and Discomfort (n=1792)	1	41.29	45.39	36.59	41.56	45.42	37.91
	2	51.89	51.06	52.85	54.58	52.56	56.49
	3	6.82	3.55	10.57	3.86	2.02	5.60
Anxiety and Depression (n=1801)	1	61.65	66.43	56.10	67.88	75.74	60.53
	2	35.71	31.47	40.65	30.49	23.05	37.45
	3	2.63	2.10	3.25	1.63	1.21	2.02

Table 4: *Table listing the share of respondents that reported which level of severity in each dimension for EQ-5D-3L. Percentages are based upon complete responses only; non-responses have been omitted. 1='No problems', 2='Some problems' and 3='Extreme problems'. Note that no respondent reported the highest level of problems for 'Mobility'.*

Figure 2 (A) & (B) - Distribution of EQ-VAS score

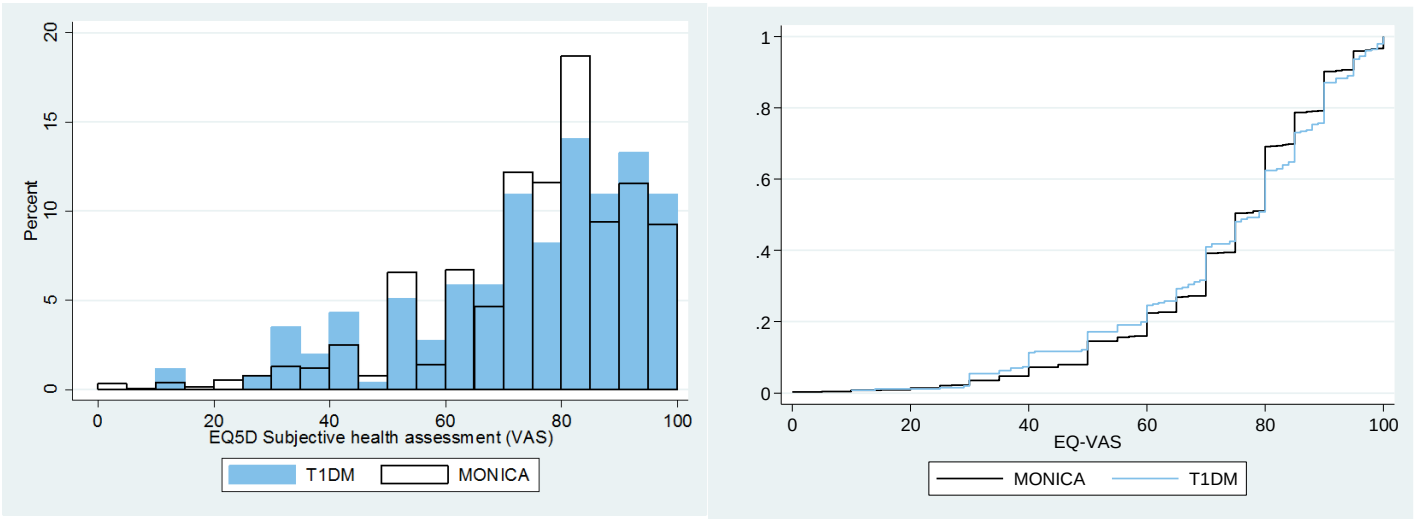

Figure 2 (A) & (B): *Figure A (left) shows the distribution of EQ-VAS scores for the T1DM and MONICA groups, respectively. The vertical axis shows percentage of all responses that landed in each score interval. Each score interval on the horizontal axis is five points wide. Figure B (right) shows cumulative distribution of EQ-VAS scores for the T1DM and MONICA groups, respectively.*

7. Results

7.1 Overall health

Using value sets, a utility value between 0 and 1, i.e. a Quality of Life Weight (QLW), could be calculated for different groups. The average QLW, with and without associated complications, for the T1DM and MONICA groups respectively is presented in Table 5. The highest QLWs are obtained when applying Burström's value set (Burström et al. 2014), followed by Wittrup-Jensen's (Wittrup-Jensen et al. 2009). Dolan's value set (Dolan 1997) yields the lowest utility scores. This follows the findings of Kiadaliri et al. (Kiadaliri, Eliasson, and Gerdtham 2015). The QLWs for the T1DM patients are lower than for the MONICA group for each measurement tool; Burström ($p<0.001$), Wittrup-Jensen and Dolan's value sets ($p<0.05$).

Table 5 - Quality of Life Weights: average sub-group values

	Quality of Life Weight (QLW)	
	Without CVD	With CVD
T1DM		
Dolan	0.796	0.653
Wittrup	0.822	0.715
Burström	0.894	0.842
MONICA		
Dolan	0.822	0.708
Wittrup	0.844	0.760
Burström	0.915	0.867

Table 5: *Summary of Quality of Life Weights (QLW) for the T1DM and MONICA groups, both with and without cardiovascular complications, for each value set. Note that values are group averages only, other determinants of Health-Related Quality of Life (HRQOL) has not been controlled for.*

Comparing average values between groups gives an idea of the connection between T1DM and HRQOL but is insufficient for extended analysis. Amongst other things, differences in QLWs between the T1DM and the MONICA group can be driven by underlying differences in characteristics between the groups. To account for this, regression analysis is needed. Several regression setups were used, both controlling for and not controlling for associated diabetic complications.

Table 6 shows the overall HRQOL for different measurements tools, when regressions do not control for associated complications. The T1DM patients showed worse HRQOL than their MONICA counterparts, for all measurements of HRQOL. Just as for the group averages, the differences between T1DM and MONICA patients were greatest for Dolan's value set and lowest for Burström's. The statistical significance for differences in QLWs was strongest for Burström's value set, but significance was also found for Dolan's and Wittrup-Jensen's sets.

Table 6 - Effects upon HRQOL without controlling for associated complications

	Dolan			Wittrup-Jensen			Burström		
	Coefficient	Std. Dev.	T-value	Coefficient	Std. Dev.	T-value	Coefficient	Std. Dev.	T-value
Constant	0.918 ***	0.018	50.8	0.912 ***	0.014	63.52	0.942 ***	0.007	127.66
T1DM	-0.038 **	0.013	-2.89	-0.031 **	0.010	-3.01	-0.024 ***	0.005	-4.49
Gender	-0.056 ***	0.009	-6.00	-0.045 ***	0.007	-6.12	-0.022 ***	0.004	-5.70
Age	-0.001 ***	0.000	-4.26	-0.001 ***	0.000	-3.50	-3.41E-04 **	-1.33E-04	-2.56
Smoking	-0.052 **	0.018	-2.95	-0.046 ***	0.014	-3.30	-0.024 ***	0.007	-3.31
R-squared	0.038			0.037			0.037		
n=	1756			1756			1756		

Table 6: *OLS regression using HRQOL as dependent variable. HRQOL is measured through three different value sets. Variables on cardiovascular diseases (CVD) is omitted. *=p<0.05, **=p<0.01, and ***=p<0.001*

To see if the differences in HRQOL between T1DM is caused by associated complications, the macrovascular complications Ischemic Heart Disease (IHD) and stroke were controlled for in the regression framework. The results are shown in Table 7. Both IHD and stroke are significantly negatively correlated to HRQOL. Their estimated severity differs substantially between the measurements tools, with the greatest impact for Dolan's value set and smallest for Burström's set, but remain statistically significant across all regression setups. Controlling for these complications lessens the estimated impact of T1DM upon HRQOL, as indicated by smaller estimated coefficients for T1DM compared to Table 6. It is clear that these macrovascular complications can explain some – but not all – of the differences in QLWs between the T1DM and MONICA groups.

Whether macrovascular complications are included or omitted from the analysis, the other control variables show the same pattern. Women, on average, report significantly lower HRQOL than men, much in line with results from other studies (Dolan et al. 1996; Månsdotter, Lindholm, and Ohman 2004). Age showed an expected negative correlation to HRQOL, although Dolan's value set was the only for which age was significant regardless of whether macrovascular complications were included.

Table 7 - Effects upon HRQOL, controlling for associated complications

	Dolan			Wittrup-Jensen			Burström		
	Coefficient	Std. Dev.	T-value	Coefficient	Std. Dev.	T-value	Coefficient	Std. Dev.	T-value
Constant	0.899 ***	0.018	49.46	0.897 ***	0.014	62.04	0.933 ***	0.007	125.76
T1DM	-0.032 *	0.013	-2.44	-0.027 *	0.010	-2.57	-0.021 ***	0.005	-4.00
Gender	-0.059 ***	0.009	-6.38	-0.047 ***	0.007	-6.46	-0.023 ***	0.004	-6.13
Age	-0.001 *	0.000	-2.47	-4.74E-04	2.66E-04	-1.78	-9.59E-05	1.37E-04	-0.70
Smoking	-0.052 **	0.017	-3.01	-0.047 ***	0.014	-3.38	-0.024 **	0.007	-3.32
IHD	-0.077 ***	0.022	-3.55	-0.060 ***	0.017	-3.49	-0.036 ***	0.009	-4.08
Stroke	-0.174 ***	0.031	-5.66	-0.130 ***	0.024	-5.31	-0.069 ***	0.013	-5.46
R-squared	0.065			0.062			0.065		
n=	1735			1735			1735		

Table 7: *OLS regression using HRQOL as dependent variable. HRQOL is measured through three different value sets. Cardiovascular diseases (CVD) is measured through Ischemic Heart Disease (IHD) and stroke. *=p<0.05, **=p<0.01, and ***=p<0.001*

Table 8 summarizes the estimated drop in HRQOL associated with T1DM, as presented in Table 6 and Table 7, respectively. The drop in HRQOL is estimated to be greatest for Dolan's value set, followed by Wittrup-Jensen's set. Usage of Burström's value set, the only experienced-based one, yields the smallest estimated T1DM-related drop in HRQOL among the EQ-5D-3L tools. To give an idea of the expected range of this drop, 95% confidence intervals for the coefficient are shown in Table 8 for each value set.

Table 8 - Summary of effects to Health-Related Quality of Life from T1DM

Estimated effect upon Quality of Life Weights (QLW) from T1DM				
		Coefficient	95% Conf. Interval	
Not controlling for macrovascular complications	Dolan	-0.038	-0.063	-0.012
	Wittrup-Jensen	-0.031	-0.052	-0.011
	Burström	-0.024	-0.034	-0.014
Controlling for macrovascular complications	Dolan	-0.032	-0.057	-0.006
	Wittrup-Jensen	-0.027	-0.047	-0.006
	Burström	-0.021	-0.032	-0.011

Table 8: *Summary of estimated drop in Health-Related Quality of Life (HRQOL) associated with presence of T1DM, as reported in Tables 6 and 7. Regression coefficients are estimated using OLS. The confidence intervals are calculated based upon the respective standard deviations reported in Tables 6 and 7.*

7.2 Individual dimensions of health

The results of EQ-5D-3L data can also be analyzed in a more straightforward way by simply analyzing each dimension of health separately. This has two advantages. First, it allows an extended analysis of how T1DM impacts upon HRQOL. Second, it avoids the potential risk of skewing the results due to usage of an inaccurate value set; analysis in single dimension only concerns the respondents' own answers and no weighting index is necessary. The outcome of these regressions are shown in Tables 12-16 in the Appendix.

T1DM was associated with higher levels of problems for all five dimensions of health. This correlation was statistically significant for all dimensions, except 'Anxiety & Depression' and 'Pain & Discomfort'. Women reported more problems than men in all dimensions (p=0.05) except for 'Self-care'. Increased age was significantly correlated with more problems with mobility and pain/discomfort, but interestingly enough was associated with less problems of anxiety/depression. Stroke was significantly associated with more problems in each dimension. Respondents with a history of IHD reported more problems in each dimension, but this correlation was not statistically significant for 'Self-care' and only borderline significant for 'Anxiety & depression'. As a sensitivity analysis, regressions were also performed for a binary dependent variable ('No problems'/'Problems'), but all conclusions regarding T1DM remained unchanged.

7.3 Health-Related Quality of Life and associated diabetic complications

This study has found that macrovascular complications, often associated with T1DM, can explain a significant – but not complete – part of the negative correlation between T1DM and HRQOL. The extent to which the remaining correlation can be explained through other associated complications, or is to be attributed to direct effects from T1DM, is unfortunately not possible to determine, due to lack of data on other such associated complications in the MONICA group. However, to get an idea of the extent to which microvascular complications may affect HRQOL, regressions were performed for the T1DM group only, where these complications were recorded. The outcome when HRQOL was

measured through Dolan's value set is shown in Table 9. To conserve statistical power in the small sample, the insignificant variable for smoking was dropped from the regressions. For all value sets, microvascular complications were significantly correlated to lower HRQOL, although their effect was somewhat smaller than that of the macrovascular complications.

Table 9 - Microvascular complications and Health-Related Quality of Life

	Effect upon HRQOL (Dolan's value set)			
	Coefficient	Std. Dev.	T-value	p-value
Constant	0.912	0.050	18.33	0.000
Gender	-0.072	0.029	-2.48	0.014
Age	-0.001	0.001	-0.61	0.540
Smoking	-0.002	0.064	-0.04	0.970
CVD	-0.099	0.049	-2.02	0.044
Microvascular	-0.084	0.031	-2.74	0.007
R-squared	0.088			
n=	251			

Table 9: *OLS regression for the T1DM group only, using HRQOL as dependent variable. Results are presented for the regression using Dolan's value set to measure Health-Related Quality of Life (HRQOL). Cardiovascular diseases (CVD) and microvascular complications (Microvascular) are both included. CVD is defined as history of either Ischemic Heart Disease (IHD) or stroke*.

So far, the question of whether associated complications have a different effect for HRQOL among T1DM patients than for a general population has not been attended. To test this, an interaction term between T1DM and cardiovascular disease (CVD) was included in the regression framework. Results from this regression outcome with HRQOL measured through Dolan's value is presented in Table 10. No significance was found for the interaction term for any of the three value sets.

Table 10 - T1DM-specific impacts from cardiovascular complications

	Effect upon HRQOL (Dolan's value set)			
	Coefficient	Std. Dev.	T-value	p-value
Constant	0.899	0.018	49.36	0.000
T1DM	-0.032	0.014	-2.36	0.019
Gender	-0.059	0.009	-6.38	0.000
Age	-8.27E-04	3.35E-04	-2.47	0.014
Smoking	-0.053	0.017	-3.01	0.003
IHD	-0.078	0.024	-3.28	0.001
Stroke	-0.175	0.031	-5.58	0.000
T1DM-CVD	0.004	0.044	0.10	0.920
R-squared	0.065			
n=	1735			

Table 10: *OLS regression using HRQOL as dependent variable. HRQOL is measured through Dolan's value set. T1DM-CVD is an interaction dummy, taking the value 1 if the respondent has both T1DM and a history of either Ischemic Heart Disease (IHD) or stroke, and zero otherwise.*

7.4 EQ-VAS

When HRQOL is measured through EQ-VAS the results look a little bit different. Results are shown in Table 11. Two main findings differ, both when controlling for macrovascular complications and not. First, the correlation between T1DM and HRQOL is no longer negative, nor significant. Second, age is no longer negatively correlated to HRQOL; when macrovascular complications are included, significance is even found for a positive relationship. Apart from this, results were highly similar to those for EQ-5D-3L, both when macrovascular complications were included and not.

Compared to the EQ-5D-3L tools, EQ-VAS yielded considerably lower QLW, both for T1DM patients and the general population. The results were 0.730 and 0.706 for the T1DM patients, without and with macrovascular complications[4]. The corresponding QLWs for the general population were 0.738 and 0.646.

It is noteworthy that when only respondents with a history of cardiovascular disease were considered, patients with T1DM reported higher EQ-VAS scores than the general population. This difference was, however, not significant (p=0.173). A regression with an interaction variable between T1DM and CVD, analogous to the one showed in Table 10, was also performed when HRQOL was measured through EQ-VAS. However, the interaction term was not statistically significant (p>0.05), and no evidence was found that the presence of CVD would affect T1DM patients differently than a general population.

Table 11 - Effects upon HRQOL when measured through EQ-VAS

	Effect upon HRQOL (EQ-VAS)			
	Coefficient	Std. Dev.	T-value	p-value
Constant	70.822	1.695	41.77	0.000
T1DM	0.317	1.220	0.26	0.795
Gender	-2.150	0.851	-2.53	0.012
Age	0.091	0.031	2.92	0.004
Smoking	-6.252	1.629	-3.84	0.000
IHD	-7.502	2.016	-3.72	0.000
Stroke	-11.829	2.788	-4.24	0.000
R-squared	0.0327			
n	1748			

Table 11: *OLS regression using Health-Related Quality of Life (HRQOL) as dependent variable. HRQOL is measured through EuroQol Visual Analogue Scale (EQ-VAS). IHD=Ischemic Heart Disease.*

[4] Notice that since EQ-VAS is measured on a scale from 0 to 100, the average scores had to be divided by 100 to yield QLWs.

8. Discussion

This work has found T1DM to be negatively correlated with lower Health-Related Quality of Life (HRQOL). This result can partly be attributed to the increased risk of macrovascular complications for people with T1DM, but even when such correlations are controlled for a T1DM-specific negative correlation persists. The estimated magnitude of this correlation, however, differ depending on which tool is used to measure HRQOL. Usage of the value set by Dolan (1997) leads to the lowest QLW for T1DM and the largest difference in HRQOL between people with and without T1DM. The experienced-based value set by Burström et al. (2014) yields the highest QLW for T1DM and the smallest difference compared to a general population.

The results conform well with both theory and previous studies on the topic. That the experienced-based value set by Burström et al. would lead to a more positive outlook on burden of T1DM than hypothetical sets is in line with what other studies have found, e.g. Kiadaliri et al. (2015). The fact that those who have themselves experienced certain health-states give them higher utility rating than general respondents confirms that people, when asked to imagine an ailing condition, tends to overestimate its negative impact (Dolan 2011).

How do the QLWs of this study relate to those of previous research on the topic? Although differences in methodology requires conclusions to be drawn with great caution, some points should be made. Using Dolan's value set for comparability, QLWs are similar to those of Northern European populations. The Norwegian study by Solli et al. (2010), also using Dolan's set, found overall utility for T1DM patients to be 0.83, close to the results of this study (see Table 5). Hart et al. (2003) found T1DM (measured through EQ-5D-3L with Dolan's value set) to be associated with a HRQOL decrease of 3 percentage points, also very close to this study (see summary in Table 8). Solli et al. also calculated the QLW to be 0.68 for T1DM patients with any form of associated complications, close to the findings from this study for T1DM patients with history of either IHD or stroke. The fact that results align strengthens the credibility of both this and previous studies. The similar results suggest that the T1DM effect upon HRQOL found in this study could be valid for other Northern European populations as well.

Following recommendations from the EuroQol group (Szende 2007), this study has used multiple value sets as a sensitivity analysis. Just like Kiadaliri et al. (2015), this study has found that the value sets provide different results. The two hypothetical value sets only differed modestly, however, showing that the general method and underlying health of the studied population is more important than the choice of value set. A similar sensitivity analysis could not be performed for experienced-based value sets due to lack of credible alternative value sets beside the one by Burström et al. Unfortunately, which value set gives the most accurate results cannot easily be tested. Instead, which results health-practitioners would want to use has to be based upon their own needs and beliefs. The results from Dolan's value set offer easily comparison to work by others, which may simplify incorporating conclusions from other studies into QLWs. The Danish set may be chosen for geographical reasons. For all actors with a preference for experienced-based values, the choice should favor the set by Burström et al. This study can only agree with the EuroQol group in that sensitivity analysis is important before drawing conclusions based upon results derived from EQ-5D-3L. User of the QLWs should also be aware that the choice of value set will influence health care priorities. Application of the more positive value sets for T1DM (in particular the experience-based one) will assign less importance to morbidity and more to mortality. Therefore, they will favor interventions that increases longevity and, relatively, disfavor those leading to higher quality of life.

This study has attempted to find if T1DM has a direct effect upon HRQOL or if all changes in HRQOL are only indirectly caused by T1DM since people with the disease suffer an increased risk of other

complications. The extent to which direct effects account for the T1DM-related difference in HRQOL is hard to know. As previously stated, their size can only be known by estimating the size of indirect effects. This study has found that indirect effects explain part of the T1DM-related drop in HRQOL through macrovascular complications and that microvascular complications are likely to explain a further part. It is possible that other complications would offer even further explanation, but unfortunately this study has been unable to investigate this due to lack of data, particularly for the MONICA group. Even so, omitted variables seem unlikely to explain the entire HRQOL-difference, which would mean that T1DM also has direct effects upon HRQOL.

Exactly what constitute these direct effects is beyond the scope of this study, but one can still speculate based upon its results. For example, the fact that T1DM was a significant determinant of problems with 'Usual activities' (see Table 14) indicates that e.g. the lifestyle limitations found by Gåfvels et al. (1993) could be part of the explanation. However, the fact that no strong significance was found for increased problems with 'Anxiety & depression' (see Table 16) among T1DM patients suggests that the impact of fear for hypoglycemia and worsening condition reported by the same study may have been overstated.

Parallel to its main objective, this study has also tested whether the consequences for HRQOL from macrovascular complications are different for T1DM patients than the general population. This was tested through inclusion of interaction terms between cardiovascular complication and T1DM-status. The fact that this term was not significant, despite significance for T1DM, Ischemic Heart Disease (IHD) and stroke (see Table 10), indicates that these complications are neither more or less severe for people with T1DM. This conclusion is important since it suggests that the relationship between QLWs for T1DM patients with and without complications is similar to the difference in QLWs between a general population, with and without complications. Due to this, QLWs for T1DM patients with complications could be estimated through adjustment of the QLWs of other groups.

To provide an alternative to QLWs based upon indirect valuation methods, differences between the T1DM patients and the MONICA group were also analyzed using EQ-VAS as a measure for HRQOL. This yielded quite different results to those from EQ-5D-3L. T1DM was not significantly correlated to a drop in EQ-VAS values, regardless of whether macrovascular complications were controlled for or not. This difference in results highlight how crucial the method choice is for the derivation of QLWs. QLWs, both with and without T1DM, were also considerably lower than for EQ-5D-3L. Perhaps this fact reflects that the tools were anchored at different lower levels: 0 points in EQ-VAS meant "the worst health imaginable", whereas 0 for EQ-5D-3L meant "health equivalent to death". If respondents believe the worst imaginable health to be worse than death, EQ-VAS values would naturally be skewed downwards compared to the results for EQ-5D-3L. The fact that both hypothetical value sets contained health-states of negative utility makes this a rather likely explanation to at least part of the difference in QLWs between the methods.

The fact that age was positively correlated to HRQOL when measured through EQ-VAS seems counterintuitive, as health generally declines with age. However, the lack of this pattern is not surprising for EQ-VAS. The EQ-VAS tool simply asks the respondent how the respondent's health is today and it seems likely that peoples' expectation of their own health adjust with increasing age. That age is a poor predictor of EQ-VAS has also been shown elsewhere (Braga de Souza et al. 2015). In general, adaptation to T1DM may mean that the problems with the disease is perceived smaller among T1DM patients than a general population, at least over a short time-frame.

Given the unclear anchoring of EQ-VAS and that it only measures momentary health compared to lasting health function, EQ-5D appears the more credible tool for calculation of QLWs. It has also been

the more common of the two. It is likely that EQ-VAS is better at detecting instant changes to health at the expense of detecting more lasting impacts, for which a high degree of adaptation exists. Perhaps the two methods are best thought of as complementary in the sense that they can assess different domains of HRQOL, rather than that they can confirm each other's results.

It has been hypothesized that EQ-5D-3L suffer from a lack of responsiveness and is unable to detect finer changes in health. It is possible that the five-level version of EQ-5D – the EQ-5D-5L – would have been better suited for this study. However, it should also be noted that EQ-VAS, the more responsive measure, showed less overall effect to HRQOL from T1DM than any of the measures based upon EQ-5D-3L did. Perhaps the lack of responsiveness for EQ-5D-3L has been previously exaggerated. Another concern for EQ-5D-3L is that the value for the individual's overall health has to be imputed by others and hence does not necessarily reflect the individual's own opinion. Indeed, as EQ-VAS, a direct valuation method, found no significant relationship between T1DM and lower HRQOL, there is cause for concern in regards to the method. However, if this is a shortcoming of the EQ-5D-3L tool, it is a shortcoming it shares with all other indirect health valuation methods as well.

This study has used a geographically and demographically suitable reference group to the T1DM patients. This increases the likelihood that the differences between the groups can be attributed to the presence of T1DM. This does, however, not necessarily need to be the only explanation. There is still a risk that differences in QLWs would partly be explained by differences in underlying characteristics between the groups. This study has attempted to account for this where possible, for example through inclusion of a lifestyle factor like smoking that may pick up more than just differences in biological health. Also, the fact that the cause of T1DM has not been linked to lifestyle factors strengthens credibility of the findings. The seemingly random occurrence of T1DM also makes it more likely that the observed differences really are caused by T1DM. Nonetheless, one cannot rule out that differences in underlying characteristics can explain at least part of the difference in HRQOL between the two groups, especially given the lack of more data on lifestyle. Since T1DM is a chronic disease which often traces back to childhood or adolescence, it is possible that T1DM patients systematically differ from the general population in how they view health as a direct consequence of their disease. Another cause for concern is that, since the presence of macrovascular diseases were assessed in different ways for the T1DM patients and the MONICA group, there is a risk that the two groups are not perfectly comparable. However, given the great impact both Ischemic Heart Disease (IHD) and stroke has on the individual, the MONICA data is likely to be fairly accurate and such differences can be expected to be minor.

T1DM is a gradually progressing disease, to a high extent affected by self-management. It is hence characterized by substantial individualized differences in severity. The impacts of the disease will therefore differ from one person to another and no QLW will perfectly describe the experience of the disease for a single individual. However, the QLWs provided through this study may be of importance for policy makers. By analyzing effects, both when controlling for cardiovascular complications and not, the QLWs derived in this study also offer extended guidance for decisions targeting sub-groups of T1DM patients.

Among this study's strengths are that the HRQOL impact of T1DM has been assessed using a suitable reference group. To the best of knowledge, this is the first study to derive such differences in QLWs using two populations from the same region. This strengthens credibility that the differences accurately reflect the impact of T1DM. Another strength is the plurality of methods used. HRQOL has been measured using three different value sets, as well as both direct and indirect tools for health utility measurement.

Limitations to this study includes the modest number of T1DM patients in the sample and the lack of data on associated diabetic complications beyond macrovascular ones for the MONICA group. Future studies should include more data on background characteristics and biological markers to ensure that HRQOL-differences between T1DM patients and the general population can really be accredited to T1DM and nothing else. Research should also investigate whether the relative drop in HRQOL from T1DM is similar for other population and countries as well. If so, one would only need to apply the differences found in this study to QLWs of general populations, to obtain a fair estimation of the QLW for T1DM patients.

9. Conclusions

Comparing the results of two health surveys in Northern Sweden, this study has found that Type 1 Diabetes Mellitus (T1DM) is related to a lower Health Related Quality of Life (HRQOL). The elevated risk of associated complications for T1DM patients – in particular the cardiovascular complications Ischemic Heart Disease (IHD) and stroke – explain part of, but not all this decrease in HRQOL. Both Quality of Life Weights (QLW) and the relative severity of T1DM, varies between different ways of measuring overall HRQOL. Using hypothetical value sets yields the lowest QLWs and greatest decrease compared to a general population; HRQOL decreases was estimated to span between 2.4 and 3.8 percentage points, depending on the value set used and whether macrovascular complications are known. Usage of an experienced-based value set has been linked to a decrease in HRQOL by 2.1-2.4 percentage points.

The QLWs for people from Northern Sweden with T1DM and no history of cardiovascular complications ranges between 0.80 and 0.89, depending on the value set used. For T1DM patients with such complications, the range is 0.65-0.84. The corresponding QLW ranges for a general population is 0.82-0.92 without cardiovascular complications, and 0.71-0.87 with them. Men reported significantly better HRQOL than women, and increased age was negatively correlated with HRQOL for all measurement tools of overall health, except for EQ-VAS.

Sensitivity analysis with HRQOL measured through EQ-VAS has shown that although T1DM may lead to lower HRQOL, it is not clear that such an effect is noticeable for everyday life. It is also likely that a considerable degree of adaptation to living with T1DM exists, mitigating HRQOL-impacts from the disease.

This study has found the impact of T1DM upon HRQOL to be in line with, or somewhat smaller than, the results of other similar studies, depending on how HRQOL is measured. Results by the conventional hypothetical value sets are similar as previous research, whereas both experienced-based value set and EQ-VAS has found negative HRQOL effects of T1DM to be smaller. As a consequence, health care policies based upon the latter methods may relatively favor interventions that prolong life and disfavor those that increases health quality.

Among this study's strengths are the multiple ways of measuring health through EuroQol, including the experienced-based value set by Burström et al. (Burström et al. 2014). The usage of a geographically relevant reference group is another strength which sets this study apart from previous research.

Limitations of the study includes the lack of data on biomarkers, such as blood glucose values, and additional associated complications. Other problems are that the T1DM and MONICA may systematically differ in their expectations of health, and the modest sample size of T1DM patients.

Further research should test if the decline in HRQOL associated with T1DM are the same in other populations as well. If so, QLWs for populations of different characteristics could more easily be estimated from already available utility weights. It should also focus on the association between disease management and HRQOL in T1DM patients; since T1DM is a self-managed disease it is possible that T1DM patients can substantially affect their own HRQOL.

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Appendix

Table 12 - Determinants of problems with 'Mobility'

	Mobility			
	Coefficient	Std. Dev.	Z-value	p-value
T1DM	0.398	0.110	3.60	0.000
Gender	0.050	0.087	0.57	0.567
Age	0.023	0.003	6.81	0.000
Smoking	0.223	0.149	1.50	0.134
IHD	0.400	0.155	2.57	0.010
Stroke	0.602	0.208	2.90	0.004
Cut 1	2.709	0.201		
Cut 2	N/A			
n=	1,772			

Table 12: *Ordered probit regression with 'Mobility' as limited dependent variable. Possible outcomes were 'No problems', 'Some problems', and 'Extreme problems'. IHD= Ischemic Heart Disease. Note that no respondent reported the highest level of problems in this dimension.*

Table 13 - Determinants of problems with 'Self-care'

	Self-care			
	Coefficient	Std. Dev.	Z-value	p-value
T1DM	0.837	0.185	4.52	0.000
Gender	0.445	0.196	2.27	0.023
Age	0.004	0.006	0.65	0.516
Smoking	0.108	0.299	0.36	0.717
IHD	0.341	0.290	1.18	0.239
Stroke	0.957	0.311	3.08	0.002
Cut 1	3.082	0.384		
Cut 2	3.856665	0.4213		
n=	1,780			

Table 13: *Ordered probit regression with 'Self-care' as limited dependent variable. Possible outcomes were 'No problems', 'Some problems', and 'Extreme problems'. IHD= Ischemic Heart Disease.*

Table 14 - Determinants of problems with 'Usual activities'

	Usual activities			
	Coefficient	Std. Dev.	Z-value	p-value
T1DM	0.484	0.107	4.53	0.000
Gender	0.411	0.091	4.54	0.000
Age	0.000	0.003	-0.04	0.967
Smoking	0.342	0.143	2.40	0.016
IHD	0.584	0.165	3.54	0.000
Stroke	0.558	0.222	2.51	0.012
Cut 1	1.791	0.179		
Cut 2	3.225099	0.229615		
n=	1,781			

Table 14: *Ordered probit regression with 'Usual activities' as limited dependent variable. Possible outcomes were 'No problems', 'Some problems', and 'Extreme problems'. IHD= Ischemic Heart Disease.*

Table 15 - Determinants of problems with 'Pain & discomfort'

	Pain & discomfort			
	Coefficient	Std. Dev.	Z-value	p-value
T1DM	0.098	0.081	1.22	0.223
Gender	0.283	0.057	4.93	0.000
Age	0.014	0.002	6.75	0.000
Smoking	0.318	0.107	2.97	0.003
IHD	0.412	0.132	3.12	0.002
Stroke	0.561	0.185	3.03	0.002
Cut 1	0.710	0.115		
Cut 2	2.752511	0.130843		
n=	1,761			

Table 15: *Ordered probit regression with 'Pain & discomfort' as limited dependent variable. Possible outcomes were 'No problems', 'Some problems', and 'Extreme problems'. IHD= Ischemic Heart Disease.*

Table 16 - Determinants of problems with 'Anxiety & depression'

	Anxiety & depression			
	Coefficient	Std. Dev.	Z-value	p-value
T1DM	0.150	0.084	1.79	0.073
Gender	0.396	0.062	6.43	0.000
Age	-0.014	0.002	-6.21	0.000
Smoking	0.173	0.113	1.53	0.126
IHD	0.277	0.142	1.95	0.051
Stroke	0.475	0.189	2.51	0.012
Cut 1	0.019	0.119		
Cut 2	1.743735	0.133867		
n=	1,768			

Table 16: *Ordered probit regression with 'Anxiety & depression' as limited dependent variable. Possible outcomes were 'No problems', 'Some problems', and 'Extreme problems'. IHD= Ischemic Heart Disease.*