VALUE IN HEALTH ∎ (2015) ∎∎∎–∎∎∎

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The Burden of Diabetes Mellitus in Patients with Coronary Heart Disease: A Methodological Approach to Assess Quality-Adjusted Life-Years Based on Individual-Level Longitudinal Survey Data

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ABSTRACT

Background: Reliable burden of disease (BOD) estimates are needed to support decision making in health care. **Objectives:** The objective of this study was to introduce an analysis approach based on individual-level longitudinal survey data that estimates the burden of diabetes in patients with coronary heart disease in terms of quality-adjusted life-years (QALYs) lost. **Methods:** Data from two postal surveys (2006, N = 1022; 2010–2011, N = 716) of survivors from the KORA Myocardial Infarction Registry in Southern Germany were analyzed. Accumulated QALYs were calculated for each participant over a mean observation time of 4.1 years, considering the non-informative censoring structure of the follow-up study. Linear regression models were used to estimate the loss in (quality-unadjusted) life-years and QALYs between patients with and without diabetes, and generalized additive models were used to analyze the nonlinear association with age. The cross-sectional and longitudinal association with quality of life (QOL) and QOL change and the impact on mortality were analyzed to enhance the understanding of the observed results. **Results:** Diabetes was associated with a reduced QOL at baseline (cross-sectional: $\beta = -0.069$; $P < 0.001$), but not with a significant longitudinal QOL change. Mortality in patients with diabetes was increased (hazard ratio = 1.68; $P < 0.005$). This resulted in a loss of 0.14 life-years ($P = 0.003$) and 0.37 QALYs ($P < 0.001$). Results from generalized additive models indicated that the burden of diabetes is less pronounced in older subjects. **Conclusions:** The application of the proposed approach provides confounder-adjusted BOD estimates for the studied time horizon and can be used to compare the BOD across different chronic conditions. Curative efforts are needed to diminish the substantial diabetes-related QALY gap.

Keywords: burden of disease, coronary heart disease, diabetes, population-based, QALYs.

Introduction

Diabetes and cardiovascular diseases, such as coronary heart disease (CHD), are major public health problems [1,2]. Particularly, the coexistence of metabolic and cardiovascular conditions is frequent and known to have an overproportional impact on health outcomes [3–5]. Currently, around 10% of the German adult population has a diagnosis of CHD and around one-third of them suffer from diabetes mellitus [6,7]. Although the influence of diabetes and CHD on quality of life (QOL) or survival is well studied, there are few studies investigating the impact of these conditions on combined measures of morbidity and mortality [3,4,8]. To comprehensively quantify the burden of diseases (BODs), measures such as quality-adjusted (QA) life-years (QALYs) that account for both the length and the quality of life are needed. The QALY concept is based on utility theory and welfare economics and was established to evaluate the cost-effectiveness of health care interventions over a certain time horizon [8]. It relies on the idea that each health state has a preference-based utility value attached to it and that health can be understood as "value-weighted time," or more concretely, as the accumulated product of QOL and life years (LY), the QALYs [9].

Conflict of interest: The authors have indicated that they have no conflicts of interest with regard to the content of this article.

Parts of this study were presented in abstract form at the IHEA 10th World Congress, Dublin, in July 2014 (oral presentation), and as a poster at the ISPOR 17th Annual European Congress, Amsterdam, in November 2014.

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http://dx.doi.org/10.1016/j.jval.2015.07.003

Representative and reliable BOD estimates are important, first, to quantify the relative impact of a disease on the society's health; and, second, to feed decision analytic models to assess the cost-effectiveness of large-scale interventions outside of controlled trials. To date, different methodological approaches have been used to estimate the burden of specific conditions quantitatively. Jia et al. [10–12] proposed to combine aggregated cross-sectional QOL data sources with abridged life table statistics to estimate the reduction in quality-adjusted life expectancy (QALE) due to a specific condition nationwide. Other researchers estimated the QALYs lost over a certain time horizon by using the method of quality-adjusted survival, either by matching longitudinal primary mortality data with aggregated cross-sectional QOL data [13,14] or by using longitudinal primary data [15,16].

While model-based long-term predictions might be limited in precision and validity, the method of quality-adjusted survival analyses was not specifically designed to handle varying follow-up times resulting from varying study start and termination dates, as is often the case in population-based follow-up studies. Although methodological extensions to handle censoring for quality-adjusted survival have been published and a lot of data from prospective cohort studies are available, population-based longitudinal data have rarely been used for comprehensive BOD studies [17]. A method based on individual-level longitudinal QOL and respective survival times that considers the censoring structure in population-based studies and provides reliable BOD estimates can therefore be expected to be a valuable extension of current methodological approaches.

The primary objective of this study was to present an analysis approach that estimates the burden of diabetes in patients with CHD in terms of QALYs lost on the basis of individual-level data from a population-based follow-up study. The study further analyzes the cross-sectional and longitudinal association with QOL and QOL change and the impact on mortality to enhance the understanding of the observed results and suggests an approach regarding how to consider the potentially nonlinear relationship between age and BOD.

Methods

Data Sources

Data for this analysis originated from the KORA (Cooperative Health Research in the Region of Augsburg) Myocardial Infarction (MI) registry. This population-based registry has been collecting information on all cases of coronary deaths and acute nonfatal MI in inhabitants aged 25 to 74 years in the city of Augsburg and the two surrounding counties in Southern Germany [18,19]. A total of 2950 patients who were registered with an acute MI between 1985 and 2004 and were known to be alive (n = 4394) answered an initial postal survey between August and December 2006 (67% participated). Because of feasibility issues and prioritization of research questions to be answered, only a subset (n = 1022) of statutorily insured patients (~88% of the German population is statutorily insured) of the baseline sample was followed and patients known to be alive by the end of 2010 were contacted again in a postal "follow-up" survey in 2011. During the mean observation time of 4.1 years (mean follow-up time until censoring), 141 participants died and 716 replied to this follow-up survey (85% participated). A brief overview of the design of this follow-up study is provided in the upper part of Figure 1. Both the 2006 and 2011 surveys included standardized questions, assessing socioeconomic characteristics, medical history, current medication, lifestyle habits, quality of medical care, and QOL. Medical and sociodemographic information recorded at the time of the last MI were available from the MI registry. The study was granted full ethical approval by the ethics commission of the Bavarian Medical Association (registration no. 12057).

Measures

Outcomes

QOL was assessed by using the EuroQol five-dimensional questionnaire (EQ-5D). The EQ-5D is a multiattribute descriptive system comprising five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each of which has three response levels (no problems/some or moderate problems/extreme problems). The 243 resulting health states can

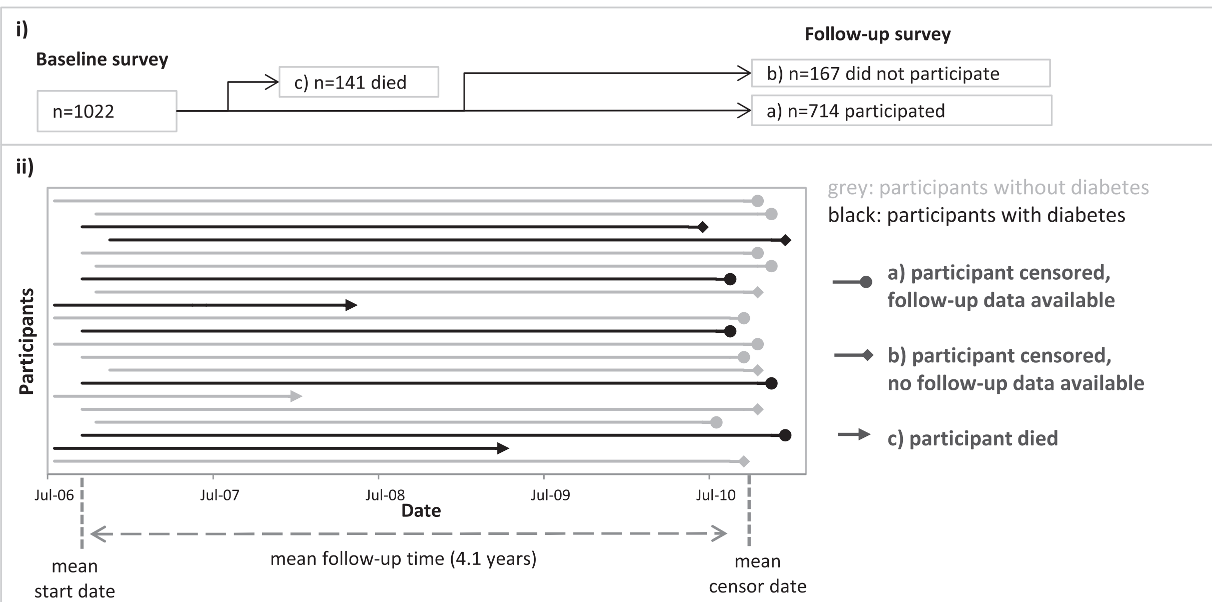

Fig. 1 – Qualitative description of the data and censoring structure of the follow-up study.

be converted into a single utility value, the EQ-5D index score, ranging from –0.205 to 1, using a scoring algorithm based on time trade-off valuations, that has been derived from valuations of the general German population [20,21]. Validated information on mortality of participants was obtained by address search and by contacting the regional registration authorities (until December 2010) before the follow-up survey was rolled out (2011).

In general, QALYs gained by an individual from the start of the observation time (i.e., baseline date) to the end of the observation time (i.e. date of censoring for patients who moved away or were lost to follow-up, or date of death for those who died) can be described as the area under the QOL curve, which is given by the EQ-5D trajectory over time [22]. Unlike randomized controlled trials, population-based studies have no prespecified study start or end. Therefore, individual accumulated (QA)LYs depend on the length of observation times, which may differ individually because of early or late study enrollment and censoring. As graphically illustrated in Figure 1, the study start of an individual in our follow-up study is typically scattered within a range of weeks or months around the "mean study start," depending on the sample size and the recruitment capacities. The technical censoring reflects the assessment of the vitality status (national death registries, registration authorities) before conducting the follow-up survey, and censoring dates of survivors (both follow-up participants and nonparticipants) therefore commonly deviate within a certain range around a mean censoring date. Only those participants who moved abroad or cannot be tracked because of other reasons might have significantly earlier censoring dates (only two in this study).

As in a classical survival analysis, the difference between the mean study start and the mean censoring date is referred to as the mean follow-up time of the study (4.1 years in this study). Because all censored subjects could be followed until the end of the study period, it can be assumed that the censoring, whether it is due to the end of the study or due to nonresponse, is of a noninformative nature, that is, that the distribution of censoring dates is independent of personal characteristics or expected outcomes. The noninformative censoring assumption is supported by the data of our study. They show that personal characteristics such as sex, education, smoking, weight status, diabetes, and myocardial reinfarction lead to small differences in raw follow-up times, which are in the range of expected random error (~0.01 years). Thus, the raw follow-up times until censoring or death can be expected to reflect the quality-unadjusted survival in an unbiased manner and can be used for the calculation of QALYs and subsequently for (QA)LY gap estimations.

Because only one (baseline) or two (baseline and follow-up) EQ-5D measurements were available in this study, we differentiated between three different cases for the quantification of accumulated QALYs over the follow-up period: 1) an individual is alive at the date of censoring and participates in the subsequent follow-up survey (QOL is known at baseline and follow-up); 2) an individual is alive at the date of censoring but does not participate in the follow-up survey (QOL is known only at baseline); and 3) an individual dies within the follow-up period and the date of death is known (QOL is known only at baseline).

Case 1: QOL is known at baseline and follow-up

Although the exact individual trajectory of QOL between the baseline and follow-up surveys is not known, one can approximate the accumulated QALYs until the date of censoring by assuming a linear change in QOL values from the baseline survey to the follow-up survey. For example, a person with a raw follow-up time of 4.0 years (from baseline survey to censoring), an EQ-5D value of 0.88 at baseline, and an EQ-5D value of 0.84 at date of censoring accumulates 4.00 (unadjusted) LYs and $4.0 \times (0.88 + 0.84) / 2 = 3.44$ QALYs. The QOL value at the date of censoring can be estimated by the use of linear interpolation using the QOL values at baseline and follow-up date.

Case 2: QOL is known only at baseline, the person does not participate in the follow-up survey

To get an approximation for unknown QOL values at the time of censoring, we imputed missing QOL values using the method of multiple ($n = 10$) predicted mean matching given the covariate and QOL values of the sample at baseline and the QOL values of the participating subsample at follow-up. This imputation procedure was based on a missing-at-random assumption. Accumulated QALYs can be calculated analogous to case 1, assuming a linear change in QOL from baseline to the date of censoring.

Case 3: QOL is known only at baseline, the person dies

Because it is known that the QOL of an individual depends on the remaining time until death (people close to death commonly report lower QOL values), we used a pragmatic data-driven approach to account for this relationship [23]. For this, we fitted a linear regression model for study participants who died, with baseline QOL value as dependent variable and "time until death" as dependent variable. The obtained slope (β estimate) from this model indicated that for each year a person moves closer to the date of death, the EQ-5D score declines by 0.035 points ($P = 0.13$). We used this estimate of yearly decline in QOL to approximate the QOL trajectory from baseline to death. For example, a person with a baseline EQ-5D of 0.60 who died after 2.0 years accumulated 2.0 unadjusted LYs and $2 \times [0.60 + (0.60 - 2 \times 0.035)] / 2 = 1.13$ QALYs. To assess the sensitivity of the assumptions made for the trajectory of QOL from baseline to death, we examined two other simple scenarios. First, we assumed an unchanged course of baseline EQ-5D until death as a conservative approach, which potentially underestimates the decline in QOL: $2 \times (0.60 + 0.60) / 2 = 1.20$ QALYs. Second, a linear EQ-5D score change from baseline to "0" at point of death was examined as a nonconservative approach, which probably overestimates the decline in QOL: $2 \times (0.60 + 0.00) / 2 = 0.60$ QALYs.

Predictor variables and covariates

The status of diabetes was based on self-reported information documented in the baseline questionnaire in 2006. Participants were asked whether they have diabetes and if so, what kind of treatment they currently receive (no treatment/diet, oral antidiabetic medication only, or insulin therapy/insulin therapy combined with oral antidiabetic medication). Validated information about reoccurrence of cardiac events was obtained from the core documentation of the MI registry.

Baseline covariates—age (continuous), sex, educational status (primary education $\leq$9 years of school; secondary and tertiary education >9 years of school), smoking status (never smoker, ex-smoker, current smoker), and weight status (normal weight body mass index [BMI], <25; overweight, $25 \leq \text{BMI} < 30$; obese, BMI $\geq$ 30)—were extracted from self-reports of the baseline survey and from the database of the MI registry.

Statistical Analysis

We first analyzed the cross-sectional association between the predictor variables and baseline EQ-5D scores, using ordinary least square linear regression models. Analogously, we analyzed the EQ-5D score changes between baseline and follow-up in the subsample of patients who also participated in the follow-up survey to describe the effect of diabetes and reinfarction status prospectively over time. Cox proportional hazard regression was applied to estimate the effect of diabetes and reinfarction and QOL on mortality. To test whether systematic nonresponse has occurred, we fitted a logistic model in which the odds of not responding were regressed on baseline variables in the subsample of survivors.

To obtain a confounder-adjusted absolute BOD measure, we analyzed the (QA)LY gap over the 4.1-year time horizon, that is, the (QA)LY difference between people with and without diabetes and reinfarction. For this, LYs (raw follow-up times until censoring or death) and QALYs were regressed on the baseline diabetes and myocardial reinfarction status, by using ordinary least square regression (OLS) models. As justified above, the use of unadjusted LYs and derived QALYs can be expected to lead to unbiased (QA)LY-gap estimations.

Because it is known from previous studies that, first, the relationship between age and QOL is nonlinear [5] and, second, that the impact of diabetes on QOL decreases with age [24], a sophisticated analysis and description of the disease burden needs to take into account these important factors. Previous studies have shown that generalized additive models (GAMs) are a useful method to describe and visualize nonlinear relationships in the field of outcomes research [5,25]. Beside the main OLS-based analyses, we therefore also fitted a GAM with and without a factor-smooth interaction between age and the predictor variable diabetes. The model with the factor-smooth interaction can be notated as

$$Y_i = \beta_0 + [f_{\text{age, diab}}(age_i) \times I(x_{\text{diab}} = 1)] + [f_{\text{age, }\overline{\text{diab}}}(age_i) \times I(x_{\text{diab}} = 0)] + \beta_{\text{diab}} x_{\text{diab}} + \beta x_i^T + \varepsilon_i$$

where Y_i is the response of the individual i, namely, the accumulated (QA)LYs over the follow-up period; f_{age} is the nonparametric smooth function of the covariate age; $\beta_{diab}x_{diab}$ is the main effect of the predictor variable diabetes; $x_i^T\beta$ is the linear predictor of other categorical covariates; and ε_i are the error terms, which are assumed to be normally distributed [26]. As in the main (OLS-based) analysis, a Gaussian distribution and an identity link were used for this analysis [27]. Likelihood ratio tests were performed to check whether the introduction of the interaction term significantly improves the model fit, that is, whether the QALY gap remains constant over age. To check whether the choice of the GAM is appropriate, we compared the predictive ability of GAMs with that of OLS-based regression models. For both outcomes, LYs and QALYs, the predictive ability (adjusted R^2) of GAMs was substantially higher. We further cross-checked the results with an extended (i.e., with interaction between a categorical age variable and diabetes) OLS-based model.

All data analyses, except the GAMs, were performed with the software package SAS 9.2 (SAS Institute, Cary, NC, USA). The SAS *MI* and *MIANALYZE* procedure was used for the calculation of the (QA) LY gap, to account for the variability in the structure of multiple imputed data sets. The estimation of the additive model was carried out with the statistical software R (R Foundation for Statistical Computing, version 3.1.0, Vienna, Austria) by applying the *mgcv-package*. Because of the high computational effort that is related with the analysis of GAMs based on multiple imputed data sets, we calculated this model on a single data set. All models were adjusted for the previously specified set of covariates.

Results

Studied Sample

The characteristics of the cohort are presented in Table 1. The mean age at baseline was 67.6 years, and the majority of the patients were men (79%). 12% of the participants suffered from a reinfarction, and the time since the last MI averaged 8.5 years. Furthermore, almost one-third of the sample had diabetes, with 9% reporting receiving no specific treatment, 51% the intake of oral antidiabetic medication, and 40% the use of insulin.

Table 1 – Characteristics of sample at baseline (2006) and follow-up participation (2010–2011).

Characteristic	Value
Age (y), mean ± SD	67.6 ± 9.7
Sex, n (%)	
Women	215 (21.0)
Men	807 (79.0)
Education, n (%)	
Primary	707 (74.6)
Secondary	241 (25.4)
Weight status, n (%)	
Normal	265 (25.9)
Overweight	499 (48.8)
Obese	258 (25.2)
Smoking status, n (%)	
Never smoker	327 (32.5)
Ex-smoker	562 (55.8)
Current smoker	118 (11.7)
One or more myocardial reinfarctions, n (%)	121 (11.8)
Diabetes, n (%)	277 (28.0)
Diabetes treatment, n (%)	
No treatment/diet	24 (8.8)
Oral medication*	139 (50.9)
Insulin therapy†	110 (40.3)
Diabetes duration (y), mean ± SD	10.4 ± 9.5
Time since last MI (y), mean ± SD	8.5 ± 5.2
Follow-up participation (2010–2011)	
Observation time until censoring (y), mean ± SD	4.09 ± 0.1
Alive, follow-up QOL data	716 (70.1)
Alive, no follow-up QOL data	165 (16.1)
Died during follow-up	141 (13.8)

MI, myocardial infarction; QOL, quality of life.
*Oral antidiabetic medication only.
†Insulin therapy or insulin therapy combined with oral antidiabetic medication.

Cross-Sectional and Longitudinal Association between Diabetes, Reinfarction, and QOL

Effect estimates for cross-sectional and longitudinal associations with QOL are presented in Table 2. The mean EQ-5D score of the cohort at baseline was 0.869 ± 0.181. In the cross-sectional perspective, diabetes (β = –0.069; $P < 0.001$) and myocardial reinfarction (β = –0.064; $P < 0.001$) were associated with reduced EQ-5D scores. Insulin-dependent patients reported considerably lower QOL values than did people without diabetes (β = –0.129; $P < 0.001$) and patients with diabetes not taking insulin (β = –0.098; $P < 0.001$).

The yearly change in QOL over the follow-up period averaged –0.012 ± 0.041 points. Neither myocardial reinfarction nor diabetes and treatment status had a significant impact on the QOL change over the 4.1-year follow-up period.

Association between Diabetes, Reinfarction, QOL, and Mortality

Hazard ratios (HRs) from the Cox regression models are presented in Table 3. Although patients who suffered from a myocardial reinfarction did not have a significantly increased mortality risk (HR = 1.54; $P = 0.07$), patients with diabetes (HR = 1.68; $P = 0.005$), and particularly those taking insulin (HR = 2.25; $P < 0.001$), were at a higher risk of dying. QOL was found to be an independent predictor for mortality. A 0.01-point higher baseline EQ-5D score reduced the mortality risk by around 2.3% ($P < 0.001$).

Table 2 – Adjusted effect estimates of linear regression models for the cross-sectional and longitudinal association between myocardial reinfarction/diabetes and QOL (change) at baseline and over the follow-up period.

Model	Cross-sectional association, EQ-5D score at baseline (0.869 ± 0.181) (SD)		Longitudinal association, EQ-5D score change (per year) (–0.012 ± 0.041) (SD)	
	Adjusted mean (95% CI)	Difference (P value)	Adjusted mean (95% CI)	Difference (P value)
No reinfarction*	0.878 (0.866–0.890)	Reference	–0.012 (–0.015 to –0.009)	Reference
Reinfarction*	0.815 (0.782–0.847)	–0.064 (<0.001)	–0.012 (–0.022 to –0.003)	0.000 (0.999)
No diabetes†	0.890 (0.877–0.903)	Reference	–0.011 (–0.015 to –0.008)	Reference
Diabetes†	0.821 (0.799–0.842)	–0.069 (<0.001)	–0.015 (–0.022 to –0.009)	–0.004 (0.268)
No diabetes†	0.890 (0.877–0.903)	Reference	–0.011 (–0.015 to –0.008)	Reference
Diabetes (no insulin therapy)†	0.859 (0.831–0.887)	–0.031 (0.052)	–0.013 (–0.021 to –0.005)	–0.002 (0.676)
Diabetes (insulin therapy)†	0.761 (0.727–0.794)	–0.129 (<0.001)	–0.020 (–0.031 to –0.009)	–0.009 (0.135)

CI, confidence interval; EQ-5D, EuroQol five-dimensional questionnaire; QOL, quality of life.
* Model adjusted for age, sex, education, smoking, weight status, and diabetes.
† Model adjusted for age, sex, education, smoking, weight status, and myocardial infarction.

Nonresponder Analysis

Results from the logistic regression model showed that most of the personal baseline characteristics were not predictive for participation in the follow-up study. Only people with diabetes (odds ratio = 1.57; 95% confidence interval 1.06–2.33) and those with lower baseline QOL values (odds ratio = 1.016; 95% confidence interval 1.006–1.026) were more likely to not answer the follow-up survey.

Association between Diabetes, Reinfarction, and Accumulated (QA)LYs over the Follow-Up Period

The ordinary least square means estimates for accumulated LYs and QALYs are presented in Table 4. Over a mean observation time of 4.1 years, the cohort gained on average 3.87 unadjusted LYs and 3.27 QALYs. Having a history of a myocardial reinfarction did not significantly decrease the accumulated LYs but decreased the accumulated QALYs by 8% (–0.27 QALYs; $P = 0.003$). The gap between people with and without diabetes averaged −0.14 LYs (–3.5%; $P = 0.003$) and –0.37 QALYs (–10.9%; $P < 0.001$), respectively. Particularly, patients with diabetes taking insulin accumulated substantially less QALYs than did those not having diabetes (–0.65; $P < 0.001$) and those with diabetes receiving no or oral antidiabetic medication (–0.35 QALYs; $P < 0.001$). Taking the conservative assumption for the trajectory of QOL from baseline until death yielded almost identical results compared with the data-driven scenario. Applying the nonconservative approach resulted in fewer accumulated QALYs (mean 3.15) and an approximately 10% larger relative QALY gap.

Figure 2 displays the estimated (QA)LYs and 95% confidence interval from the smooth functions $\hat{f}_{age}$ of covariate-adjusted GAMs in general (Fig. 2A) and in patients with and without diabetes (Fig. 2B,C). Expected accumulated (QA)Lys declined from approximately 4 LYs and approximately 3.6 QALYs at the age of 55 years to around approximately 3.2 LYs and approximately 2.3 QALYs at the age of 85 years, respectively. Both accumulated LYs and QALYs deteriorated in a nonlinear manner over the age range (P values < 0.001). The curves in Figure 2C indicate that the burden from diabetes slightly diminishes with growing age (likelihood ratio test, $P = 0.015$). The smooth functions from the GAM and the adjusted means from the OLS regression model, including an interaction term consisting of diabetes and categorized age, showed comparable results.

Table 3 – Adjusted hazard ratios (HRs) of Cox regression models for the association between myocardial reinfarction, diabetes, EQ-5D scores, and mortality.

Model	HR (95% CI)	P value
No reinfarction*	1	Reference
Reinfarction*	1.54 (0.97–2.44)	0.067
No diabetes†	1	Reference
Diabetes†	1.68 (1.17–2.40)	0.005
No diabetes†	1	Reference
Diabetes (no insulin therapy)†	1.33 (0.85–2.10)	0.217
Diabetes (insulin therapy)†	2.25 (1.42–3.56)	<0.001
EQ-5D score‡,§	0.977 (0.970–0.984)	<0.0001

CI, confidence interval; EQ-5D, EuroQol five-dimensional questionnaire.
* Model adjusted for age, sex, education, smoking, weight status, and diabetes.
† Model adjusted for age, sex, education, smoking, weight status, and myocardial infarction.
‡ Model adjusted for age, sex, education, smoking, weight status, myocardial infarction, and diabetes.
§ HR per 0.01 point increase.

Discussion

The use of individual-level QOL and mortality data from population-based longitudinal studies is a valuable extension of current methodological approaches that provides confounder-adjusted BOD estimates. The resulting measure can be understood as the difference in expected QALYs over a certain time period between patients at different stages of a disease (i.e., an "average patient") compared with those without this disease. This study shows that in patients with CHD, diabetes is associated with an 11% reduction in QALYs over a time horizon of approximately 4 years and that this QALY gap seems to diminish with growing age.

The EQ-5D has been found to be a valid and reliable outcome measure in the field of cardiovascular and metabolic diseases [28–30]. With regard to contents, this study confirms results of previous work, showing that diabetes and a history of a reinfarction in patients with CHD are associated with reduced QOL and

Table 4 – Adjusted means of linear regression for accumulated LYs and QALYs over the 4.1-y follow-up period.

Model	LYs, 3.87 (0.02)*			QALYs, 3.27 (0.03)*		
	Adjusted mean (95% CI)	Difference (P value)	% difference	Adjusted mean (95% CI)	Difference (P value)	% difference
No reinfarction†	3.89 (3.85–3.93)	Reference	Reference	3.31 (3.26–3.38)	Reference	Reference
Reinfarction†	3.81 (3.69–3.93)	–0.08 (0.210)	–2.1	3.05 (2.88–3.22)	–0.27 (0.003)	–7.9
No diabetes‡	3.92 (3.87–3.97)	Reference	Reference	3.39 (3.32–3.46)	Reference	Reference
Diabetes‡	3.78 (3.7–3.86)	–0.14 (0.003)	–3.6	3.02 (2.91–3.13)	–0.37 (<0.001)	–10.9
No diabetes‡	3.92 (3.87–3.97)	Reference	Reference	3.39 (3.32–3.46)	Reference	Reference
Diabetes (no insulin therapy)‡	3.86 (3.75–3.96)	–0.06 (0.266)	–1.5	3.19 (3.05–3.34)	–0.20 (0.015)	–5.9
Diabetes (insulin therapy)‡	3.66 (3.54–3.79)	–0.26 (<0.001)	–6.6	2.74 (2.57–2.91)	–0.65 (<0.001)	–19.2

LY, life-year; QALY, quality-adjusted life-year.
* Mean (standard error).
† Adjusted for age, sex, education, smoking, weight status, and diabetes.
‡ Adjusted for age, sex, education, smoking, weight status, and myocardial infarction.

increased mortality risk [3,4,31,32]. As already known from studies surveying the general population, it could also be shown that diabetes-related insulin dependency in patients with CHD is associated with substantially lower QOL values [4,33].

Despite a strong negative cross-sectional association, we did not find a significant longitudinal association between diabetes and QOL. Because nonresponders to the follow-up survey are assumed to be individuals with bad or declining health status [34] and because patients with diabetes were substantially overrepresented in this group, it is likely that the true longitudinal association between diabetes and QOL is underestimated. This hypothesis is supported by the fact that the only published study assessing the longitudinal relationship between diabetes and Euro-QoL scores also reported no (EuroQol-visual analogue scale) or quite small effects (EQ-5D) [35]. Selective dropout due to deteriorating health status and death, as commonly observed in the context of cohort studies including multimorbid elderly populations, therefore requires special consideration in longitudinal QOL studies and in approaches to calculate the BODs. The introduced method partly overcomes this problem and allows a comprehensive quantification of the disease burden over the studied time horizon. The results show that accumulated QALYs over a time period of approximately 4 years were considerably reduced in patients with diabetes (–11%) and specifically in those taking insulin (–19%). Because the accumulated QALYs codepend on QOL, which differs significantly (at baseline), the relative gap in unadjusted LYs is in general smaller than the gap in QALYs. Although this study indicates that the combined burden of

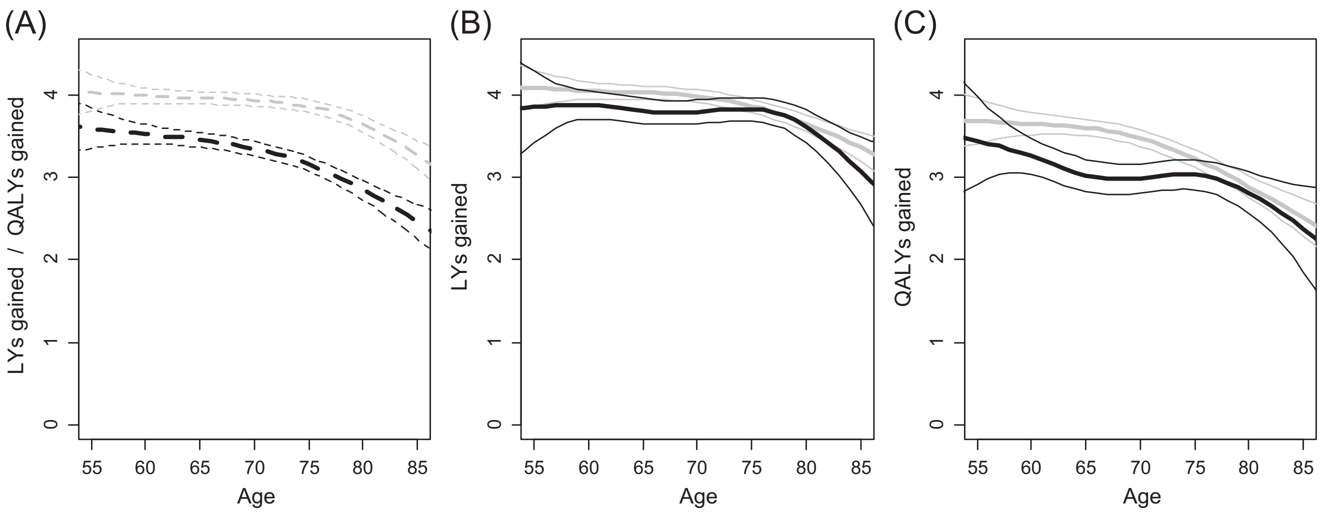

Fig. 2 – Estimated LYs and QALYs gained over the 4.1-year follow-up period of the smooth functions $\hat{f}_{age}$ fitted by generalized additive models (GAMs).
(A) Predicted mean values of LYs (dotted gray line; $df = 3.5$) and QALYs (dotted black line; $df = 2.5$) and 95% pointwise confidence intervals (thin dotted lines); models adjusted for sex, education, weight, smoking, myocardial reinfarction, and diabetes; estimated effective degrees of freedom: LYs $df = 3.5$; QALYs $df = 2.5$.
(B & C) Predicted mean values of LYs and QALYs for people with (solid black line) and without (solid gray line) diabetes and 95% pointwise confidence intervals (thin solid lines); models adjusted for sex, education, weight, smoking, and myocardial reinfarction; estimated effective degrees of freedom: LYs: for those with diabetes $df = 3.6$; for those without diabetes $df = 2.7$; QALYs: for those with diabetes $df = 3.3$; for those without diabetes $df = 2.4$.
Because of the small number of younger patients and the related uncertainty in estimation caused by outliers, models were restricted to subjects older than 55 years. LY, life-year; QALY, quality-adjusted life-year.

diabetes, in terms of QALYs lost, seems to slightly diminish with age, it also illustrates the large general burden of diabetes, diabetes-related insulin intake, and reoccurring cardiac events and highlights the great importance of secondary prevention and intensive treatment.

The proposed method has some distinct advantages compared with model-based QALY-gap estimations. Because of the use of individual-level longitudinal data from a population-based cohort study, instead of combining cross-sectional QOL data with secondary mortality statistics, we were able to adequately adjust for some underlying confounders that might actually cause differences in accumulated QALYs. In addition, although long-term (life-long) models might be more comprehensive in determining the BOD from a societal perspective [11,12], due to cohort and period effects and the unpredictability of advances in health care, these estimations remain rather hypothetical [36]. This view is supported by the fact that there is no convincing consensus on the discount rate of QALYs that accrue in later phases of life, although this issue crucially determines common QALE-gap estimations [9]. The presented approach is also not susceptible to bias that might occur from the strong interrelation between baseline QOL, the disease condition, and mortality, which has been found in previous studies [23,37]. Because QOL and survival times are strongly correlated, accumulated QALYs derived through an aggregated approach $\left(\frac{1}{n}\sum_1^i EQ\_5D_i\right) \times \left(\frac{1}{n}\sum_1^i LYs_i\right)$ are not equal to accumulated QALYs derived through an individual-level approach $(\frac{1}{n}\sum_1^i (EQ\_5D_i \times LYs_i)$.

In fact, QALY calculations based on aggregated data systematically underestimate the true accumulated QALYs and therefore can be valid only if the relationship between QOL and survival times is equal in the two comparison groups. A previous study showed that not considering the association between QOL and time to death (survival) in health economic models also leads to a misspecification of health gains (measured in QALYs) of preventive interventions [23].

Compared with other subject-based or individual-level quality-adjusted survival approaches, the proposed method is designed for use in (population-based) follow-up studies with unequal follow-up times. The suggested approach does not rely on rather complex modeling techniques for censored data, where the mean QOL at each follow-up time is multiplied with the (unadjusted) probability of surviving to that time point [14,15,17]. Instead, it uses the noninformative censoring structure given in the context of (population-based) follow-up studies and assigns an LY and QALY value to each individual, which can be modeled using standard statistical procedures (OLS regression/generalized mixed models/GAMs). By including covariates and interaction terms, one can adjust the results of this approach for a broad variety of comorbidities and one can also model the burden of multimorbid conditions. The modeling flexibility is therefore substantially higher than in previously suggested methods and allows confounder-adjusted BOD comparisons across various diseases and (chronic) conditions [14,15]. Finally, slightly modified approaches can be applied in observational cohort studies to evaluate the impact of interventions on quality-adjusted survival in case of the nonapplicability of randomized study designs.

In the interpretation of the results of this study some limitations need to be considered. The nonresponse bias and exclusion of nonstatutorily insured patients limited the representativeness of the results. Furthermore, the self-reported nature of diabetes and its treatment regimen (nondifferential bias), as well as residual confounding due to unmeasured medical conditions, such as the seriousness of the heart disease or behavioral aspects, could have led to an underestimation or overestimation of the results.

The described approach also has some methodological limitations. Because of its limited time horizon, it is not suitable for quantifying the burden of a disease in terms of QALYs lost over a lifetime, which complicates the interpretability of the results and requires a consensus on the chosen time horizon. Compared with previous approaches, it does not quantify the burden of a disease from its onset, but describes the average burden of a disease over a specified time horizon on the basis of a population-based sample of patients at different stages of the disease [11,13,16]. In this study, the average time since onset of diabetes or the last reinfarction averaged 10.4 and 8.5 years, respectively. Assessing the “true” burden of diabetes (from its onset) would require the collection of QOL, mortality, lifestyle, and biomedical data before and after its onset to accurately address patient heterogeneity because previous work has shown that QOL deteriorations in patients with diabetes are mainly attributable to rather time-invariant factors [38]. In addition, assumptions made on the unknown QOL trajectory of people who died or who did not answer the follow-up survey could have biased the QALY-gap estimations. This is specifically the case because the nonresponder analysis showed that the “missing-at-random” assumption for the imputation of missing QOL follow-up values might be partially violated. Because varying assumptions on the QOL trajectory until death altered the results rather marginally and because the proportion of nonresponders (15%) was rather small, the bias produced because of miss-specified assumptions on the QOL trajectories, however, can be assumed to be rather small.

When transferring this approach to other data sources, some important practical issues should be considered. One should check initially whether follow-up times until censoring are balanced for the factors of interest. If by chance the raw follow-up time until censoring differs for the factor(s) to be studied, one can iteratively shorten the follow-up time of persons with the longest follow-up time (regardless of their characteristics) until the groups are balanced in terms of their mean follow-up time until censoring. With this approach, the mean follow-up time is artificially shortened and valuable information remains unused; however, this approach ensures that QALY-gap estimations are not subject to systematic bias. Furthermore, in case no information about the censoring date of a follow-up responder is given (i.e., the censoring date is the date of survey reply), the mean censoring date of the cohort should be used for this subject instead of using the date of survey reply to avoid systematic bias that could occur from systematic nonresponse. This technique has been also applied for our data. The applicability of the proposed approach should be checked carefully for studies with a high proportion of censored individuals in an early phase of the follow-up period because in this case the variability of follow-up times becomes large and uncertainty around QALY-gap estimates will be high.

Aiming to draw a comprehensive picture for decision makers, caregivers, and patients, we applied and suggested an approach on how to analyze the natural nonlinear pattern of expected accumulated QALYs over the age range. If applying GAMs or another modeling technique to describe nonlinear patterns, one should carefully check whether the predictive ability is substantially increased and consider whether the application outweighs potential disadvantages, such as overfitting.

Conclusions

Using individual-level longitudinal data of population-based studies in the context of noninformative censoring provides confounder-adjusted BOD estimates without the need for complex modeling approaches. Results indicate that the burden of diabetes in terms of QALYs is substantial, but diminishes with increasing age. Further methodological advances are needed to accurately and comprehensively describe the burden of chronic conditions, and preventive and curative efforts are needed to diminish the observed QALY gaps.

Acknowledgments

The KORA (Cooperative Research in the Region of Augsburg) research platform was initiated and financed by Helmholtz Zentrum München – German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education and Research and by the State of Bavaria. Since the year 2000, the collection of myocardial infarction (MI) data has been cofinanced by the German Federal Ministry of Health to provide population-based MI morbidity data for the official German Health Report (see www.gbe-bund.de). Steering partners of the MONICA/KORA Infarction Registry, Augsburg, include the KORA research platform, Helmholtz Zentrum München, and the Department of Internal Medicine I, Cardiology, Central Hospital of Augsburg. This work was further supported by the German Center for Diabetes Research, which is funded by the Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung).

Source of financial support: No funding was received for this study.

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