Statistical methods and epidemiology of chronic conditions in the field of general practice and family medicine

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Contents

List of abbreviations

BMI	Body Mass Index
CI	Confidence Interval
DEGS1	First wave of the German Health Interview and Examination Survey for Adults (German: “Studie zur Gesundheit Erwachsener in Deutschland, Welle 1”)
GEDA 2012	German Health Update 2012 (German: „Gesundheit in Deutschland aktuell“)
GP	General Practitioner
RKI	Robert Koch Institute
SES	Socioeconomic Status
TSVC	Tree-Structured Varying Coefficients

1. Summary

The field of general practice and family medicine is diverse and has to deal with several complex health problems. Essential characteristics of general practitioner (GP) services cover among others a comprehensive, patient-focused care and the coordination of treatment through the wider health care system to sufficiently meet the patients' needs. By providing primary health care for all, GP services may contribute to a more coherent level of care across different population groups. The focus of this dissertation was on analyzing patterns and determinants of major topics on chronic conditions in relation to social discrepancies in the German population. Our results show that the coexistence of multiple chronic conditions - referred to as multimorbidity - was not only more prevalent but also occurred earlier in age in socially deprived groups, which requires appropriate management. More advanced methods are vital to analyze trends and developments over time to adequately capture the population needs. Accordingly, an algorithm for modeling time-varying coefficients in discrete time-to-event settings by recursive partitioning was proposed. It was shown that the proposed algorithm can be useful in applications in medical and social science. All research articles have been accepted for publication in international peer-reviewed journals (see **Appendix A-D**). **Appendix E** comprises a list of additional research articles resulting from the cooperation of the Institute of General Practice and Family Medicine and the Department of Medical Biometry, Informatics and Epidemiology during the past years.

2. Introduction

General practitioners (GPs) provide primary health care for people of all ages and social classes. GPs treat their patients on a variety of acute and chronic conditions, and their responsibility also includes providing advice on disease prevention programs (German Medical Association, 2012). In contrast to other medical specialists, GP services are patient-focused rather than disease-focused, meaning that they do not only concentrate on one certain part of the body but gain a comprehensive view of their patients (German Medical Association, 2012; Starfield, 2012). That implies that GP services as part of primary care are one of the most important elements of the health care system (Kringos et al., 2010). Similar to the assorted role of GPs, research in the area of general practice and family medicine is diverse (Hong et al., 2016). It reaches from issues regarding

single chronic conditions in the general population, such as the treatment of hypertensive patients, to more complex disease-associated problems or health services related topics to identify the most effective ways to improve a patient's life. Multimorbidity, commonly defined as the coexistence of multiple chronic conditions in one person (Johnston et al., 2019), is one of the more severe health-related challenges GPs have to deal with. Over the past years, individuals with multimorbidity form the majority of patients in primary care practices (Fortin et al., 2005; Nicholson et al., 2019b; Salisbury et al., 2011). The increased health burden, a decreased quality of life or the need of complex therapeutic management with multiple medications (referred to as polypharmacy), that for example may cause higher risks for adverse drug events or medication nonadherence, are only some of the difficulties people with multimorbidity have to face (Marengoni et al., 2011; Ryan et al., 2015). As the population structure is constantly changing towards a higher median age, multimorbidity and its difficulties continue to be a serious public health challenge (Moffat and Mercer, 2015). Beside the strong association with age, there is evidence that multimorbidity varies with socioeconomic characteristics such as residential areas or educational levels (Barnett et al., 2012; Violan et al., 2014). In Germany, research on multimorbidity in different socioeconomic levels or in the younger population is still rare. As there is no internationally well-established definition and no gold standard for the measurement of multimorbidity (Johnston et al., 2019; Willadsen et al., 2016), both the comparison and adoption of international findings across different settings to the German population is only possible to a limited extent.

Aside from treating acute diseases, GPs are well able to assess risk factors of chronic health conditions and to advise on appropriate prevention programs (German Medical Association, 2012). For osteoporosis, for example, a so-called silent chronic disease characterized by low bone mass with increased fracture risk and of major public health concern (Hernlund et al., 2013), the identification and awareness of risk factors is a key in prevention. In their everyday routine consultation, GPs may be in a good position to perform a thorough assessment for osteoporosis and identify those patients at higher risk. Aside from genetic risk factors such as female gender, ethnicity or family history of fractures, many poor lifestyle habits like smoking, physical inactivity, underweight or alcohol consumption are known to have an impact on osteoporosis (Bijelic et al., 2017;

Schürer et al., 2015). With a steadily increase in bone fragility the main health burden of osteoporosis patients usually lies in bone fractures. There is, however, not much known about coexisting chronic conditions that are linked with osteoporosis and that equally impair the patients' quality of life (Holm et al., 2016).

In view of health services research, primary care physicians act as gatekeepers to the wider health care system and for their role as coordinator at all steps of treatment, it is essential to continuously improve their services (Höhne et al., 2009; Kringos et al., 2010). In Germany, the free choice of a health care provider is regulated by law (§ 76 SGB V (Social Code Book V)), though it is intended that primary care is mostly taken on by GPs. Knowledge on the frequency of use and on predictors for primary health care utilization is crucial to efficiently meet the population needs. Better equality and quality of care through GP-centered health care, especially among the elderly or the chronically ill, has already been reported (Freytag et al., 2016; Schnitzer et al., 2011). Accordingly, GPs seem to be in the best position to act as first persons of contact in case of any health problem. International research on GP services mostly focused on the frequency of use (Jørgensen et al., 2016; Nie et al., 2010; Schlichthorst et al., 2016). Only little is known on factors which affect the presence or non-existence of GPs as first point of contact for health problems in German adults.

When analyzing data in the field of general practice and family medicine, analyses often focus on cross-sectional observations, though observations on trends and developments are equally relevant. For multimorbidity for example, next to point prevalence derived from a single examination, research on how the disease burden changes over time might be of interest. More precisely, the time-to-event patterns by the time between successive chronic disease diagnoses are currently investigated in a Canadian primary health care setting (Nicholson et al., 2015). Traditional methods for analyzing time-to event data usually assume that the event times are measured on a continuous scale (Cox, 1972; Klein and Moeschberger, 2003). In practice however, observations are mostly measured annually, monthly or (when using routine data) quarterly which result in discrete measurements by nature. Concepts of the statistical methodology for discrete time-to-event models have extensively been presented (Berger and Schmid, 2018; Tutz and Schmid, 2016). Specifically, different approaches have been established for the modeling of discrete time-to-event data: In parametric models with linear predictor it is

assumed that the effects of the explanatory variables on the outcome are constant over the entire observation time. Alternatively, semiparametric regression models allow the effects of the explanatory variables to vary smoothly over time, e.g. via P-splines (Eilers and Marx, 1996). But both modeling strategies may not adequately reflect the effects of explanatory variables in discrete settings where the effects may be piecewise constant. Hence, the use of a tree-based method for modeling piecewise constant time-varying coefficients is proposed.

3. Objective

This cumulative dissertation covers different projects dealing with health-related topics on chronic conditions in the field of general practice and family medicine. Specifically, using cross-sectional data sets and epidemiological measures, we determined (i) age-specific prevalence rates of multimorbidity with respect to socioeconomic differences in the German population, (ii) gender-specific prevalence rates of osteoporosis in the German adult population aged at least 50 years and its association to a range of coexisting chronic health conditions and (iii) the prevalence rate plus factors among a number of sociodemographic and health related characteristics of having no GP in German adults. Our fourth project focused on an algorithm for modeling time-varying coefficients by a tree-based method in settings with discrete time-to-event data.

4. Methods

This section shortly summarizes the methods of each article. For more details, we refer to **Appendix A-D**.

4.1 Prevalence of multimorbidity

Our cross-sectional analysis used data of the national telephone health interview survey “German Health Update 2012” (GEDA 2012), which is part of the national health monitoring program of the Robert Koch Institute (RKI) (Lange et al., 2015). The survey was carried out between 2012 and 2013 and data on 19,294 German-speaking adults, who were at least 18 years old and living in private households with landline telephone, are available for public use (Robert Koch Institute, 2014b). GEDA 2012 provides information on 15 self-reported health conditions, such as hypertension, coronary heart

disease or diabetes mellitus along with self-reported chronic low back pain and an evaluation of obesity using the world health organization's criteria based on the body mass index (BMI) (Robert Koch Institute, 2014a). We defined multimorbidity by the presence of at least two of the 17 health conditions in one person at the same time. Educational qualification, which was used to evaluate socioeconomic differences, was classified into three categories (low, medium, high) according to the International Standard Classification of Education (UNESCO United Nations Educational, Scientific and Cultural Organization, 2003). Prevalence rates with 95 % confidence intervals (CI) were computed and in line with recommendations of the RKI, these were weighted by the standardized weighting factor to match the German population structure (Lange et al., 2015; Robert Koch Institute, 2014a). Subsequently, a weighted multiple logistic regression analysis was used to assess associations between multimorbidity and age, gender and educational qualification.

4.2 Prevalence and comorbidity of osteoporosis

The second project, which also made use of the public use file of GEDA 2012, was restricted to participants aged 50 years and older, as only these were asked about a medical history of osteoporosis (Robert Koch Institute, 2014a). Potentially osteoporosis-related characteristics included in our analyses were gender, age, educational qualification, self-reported BMI, alcohol consumption and smoking status. The analysis of associations between osteoporosis and coexisting health conditions were limited to chronic low back pain and the remaining 14 self-reported health conditions captured within GEDA 2012 (Robert Koch Institute, 2014a). We determined prevalence rates with 95 % CI, which were weighted according to the standardized weighting factor to correct for any deviations of the GEDA 2012 study population from the German population (Lange et al., 2015). Weighted logistic regression analysis was used to evaluate the associations between osteoporosis and coexisting chronic conditions, adjusted for the aforementioned characteristics.

4.3 Characteristics of having no GP

This data analysis was based on the first wave of the "German Health Interview and Examination Survey for Adults" (DEGS1) (Scheidt-Nave et al., 2012). Between 2008 and 2011, the RKI conducted DEGS1 as part of the health monitoring program and data on

7,987 German adults aged between 18 and 79 years are available for public use (Robert Koch Institute, 2015; Scheidt-Nave et al., 2012). Along with information on the individual health state, quality of life and several socio-demographical characteristics, data on the utilization of different health care services including the information whether individuals have a GP to contact first in case of any health impairment were gathered (Scheidt-Nave et al., 2012). Our analyses included socioeconomic and demographical factors potentially associated with having no GP, as for instance age, residential area or socioeconomic status (SES), together with health-related factors like the general state of health or the presence of chronic diseases. Descriptive statistics were used to illustrate population characteristics and the prevalence of having no GP. Multiple logistic regression analyses were used to identify factors that were associated with having no GP. All analyses were weighted according to the standardized weighing factor as recommended by the RKI (Kamtsiuris et al., 2013).

4.4 Tree-based modeling of time-varying coefficients

This article proposes a tree-based approach for modeling piecewise constant time-varying effects in discrete time-to-event models. The method adapts the tree-structured varying coefficients (TSVC) approach by Berger et al. (2019). In the adaptation, the only allowed effect modifying variable is the time *t*. This leads to regression models with time-varying effects that were embedded into the class of varying-coefficient models originally introduced by Hastie and Tibshirani (1993). For each explanatory variable, the algorithm identifies whether the effect varies over *t* and yields a tree for each explanatory variable that shows time-varying coefficients*,* whether the effect is constant over the entire period of *t*, or whether the explanatory variable has any influence at all. In several simulation scenarios, we evaluated the performance of the TSVC model to alternative approaches. Specifically, the TSVC model fit was compared to (i) the fit of a simple discrete hazard model that did not account for possible time-varying effects and (ii) the fit of a discrete hazard model allowing for smooth time-varying effects using P-splines. Beyond that, the TSVC model approach was considered in two real-world applications.

5. Results

For each article, a summary of the main results is presented in the following sub-

sections. For more details, we refer to **Appendix A-D**.

5.1 Prevalence of multimorbidity

Of the 19,294 participants in GEDA 2012, 39.6 % (95 % CI 38.7-40.6 %) were multimorbid with only minor differences between the sexes. Age-specific multimorbidity rates showed a steep increase between the age of 30 and 69 years, which is reflected by a typical S-shaped curve (see **Appendix A**, Figure 1). There were substantial differences in prevalence rates between the educational qualification levels among middle-aged adults (30–59 years old). More precisely, a shift in the S-shaped curves was observed which indicated that adults aged 40-49 years with low educational qualification showed prevalence rates equivalent to highly educated adults at least ten years older (see **Appendix A**, Figure 2). Likewise, multiple logistic regression analyses revealed higher odds of being multimorbid for adults with a low or medium educational qualification compared to highly educated adults (see **Appendix A**, Table 2).

5.2 Prevalence and comorbidity of osteoporosis

In the second analysis using GEDA 2012, the study population consisted of 10,660 participants with non-missing data on osteoporosis. The overall prevalence rate of osteoporosis was estimated to 8.7 % with major differences between sexes (4.7 % in men versus 12.2 % in women). While the prevalence rate for women considerably increased with age, it remained nearly stable for men (see **Appendix B**, Figure 1). More than 95 % of the participants with osteoporosis reported to have at least one coexisting health condition; the most common health conditions were arthrosis, hypertension and chronic low back pain (see **Appendix B**, Table 2). After adjustment for age, gender, education, BMI, smoking and alcohol consumption, adults with osteoporosis were still exposed to more than twofold higher odds for arthrosis, arthritis, chronic low back pain, chronic heart failure and depression, respectively.

5.3 Characteristics of having no GP

Our study population using DEGS1 for public use comprised 7,755 participants with non-missing data on the outcome variable “having no GP”. Of these, 9.5 % indicated that they did not have a GP as first point of contact. Higher prevalence rates were observed among others for men, singles, and participants from urban area or with a high SES and the not chronically ill (see **Appendix C**, Table 1). Accordingly, multiple logistic

regression analysis revealed higher odds of having no GP for participants from urban areas and of younger age. Lower odds for the presence of chronic diseases were found. Men with private or any other type of health insurance displayed higher odds of having no GP. For women, both a high and low SES showed higher odds of not having a GP compared to women with medium SES (see **Appendix C**, Table 2).

5.4 Tree-based modeling of time-varying coefficients

Our simulation studies displayed that the TSVC model performed well in terms of true positive and false positive rates regarding the selection of explanatory variables, which was independent of the censoring rate. Using the predictive log-likelihood to compare the performance of the three approaches, our results showed that the TSVC model was competitive to the simple discrete hazard model which did not account for possible time-varying effects in scenarios without time-varying effects (see **Appendix D**, Figure 1). Especially in settings with strong censoring, the TSVC model was more robust than the discrete hazard model allowing for smooth time-varying effects, whose performance suffered greatly (see **Appendix D**, Figure 3 and Figure 6). Both real-world applications revealed that the TSVC model was well able to detect relevant time-varying effects that were not found by the simpler model. The TSVC model resulted in more parsimonious models than the models allowing for smooth time-varying effects which led to easier interpretations (see **Appendix D**, Section 5).

6. Discussion

The present dissertation covers several relevant topics related to chronic conditions in the field of general practice and family practice. According to the growing complexity, strategies for improving a person's health should consider programs for socially disadvantaged groups, extend the regular single disease managements to more complex ones and simplify access to health care systems along with adequate methods to analyze those trends.

In Puth et al. (2017), a higher occurrence of multimorbidity in socioeconomically deprived adults in Germany was revealed. Using education as proxy for SES, prevalence rates of middle-aged low-educated individuals matched those of highly educated adults at least ten years older. Generally, the lack of a standard definition of

multimorbidity hampers the comparison of international findings. Prevalence rates range from 13 % to 72 % at age 75 in the general population (Fortin et al., 2012), and among others vary with age and socioeconomic deprivation (Barnett et al., 2012; Li et al., 2016). Results strongly depend on factors like type and number of chronic conditions, the population under study and the minimal number of chronic conditions to be present to define multimorbidity (Johnston et al., 2019; Nicholson et al., 2019a). Despite that, several research showed that multimorbidity is common in primary care settings and most consultations involve people with multiple chronic conditions (Salisbury et al., 2011). Multimorbidity has to be handled effectively among younger people as it is more than just an issue of older people (Nicholson et al., 2019b). Social determinants help to understand the patients' complexity and are extremely important in health care (Mackenbach et al., 2008). The large number of unique combinations of chronic conditions in people with multimorbidity complicates simple recommendations for strategies in patient management (Nicholson et al., 2019b; van den Bussche et al., 2011). This also suggests the need for a more tailored and patient-focused approach to adequately handle multimorbidity with a more coherent set of health care services.

In Puth et al. (2018), we demonstrated the high disease burden in German adults with osteoporosis. There were no clear signs of socioeconomically differences when measured by education. Most existing literature on osteoporosis incorporates the assessment of bone mineral density measurements (Kanis et al., 2008), which were not performed within GEDA 2012 and impede the comparison. Still, prevalence rates were similar to a range of previous findings in the literature (Fuchs et al., 2013; Hadji et al., 2013; Wade et al., 2014). Osteoporosis is a silent disease causing reduced bone strength and resulting in an increased risk for fragility fractures. This affects in particular morbidity, the general state of health, the patient's quality of life and mortality (Alexiou et al., 2018; Cauley, 2013; Gold et al., 2019). As there are no obvious signs prior to a fracture, those affected are usually not diagnosed with osteoporosis until a fragility fracture. To reduce osteoporotic fractures, knowledge on clinical risk factors is of high interest in prevention and early detection. Potential risk factors include coexisting health conditions that are linked to similar pathophysiological mechanisms and physical disability or whose medical treatment contribute to drug-drug interactions that particularly affect bone metabolism (Wicklein and Gosch, 2019). Primary care physicians

have to consider the high appearance of multimorbidity in adults with osteoporosis. An assessment of adults at risk seems to be feasible in the primary care setting.

In Tillmann et al. (2019), we found that almost every tenth German adult has no GP to contact first in case of any health impairment, which was more prevalent among men than women. Factors associated with having no GP included age, residential area, SES and the type of health insurance with varying degrees between the sexes. International findings mainly analyzed the frequency of use of GP services, so a comparison is only possible to a limited extent. But results are in line with already reported associations and characteristics of frequent users of primary care services (Jørgensen et al., 2016; Nie et al., 2010; Schlichthorst et al., 2016). As first point of contact to health care and by providing health advice at all steps through treatment, GPs as primary care physicians are in the best position to identify health problems that are for example caused by drug-drug interactions or adverse events (Ko et al., 2008; Starfield et al., 2005). If adults visit a GP regularly in case of any health issue, the GP becomes more familiar with them and is able to develop a clear understanding of their needs (Maarsingh et al., 2016; van Walraven et al., 2010). The advantage of efficient primary care settings is supported by a continuous treatment of all types of health problems to prevent or shorten hospitalization (Hansen et al., 2013; Starfield et al., 2005). Improved patient management strategies by enabling adequate access to primary care and GP services for socioeconomically deprived and young adults are necessary to counter the present lack in care.

In Puth et al. (2019), we showed that the TSVC model was comparable to the simple discrete hazard model in scenarios without time-varying effects, mainly because the TSVC model reduces to a simple discrete hazard model if not one explanatory variable is selected for splitting. In both applications, the beneficial effect of the TSVC model in comparison to the simple model was demonstrated by identifying meaningful time-varying effects. Further, the TSVC model was more compelling than the discrete hazard model allowing for smooth time-varying effects for settings with strong censoring. In these settings, the performance of detecting time-varying effects by smooth functions was limited, possibly attributable to a smaller number of observations at later time points. In both applications, the TSVC model yielded easier interpretations of the effects which make it more favorable to use in practice.

In summary, the contributions of the present four research articles help to underline key determinants along with promising methods to achieve a better understanding of health issues of individuals with chronic conditions in primary care settings. Our results highlight the need for a greater awareness of the varying disease burden and/or the early onset of chronic conditions in different population groups to appropriately manage the treatment of the affected along with strategies to match their current life situation (like work life for the younger population). Access to GP services should be further strengthened for population groups at higher risks. Future research should focus on combinations of coexisting chronic conditions across all age groups. Beyond that, the change of the disease burden over time should be of interest, for which appropriate statistical methods are essential to adequately analyze its complexity.

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Appendix A

Puth M-T, Weckbecker K, Schmid M, Münster E: Prevalence of multimorbidity in Germany: impact of age and educational level in a cross-sectional study on 19,294 adults. BMC Public Health 2017; 17(1): 826

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RESEARCH ARTICLE Open Access

Prevalence of multimorbidity in Germany: impact of age and educational level in a cross-sectional study on 19,294 adults

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Abstract

Background: Multimorbidity is one of the most important and challenging aspects in public health. Multimorbid people are associated with more hospital admissions, a large number of drug prescriptions and higher risks of mortality. As there is evidence that multimorbidity varies with age and socioeconomic disparity, the main objective aimed at determining age-specific prevalence rates as well as exploring educational differences relating to multimorbidity in Germany.

Methods: This cross-sectional analysis is based on the national telephone health interview survey "German Health Update" (GEDA2012) conducted between March 2012 and March 2013 with nearly 20,000 adults. GEDA2012 provides information on 17 self-reported health conditions along with sociodemographic characteristics. Multimorbidity was defined as the occurrence of two or more chronic conditions in one individual at the same time. Descriptive statistical analysis was used to examine multimorbidity according to age and education, which was defined by the International Standard Classification of Education (ISCED 1997).

Results: Overall, 39.6% (95% confidence interval (CI) 38.7%–40.6%) of the 19,294 participants were multimorbid and the proportion of adults with multimorbidity increased substantially with age: nearly half (49.2%, 95% CI 46.9%–51.5%) of the adults aged 50–59 years had already two or more chronic health conditions. Prevalence rates of multimorbidity differed considerably between the levels of education. Low-level educated adults aged 40–49 years were more likely to be multimorbid with a prevalence rate of 47.4% (95% CI 44.2%–50.5%) matching those of highly educated men and women aged about ten years older.

Conclusions: Our findings demonstrate that both, age and education are associated with a higher risk of being multimorbid in Germany. Hence, special emphasis in the development of new approaches in national public health and prevention programs on multimorbidity should be given to low-level educated people aged <65 years.

Keywords: Multimorbidity, Socioeconomic status, Age, Chronic conditions, German health update (GEDA) 2012

Background

Multimorbidity - typically defined as the presence of more than one chronic condition at the same time in one individual - represents a major challenge for health care systems [1]. Compared to people with no or only a single chronic disease, multimorbid people are more likely to need costly long-term medical care with more than twice as many contacts with physicians in the ambulatory care sector per year [2–4]. Multimorbidity is also connected to a large number of drug prescriptions (polypharmacy) [4–6] and more hospital admissions: a recent study in Canada for example showed that 26.9% of people with 5 or more conditions of their study population experienced at least one hospitalization compared to 4.6% of people with only one condition [7]. Moreover, multimorbidity negatively influences functional and cognitive abilities [5, 8, 9], reduces quality of life [5, 10] and is associated with a higher risk of mortality: in a recent review and meta-analysis, the risk of death for people with at least 2 morbidities was found to be 1.73 times higher compared to people without multimorbidity [11].

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There is no gold standard for the definition of multimorbidity [12, 13], so prevalence rates vary from 12.9% to 95.1% depending on the number of chronic conditions examined or the population under study [14]. As multimorbidity becomes more frequent with age, the majority of studies examining patterns of multimorbidity in Germany focused on the elderly [15–17]. Less emphasis has been given to young or middle-aged people. In addition to the strong association with age, there is some evidence that prevalence rates also depend on socioeconomic characteristics [14, 17–19]. In a recent study in Yorkshire in England for example, prevalence of multimorbidity by age was strongly associated with deprivation. Li et al. found differences between people living in the least deprived area and people living in the most deprived area of nearly 20% [19], while in Germany only little knowledge on these issues is available [17, 20]. However, specific knowledge on national patterns and effects of multimorbidity is required in order to be able to develop effective prevention measures. Differences in health care and educational systems as well as people's mentality make it difficult to transfer international intervention and prevention programs to public health measures in Germany.

Using data of the national telephone health interview survey "German Health Update 2012", the present study is the first study that aimed at determining age-specific prevalence rates of multimorbidity stratified by educational level in German adults.

Methods

Our secondary data analysis is based on the Public Use File (PUF) of the national telephone health interview survey "German Health Update" ("Gesundheit in Deutschland aktuell", GEDA 2012) conducted by the Robert Koch Institute [21]. The Robert Koch Institute is a federal institution financed by the German Federal Ministry of Health and is responsible for the research of infectious diseases as well as for analyzing national long-term public health trends [22]. As part of the health monitoring, the cross-sectional survey GEDA 2012 was carried out between March 2012 and March 2013 gathering information about a range of health related topics involving current health conditions and medical history along with sociodemographic characteristics [23]. The target population included nearly 20,000 fluently German-speaking adults who were at least 18 years old and were living in private households with landline telephone. Using a two-stage sampling procedure, the ADM-Sampling-System (ADM = Arbeitskreis Deutscher Markt- und Sozialforschungsinstitute e. V.) based on the Gabler-Häder method [24, 25] was used for the selection at the household level whereas random sampling at the individual level was performed by the Kish selection grid method [26, 27]. In total, 19,294 participants completed the computer assisted telephone interviews (CATI) which corresponds to a cooperation rate at respondent level of 76.7% and a response rate 3 of 22.1% (based on standards of the American Association for Public Opinion Research) [23, 27, 28]. More details on the methodological procedures are presented in the Additional file 1.

The PUF analysed here includes information on survey participants in an anonymous form. Specifically, it provides data on 17 self-reported health conditions including 15 diseases, namely hypertension, coronary heart disease, myocardial infarction, chronic heart failure, stroke, diabetes mellitus, bronchial asthma, any type of cancer, hypercholesterolemia, chronic bronchitis, chronic liver disease, arthrosis, osteoporosis (limited to participants aged ≥50 years), arthritis and depression [27]. Within the survey, participants were asked, for example, "Have you ever been diagnosed with hypertension, also referred to as high blood pressure, by a physician?" and if responding positively, they were asked "Have you been diagnosed with hypertension in the last 12 months?" By responding positively to the second question as well, it was assumed that a participant is currently suffering from hypertension. The same methodology was also used for other health conditions. In addition, data on self-reported chronic low back pain for at least 3 months and an evaluation of obesity based on WHO's criteria (BMI ≥ 30 kg/m^2) [29] using BMI values estimated by self-reported body height and weight for each participant are available. To assess current health conditions, prevalence estimates were determined by variables representing 12-month prevalence when provided. Estimates of four diagnoses associated with long-term damages (coronary heart disease, myocardial infarction, cancer and stroke) were based on lifetime prevalence.

Although various definitions of multimorbidity have been employed in the literature, the core of considered morbidities is similar in most studies and the majority is also available within the PUF [13, 30]. We defined multimorbidity by the presence of at least two (≥ 2) of the 17 health conditions in one person at the same time. The PUF contains information on the educational qualification according to the International Standard Classification of Education (ISCED 1997) that has been summarized into low education (level 1, 2), medium education (level 3A, 3B, 4A) and high education (level 5A, 5B, 6). For age-specific analyses, 10-year age groups were used that are given by 18–29 years, 30–39 years, 40–49 years, 50–59 years, 60–69 years, 70–79 years and 80 years or older.

Prevalence rates along with 95% confidence intervals were computed for both the total cohort as well as for subgroups defined by age, sex and level of education. All prevalence rates were weighted according to the standardized weighting factor based on age, sex, level of education and residential region provided by the Robert-Koch Institute in order to correct for any deviations from the German population structure [23]. Additional file 1 represents this in more detail. Additionally, the unweighted overall number of

participants in each subgroup (defined by sex, age or education) is presented. Based on logistic regression, adjusted odds ratios (OR) and 95% confidence intervals were computed to further examine associations between multimorbidity and age, sex or level of education. All analyses were performed using IBM SPSS Statistics (version 22) [31] with the complex sample module and R (version 3.1.0) [32].

Results

The analyses included data of 19,294 respondents with roughly the same proportions of men and women (48.3% men and 51.7% women). Sociodemographic characteristics of the study population are summarized in Table 1. Almost all age groups were equally represented; only the proportion of adults aged 80 years and older was lower. More than half of the participants had an educational qualification within the medium ISCED category while fewer participants had a qualification within the lowest or the highest category.

The number of self-reported morbidities in one person at the same time varied from 0 to 13. In total, 62.1% (95% CI 61.2%–63.0%) of men and women had at least one of the 17 chronic health conditions and 39.6% (95% CI 38.7%–40.6%) of the adult population were multimorbid with only small differences between men (37.3%, 95% CI 36.0%–38.7%) and women (41.8%, 95% CI 40.4%–43.1%).

The proportion of multimorbid adults increased considerably with age resulting in an S-shaped curve (Fig. 1). The prevalence of multimorbidity was still lower than 10% among young people (18–29 years old) whereas already more than a quarter (27.7%, 95% CI 25.7%–29.7%) of the people between 40 and 49 years of age were multimorbid. Nearly half (49.2%, 95% CI 46.9%–51.5%) of the adults aged 50–59 years had two or more chronic health conditions and by the age of 80 years, the prevalence rate had grown up to 77.5% (95% CI 73.2%–81.3%).

Regarding the level of education, people with a lower educational level showed higher rates of multimorbidity

Table 1 Sociodemographic characteristics of the study population (GEDA 2012)

	n (%[a])	Percentage with Multimorbidity (95% CI)	Mean number of diagnoses (95% CI)	Median number of diagnoses
All participants	19,294 (100)	39.6 (38.7–40.6)	1.6 (1.6–1.7)	1
Sex				
Male	9318 (48.3)	37.3 (36.0–38.7)	1.5 (1.5–1.6)	1
Female	9976 (51.7)	41.8 (40.4–43.1)	1.8 (1.7–1.8)	1
Age groups (years)				
18–29	2643 (16.2)	7.0 (5.9–8.3)	0.4 (0.3–0.4)	0
30–39	2242 (15.0)	17.2 (15.1–19.5)	0.7 (0.6–0.8)	0
40–49	3665 (19.7)	27.7 (25.7–29.7)	1.1 (1.0–1.2)	1
50–59	3592 (17.4)	49.2 (46.9–51.5)	1.9 (1.8–2.0)	1
60–69	3325 (13.0)	61.7 (59.3–64.1)	2.5 (2.4–2.6)	2
70–79	2936 (14.1)	72.9 (70.4–75.2)	3.1 (3.0–3.2)	3
80+	891 (4.7)	77.5 (73.2–81.3)	3.5 (3.2–3.7)	3
Level of education				
High	8098 (24.1)	31.9 (30.7–33.1)	1.3 (1.2–1.3)	1
Medium	9812 (55.4)	40.1 (39.0–41.3)	1.6 (1.6–1.7)	1
Low	1358 (20.6)	47.4 (44.2–50.5)	2.1 (1.9–2.2)	1
Number of self-reported diagnoses				
0	7043 (37.9)			
1	4349 (22.5)			
2	2899 (14.3)			
3	1929 (9.6)			
4	1254 (6.2)			
5	795 (4.0)			
6	474 (2.5)			
7	270 (1.4)			
8+	281 (1.6)			

[a]Weighted results to represent the adult population in Germany; Level of education: Missing data for 26 participants

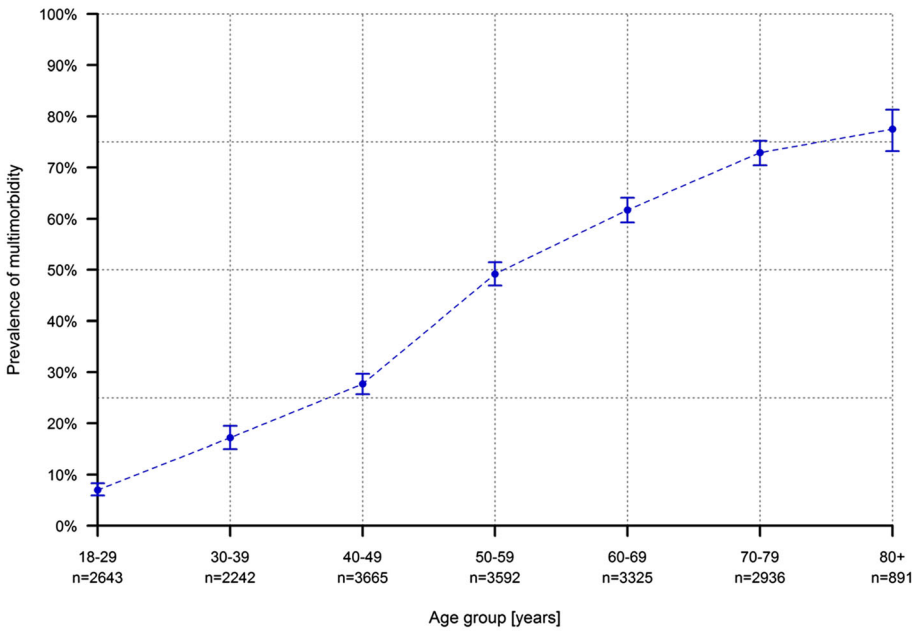

Fig. 1 Age-specific prevalence of multimorbidity with 95% confidence intervals

compared to those with a higher educational level. Specifically, 31.9% (95% CI 30.7%–33.1%) of people with an educational level of the highest category had two or more chronic conditions whereas nearly half (47.4%, 95% CI 44.2%–50.5%) of the low-level educated people were multimorbid. The association between age-specific prevalence rates of multimorbidity and the level of education is illustrated in Fig. 2. As demonstrated there, the S-shaped curves for prevalence by age varied with education: while prevalence rates for young people (18–29 years old) and elderly people (≥ 60 years old) were similar, there were substantial differences between the three educational levels among middle-aged men and women (30–59 years old). Of note, the curve of the lowest educational level had a steeper slope leading to a considerable shift to the left. As a result, adults aged 40–49 years with a low educational qualification showed prevalence rates equivalent to highly educated adults at least ten years older. Furthermore, for people aged 60–69 years with a high educational qualification, the prevalence of multimorbidity was still lower than for low-level educated people about 10 years younger (50–59 years old).

Age and level of education showed a significant association with the odds of being multimorbid (Table 2). In particular adults with a low or medium level of education had higher odds of being multimorbid than highly educated adults (Adjusted OR (low vs. high) 1.9, 95% CI 1.5–2.2; Adjusted OR (medium vs. high), 1.5, 95% CI 1.4–1.7). Using 18–29 year old adults as reference, the odds of being multimorbid increased with each additional age group, too (Table 2).

Discussion

The underlying study examined prevalence rates of multimorbidity with regard to age and level of education based on data of the adult residential population in Germany. Multimorbidity is a common issue within Germany that is not limited to the elderly (aged 65 years and older) and already shows prevalence rates >50% in younger age groups, especially in low-level educated adults. In addition to the expected association with age, prevalence rates of multimorbidity differ considerably between the three levels of education. Low-level educated middle-aged adults are more likely to be multimorbid with prevalence rates matching those of high-educated men and women aged at least ten years older.

In general, the lack of a standard definition of multimorbidity limits the comparison of different studies on multimorbidity. Results are usually strongly dependent on the definition of the population under study (e.g. statutory health insurance data or focus only on elderly people), on the number and selection of medical diagnoses and on the choice of a “threshold” describing the number of morbidities that have to be present in one person in order to be considered as multimorbid [13, 30]. Nevertheless, our results agree well with those of other studies on multimorbidity. For example, in a previous GEDA study of 2009, the prevalence rates of multimorbidity defined as two or more conditions in one person at the same time were 43.9% (women) and 36.3% (men), respectively, compared to 41.8% (women) and 37.3% (men) in the present study. Although GEDA 2009 assessed information on 22 health conditions

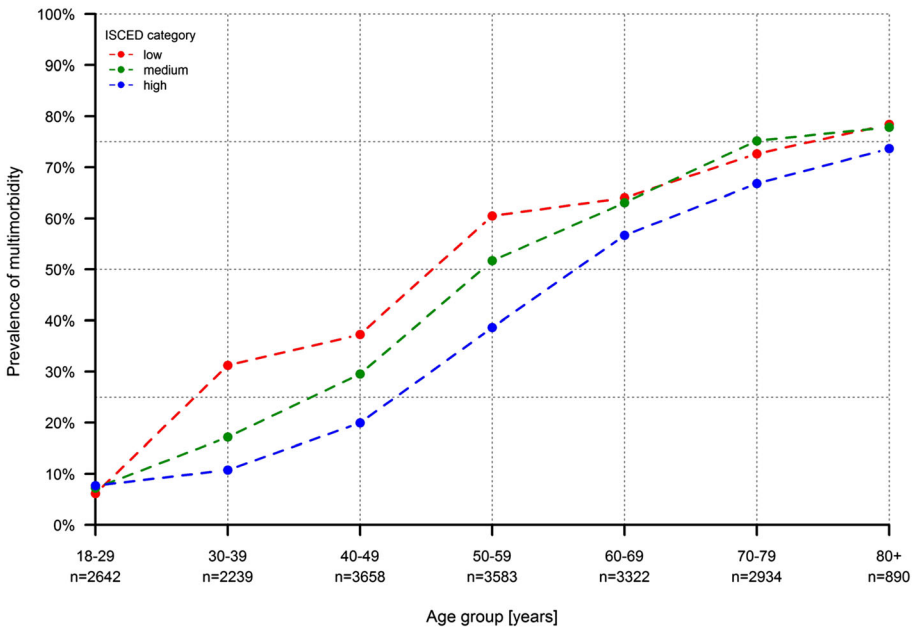

Fig. 2 Age-specific prevalence of multimorbidity by ISCED category

across five age groups only, the prevalence rates for men and women increased with age comparably to the rates of GEDA 2012 [20]. Specifically, the prevalence of multimorbidity rose up to 74.2% for men and 81.7% for women aged 75+ years [20]. In another German cross-sectional study based on claims data, patterns of multimorbidity were evaluated among policy holders aged 65 years and older [15]. The analyses included a list with 46 morbidities comprising all frequent somatic and psychic disorders. Defining multimorbidity as the presence of at least two morbidities, the prevalence rate for adults aged 65+ years was estimated to 73% [15] in comparison to 71.2% in the current study. Patterns in prevalence relating to socioeconomic characteristics are also in line with findings from two cross-sectional analyses in England and Scotland [18, 19]. Barnett et al. examined age-specific prevalence of multimorbidity in Scotland by including 40 different morbidities and evaluating socioeconomic differences by the deprivation of the area in which a patient lived. While only 23.2% in total of the Scottish patients under study had two or more concurrent morbidities (compared to 39.6% in the current study), age-specific patterns with regard to socioeconomic deprivation were similar to those obtained in the present study supporting the description of S-shaped curves as illustrated by Fortin et al. [33]. Specifically, middle-aged people living in the most deprived areas are more likely to be multimorbid with prevalence rates matching those of people living in the most affluent areas aged 10–15 years older. This matches our findings of differences between low-level and high-level educated middle-aged adults causing a shift of the corresponding s-shaped curves. Results of the recent Yorkshire Health Study survey showed that 37.2% [19] of all participants were multimorbid in accordance with 39.6% in the present study. Nearly half (45.7%) of the participants from the most deprived areas had at least two or more of the included 13 health conditions [19], that is comparable to our result of 47.2% for adults with a low educational qualification.

There is a chance that prevalence rates of multimorbidity are under- or overestimated for several reasons, although

Table 2 Odds ratios (OR) estimated from logisitc regression for multimorbidity by sex, age and level of education

	Unadjusted OR	95% CI	Adjusted OR	95% CI
Sex				
Male (ref.)	1.0		1.0	
Female	1.2	1.1–1.3	1.0	0.9–1.1
Age groups (years)				
18–29 (ref.)	1.0		1.0	
30–39	2.8	2.2–3.5	3.1	2.4–3.9
40–49	5.1	4.1–6.3	5.6	4.5–7.0
50–59	12.9	10.5–15.9	14.3	11.6–17.7
60–69	21.5	17.4–26.5	23.3	18.8–29.0
70–79	35.9	28.8–44.7	37.2	29.7–46.6
80+	46.0	34.2–61.9	45.2	33.5–60.9
Level of education				
High (ref.)	1.0		1.0	
Medium	1.4	1.3–1.5	1.5	1.4–1.7
Low	1.9	1.7–2.2	1.9	1.5–2.2

we cannot determine the direction and quality of it. As the analyses were based on secondary data, only a limited selection of medical diagnoses was available. In particular, prevalence estimates may be downward-biased by not including other relevant chronic conditions such as chronic gastrointestinal diseases. All the details on the different diagnoses are based on self-reported health conditions. Although all participants were asked whether medical diagnoses were made by a physician, information on health conditions were not clinically verified and may be biased as a consequence of misclassification (recall bias/reporting bias) [23]. Only people living in private households were interviewed, people living in nursing homes, for example, could not be contacted. The survey was also limited to people with landline telephone, hence results may be biased by not including households with mobile phones only [23]. As the interviews were carried out in German, people had to speak and understand German [23], so marginalized groups such as migrants could not be regarded [27]. Moreover, people with a low educational qualification agreed less often to participate in the telephone interview than medium-level or high-level educated people [27]. To control for differences in the willingness for participation, a weighting factor provided by the Robert Koch Institute was used to approach the adult residential population structure in Germany.

We have shown above that our results agree with those of other countries. However, since there are considerable differences in health care systems and educational systems between other countries and Germany, international research and prevention programs can only be transferred to a limited extent. It is absolutely necessary to have national valid data in order to be able to establish precise public health interventions. One out of every two low-level educated adults aged 40–49 years in Germany is multimorbid hence the presence of multiple chronic conditions in one individual is very common. This is of high relevance, as for example, clinical recommendations still focus on single chronic diseases rather than dealing with multiple chronic conditions. Existing approaches in health care systems need to be complemented by enclosing information on risk factors and consequences of multimorbidity. Our findings with prevalence rates stratified by age and education represent contributing factors that should be considered within the development of prevention measures as well as programs for early detection of diseases in the public health sector in Germany.

The present study has analysed the association of multimorbidity, age and educational level but has not examined the relation between cause and effect. It may be possible that consequences of multimorbidity restrain the ability of young people to achieve a higher educational level. On the other hand, both, low educational qualification and being multimorbid, may be associated with poor lifestyle habits (e.g. smoking, alcohol, lack of exercise or excess weight). Multimorbidity is also associated with a higher mortality rate although it remains unclear to which extend the cumulative effects of coexisting diseases are responsible for an early death rather than functional disorder and mental disability related to the most severe disease. Hence, multimorbidity is a complex combination of effects and still not fully understood. Further research on multimorbidity is needed, in particular with regard to risk factors that seem to be associated with the early development of multiple chronic conditions in low level educated adults in Germany.

Conclusions

Multimorbidity and its consequences are still a key challenge in public health systems. Our findings suggest that both, age and education are important aspects that have to be considered in the development of new prevention measures on multimorbidity. Existing single-disease approaches are increasingly inappropriate and new approaches covering the complex interactions of multiple chronic conditions are inevitable. Public health campaigns as well as programs for early detection of coexisting diseases in Germany especially have to focus on people ≤65 years with low educational qualification.

Additional file

Additional file 1: Methodological details. The additional file provides methodological procedures in more detail. (PDF 260 kb)

Abbreviations

ADM: Arbeitskreis Deutscher Markt- und Sozialforschungsinstitute e. V; BMI: Body mass index; CATI: Computer assisted telephone interviews; CI: Confidence interval; GEDA: German Health Update; ISCED: International Standard Classification of Education; OR: Odds ratio; PUF: Public Use File; WHO: World Health Organization

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None.

Availability of data and materials

The dataset analysed during the present study is available from the Robert Koch Institute for researchers who meet the criteria for access, [doi:10.7797/29–201,213–1-1-1] [21].

Authors' contributions

EM and MTP devised the basic idea for the manuscript. MTP performed the statistical analysis, with contributions by EM. MTP drafted the manuscript; EM, KW and MS revised it critically and approved the final manuscript. All authors read and approved the final manuscript.

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Ethics approval and consent to participate

Not applicable as the analysis is based on secondary data.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Appendix B

Puth M-T, Klaschik M, Schmid M, Weckbecker K, Münster E: Prevalence and comorbidity of osteoporosis - a cross-sectional analysis on 10,660 adults aged 50 years and older in Germany. BMC Musculoskelet Disord 2018; 19(1): 144
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RESEARCH ARTICLE Open Access

Prevalence and comorbidity of osteoporosis– a cross-sectional analysis on 10,660 adults aged 50 years and older in Germany

Marie-Therese Puth[1,2*], Manuela Klaschik[1], Matthias Schmid[2], Klaus Weckbecker[1] and Eva Münster[1]

Abstract

Background: Knowledge on prevalence of osteoporosis stratifying for socioeconomic background is insufficient in Germany. Little is known in Europe about other diseases that go along with it although these aspects are important for implementing effective public health strategies.

Methods: This cross-sectional analysis was based on the national telephone survey "German Health Update" (GEDA 2012) performed in 2012/2013. GEDA 2012 provides information on self-reported diseases and sociodemographic characteristics for nearly 20,000 adults. Descriptive statistical analysis and multiple logistic regression were used to examine the association between osteoporosis and age, sex, other diseases and education defined by ISCED. Analyses were limited to participants aged 50 years and older.

Results: Overall, 8.7% of the 10,660 participants aged 50+ years had osteoporosis (men 4.7%, women 12.2%). More than 95% of the adults with osteoporosis had at least one coexisting disease. The odds for arthrosis (OR 3.3, 95% CI 2.6-4.1), arthritis (OR 3.0, 95% CI 2.2-4.2), chronic low back pain (OR 2.8, 95% CI 2.3-3.5), depression (OR 2.3, 95% CI 1.7-3.1) and chronic heart failure (OR 2.3, 95% CI 1.6-3.1), respectively, were greater for adults with osteoporosis. Education showed no significant association with osteoporosis.

Conclusions: There was no clear evidence of socioeconomic differences regarding osteoporosis for adults in Germany. However, clinicians need to be aware that multimorbidity is very common in adults with osteoporosis. Health care interventions for osteoporosis could be improved by offering preventive care for other diseases that go along with it. Over- or under-diagnosis in different socioeconomic levels has to be further explored.

Keywords: Prevalence, Socioeconomic level, Comorbidity, Osteoporosis, Multimorbidity, Germany

Background

Osteoporosis and its consequences are a major public health concern and amount in high expenses for health care systems [1, 2]. For the affected patients it results in serious impairment in quality of life [2]. The World Health Organization (WHO) estimates the lifetime risk in a developed country for an osteoporotic fracture of hip, vertebra or wrist at 30-40% [3]. Exact data of the prevalence and comorbidities for the German population are rare. The "European Prospective Osteoporosis Study" (EPOS) stated a prevalence of 15% in women aged 50-60 years und 45% in women older than 70 years. In men the prevalence was 2.4% at age 50-60 years and 17% in men older than 70 years [4]. In total numbers this sums up to an estimated 4-7 million people with osteoporosis in Germany [4]. As the population structure is constantly changing towards a higher median age the overall share of osteoporosis patients is expected to grow continuously.

We wanted to take a closer look at the prevalence of osteoporosis in Germany, stratifying not only for more

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narrowly defined age groups and sex but also for socioeconomic level. This analysis is of high interest as the link between socioeconomic level and health and health behaviour is well documented [5–8] but is still lacking for osteoporosis [9, 10].

Often, bone mineral density (BMD) measurements alone are used to diagnose osteoporosis and/or to assess the chance of fractures. Beyond BMD, however, there are additional factors that similarly contribute to the disease. In addition to unchangeable factors as female gender, age, ethnicity or family history of fractures many preventable factors as poor lifestyle habits or physical inactivity have a significant impact on osteoporosis and fracture risk [11–13].

When discussing the health problems of osteoporosis patients the main focus is usually directed towards bone fractures as these are the most immediate consequences of the disease. Little is known about other diseases that go along with osteoporosis and equally impair the patients' quality of life. Examining the association of osteoporosis with a range of different medical conditions might help to improve the health care for affected patients by offering early or even preventive care for diseases that go along with it.

Methods

Our analysis was based on the Public Use File (PUF) of the national telephone health interview survey "German Health Update" (GEDA 2012) conducted by the Robert Koch Institute between March 2012 and March 2013 [14]. The Robert Koch Institute is a federal institution financed by the German Federal Ministry of Health that in addition to the research of infectious diseases is responsible for analysing national long-term public health trends [15]. As part of the health monitoring, the cross-sectional survey GEDA 2012 collected information about a range of health related topics involving current health conditions and medical history as well as sociodemographic characteristics [16]. The target population included fluently German-speaking adults of at least 18 years of age who were living in private households with landline telephone. Using a two-stage sampling procedure, the ADM-Sampling-System covered all possible phone numbers in Germany and was applied for the selection at household level [17, 18]. Random sampling at the individual level was performed by the Kish selection grid method that randomly selected an adult aged 18+ years out of all adults aged 18+ years in a private household [19, 20]. 19,294 participants completed the computer assisted telephone interviews (CATI) which matches a 'cooperation rate at respondent level' of 76.7% and a 'response rate 3' of 22.1% using standards of the American Association for Public Opinion Research [16, 20, 21]. The study involved the use of a previously-published de-identified database (secondary data analysis) so ethics approval and participant consent was not necessary [22].

The PUF contains data on survey participants in an anonymous form and provides information on self-reported health conditions including osteoporosis and 14 other medical diagnoses. The analyses were limited to participants aged 50 years and older as only those were asked about a medical history of osteoporosis [20]. Specifically, participants were asked "Have you ever been diagnosed with osteoporosis, also referred to as bone loss, by a physician?". If it was affirmed, they were asked "Have you been diagnosed with osteoporosis in the last 12 months?"

To assess current health conditions, we considered only participants that stated suffering from osteoporosis in the past 12 months. The same criterion was used for any of the other medical diagnoses, namely hypertension, chronic heart failure, diabetes mellitus, bronchial asthma, hypercholesterolemia, chronic bronchitis, chronic liver disease, arthrosis, arthritis and depression. Lifetime history was only assessed for four diagnoses associated with long-term damages (coronary heart disease, myocardial infarction, cancer and stroke). In addition, data on self-reported chronic low back pain for at least 3 months was considered. Details on the exact definitions of the aforementioned diseases have already been published [20].

For age-specific analyses, 5-year age groups were used that were given by 50-54 years, 55-59 years, 60-64 years, 65-69 years, 70-74 years, 75-79 years, 80-84 years and 85 years or older. Information on educational qualification according to the International Standard Classification of Education (ISCED 1997) was summarized into low education (level 1, 2), medium education (level 3A, 3B, 4A) and high education (level 5A, 5B, 6) [20]. The Body Mass Index (BMI) estimated by self-reported body height and weight of each respondent was classified to underweight (BMI < 18.5 kg/m^2), normal (18.5 $kg/m^2 \leq$ BMI < 25 kg/m^2), overweight (25 $kg/m^2 \leq$ BMI < 30 kg/m^2) and obese (BMI ≥ 30 kg/m^2) according to WHO's criteria [23]. Alcohol consumption was assessed using the "Alcohol Use Disorders Identification Test-Consumption" (AUDIT-C) [20, 24] and was categorized in no alcohol consumption, moderate alcohol consumption and high alcohol consumption [20]. Self-reported smoking status was summarized into non-smoker, ex-smoker or current smoker (daily or occasional) [20].

Prevalence rates of osteoporosis with 95% confidence intervals (CI) were determined for the total cohort aged at least 50 years as well as for subgroups defined by sex, age, education, BMI, smoking status and alcohol consumption. To correct for any deviations of the GEDA 2012 study population from the German population, prevalence rates were weighted according to the

standardized weighting factor based on age, sex, education and residential region provided by the Robert-Koch Institute [20]. The unweighted number of participants in each subgroup is also displayed. Based on multiple logistic regression, odds ratios (OR) with 95% confidence intervals were computed to evaluate associations between other medical diagnoses and osteoporosis adjusted for age, sex, education, BMI, smoking status and alcohol consumption. For all independent variables in multiple regression analysis, the amount of missing responses did not exceed 2% hence missing responses were allocated to the reference category. Additional sensitivity analyses restricted to participants with valid data on all independent variables (complete cases) were performed. All analyses were realized using IBM SPSS Statistics (version 24) [25] with the complex sample module and R (version 3.3.3) [26].

Results

The total number of participants aged 50 years and older was 10,744. Of those, 84 participants were excluded from the analysis due to unknown or missing responses regarding a diagnosis of osteoporosis. Thus, the present study included data of 10,660 participants (in the following termed "study population") of which 911 stated suffering from osteoporosis within the past 12 months (hereinafter referred to as "osteoporosis population"). Sociodemographic characteristics of the study and osteoporosis population are summarized in Table 1.

In total, 8.7% (95% CI 8.0-9.6%) of the adult population aged 50 years and older had osteoporosis with significant differences between men (4.7, 95% CI 3.8-5.9%) and women (12.2, 95% CI 11.1-13.5%). The proportion of female adults with osteoporosis increased considerably with age; the prevalence of osteoporosis for men remained nearly unchanged until the age of 84 years (Fig. 1). Regarding the level of education, people with a low educational level showed higher prevalence rates of osteoporosis compared to those with a higher educational level. Overweight or obese adults had smaller prevalence rates than people with a BMI within the normal range. The prevalence of osteoporosis was higher for non-smokers in comparison to ex- and current smokers and participants with a moderate or high consumption of alcohol showed lower rates than respondents that stated to never drink alcohol (Table 1).

Age, sex, alcohol consumption and BMI showed a significant association with the odds for osteoporosis. The odds of having osteoporosis were higher for female adults than male adults. Using 50 - 54 years old adults as reference, the odds for osteoporosis increased with age. Overweight or obese adults were associated with lower odds for osteoporosis in comparison to adults with normal weight (Table 1).

More than 95% of the adults with osteoporosis had at least one comorbidity and about two thirds (65.7%) had three or more comorbid diseases. For adults without osteoporosis, only 80.6% reported at least one chronic condition and 39.2% had three or more different chronic diseases (data not shown). As illustrated in Table 2, arthrosis (63.2%) was the most common comorbidity among participants with osteoporosis followed by hypertension (51.3%), chronic low back pain (49.6%) and hypercholesterolemia (38.6%). About one in every five adults with osteoporosis suffered from coronary heart disease (21.0%) or arthritis (20.6%). In line with this, hypertension (44.2%), arthrosis (34.5%), hypercholesterolemia (30.1%) and chronic low back pain (26.8%) were also the most frequent conditions in the study population but they were followed by diabetes mellitus (13.7%), coronary heart disease (13.7%) and any type of cancer (12.2%).

Eleven out of fifteen comorbidities showed a significant association with osteoporosis. Of note, for adults with osteoporosis, the odds for arthrosis, chronic low back pain, arthritis, depression and chronic heart failure, respectively, were more than two times greater than for adults without osteoporosis (Table 2).

Sex-stratified analyses as well as analyses restricted to participants with valid data on all independent variables in regression (complete cases) showed similar results to the main analysis (data not presented).

Discussion

The underlying study provides representative data on prevalence rates and comorbidities of osteoporosis based on the German population aged 50 years and older. The overall prevalence was estimated to 8.7% (men 4.7%, women 12.2%) and, for women, the rates increased substantially with age. According to multiple regression analysis, osteoporosis was significantly related to age, sex, BMI and alcohol consumption while smoking status and education showed no significant association. Adults with osteoporosis showed more than twofold increased odds for arthrosis, arthritis, chronic low back pain, chronic heart failure and depression, respectively.

Results on prevalence rates are difficult to compare as international prevalence estimates of osteoporosis are mostly based on the assessment of bone mineral density measurements using the WHO's criteria with T-scores [3, 27, 28]. However, our results agree well with those of other studies on osteoporosis [27–32]. Using data from the National Health and Nutrition Examination Survey 2005-2010 with BMD measurements [27], Wright et al. estimated an overall prevalence of osteoporosis of 10.3% (men 4.3%, women 15.4%) in adults aged 50 years and older in the United States that is similar to the overall prevalence of 8.7% (men 4.7%, women 12.2%) in the

Table 1 Sociodemographic characteristics by osteoporosis including adjusted odds ratios and 95% confidence intervals (GEDA 2012)

Characteristics	Study population n (%[a])	%[a] with Osteoporosis (95% CI)	Osteoporosis population n (%[a])	OR[b] (95% CI)
Total	10,660 (100)	8.7 (8.0-9.6)	911 (100)	
Sex***				
Male	4961 (46.5)	4.7 (3.8-5.9)	193 (25.2)	ref.
Female	5699 (53.5)	12.2 (11.1-13.5)	718 (74.8)	2.3 (1.7-3.0)
Age groups*** (years)				
50-54	2147 (19.1)	3.2 (2.4-4.2)	62 (6.9)	ref.
55-59	1429 (16.4)	6.3 (4.7-8.5)	87 (11.9)	2.1 (1.4-3.3)
60-64	1928 (14.6)	5.8 (4.5-7.5)	119 (9.7)	2.0 (1.3-3.0)
65-69	1378 (12.0)	8.7 (6.6-11.3)	124 (11.9)	2.9 (1.9-4.5)
70-74	1645 (15.0)	11.3 (8.9-14.2)	159 (19.4)	4.2 (2.8-6.3)
75-79	1252 (13.4)	12.5 (10.2-15.3)	187 (19.2)	4.2 (2.8-6.3)
80-84	588 (6.6)	17.8 (14.1-22.3)	113 (13.5)	5.6 (3.6-8.7)
85+	293 (2.8)	23.3 (16.8-31.5)	60 (7.5)	7.5 (4.4-12.8)
Level of education				
High	4816 (22.7)	5.5 (4.9-6.3)	318 (14.4)	ref.
Medium	5155 (54.1)	8.3 (7.5-9.2)	495 (51.4)	1.2 (1.0-1.5)
Low	674 (23.2)	13.0 (10.4-16.0)	98 (34.3)	1.3 (0.9-1.9)
BMI* (kg/m^2)				
18.5 ≤ BMI < 25 (normal)	4015 (35.9)	10.8 (9.4-12.4)	396 (44.2)	ref.
18.5 > BMI (underweight)	112 (0.9)	16.9 (7.8-32.8)	19 (1.8)	1.4 (0.5-3.4)
25 ≤ BMI < 30 (overweight)	4290 (42.3)	7.4 (6.3-8.7)	318 (35.7)	0.8 (0.6-1.0)
30 ≥ BMI (obese)	2022 (20.9)	7.7 (6.2-9.5)	166 (18.3)	0.7 (0.5-0.9)
Smoking status				
Non-smoker	5220 (48.2)	10.3 (9.2-11.6)	524 (57.0)	ref.
Ex-smoker	3423 (31.4)	6.8 (5.7-8.2)	249 (24.6)	1.0 (0.8-1.3)
Current smoker	2014 (20.3)	7.9 (6.2-10.1)	138 (18.5)	1.3 (1.0-1.8)
Alcohol consumption*				
Moderate	5805 (52.3)	7.6 (6.7-8.7)	468 (46.4)	ref.
Never	2059 (23.5)	13.0 (11.1-15.2)	269 (35.3)	1.3 (1.0-1.6)
High	2716 (24.2)	6.5 (5.1-8.3)	164 (18.3)	0.9 (0.6-1.2)

[a]Weighted results to represent the adult population in Germany. Unweighted *n* may not add up to total *n* due to missing responses
[b]Odds ratios estimated from logistic regression adjusted for age, sex, education, BMI, smoking status and alcohol consumption, *** $p < 0.001$ ** $p < 0.01$ * $p < 0.05$. Missing responses were allocated to the reference category

present analysis. In comparison to other German studies [29–32], results on prevalence rates vary with regard to the methodology of measuring osteoporosis as well. On the one hand, our results are in line with those obtained in the first wave of the "German Health Interview and Examination Survey for Adults" (DEGS1) [29]. Similar to GEDA 2012, DEGS1 provides nationally representative data on the health status of the adult population between 18 and 79 years of age and estimated a lifetime prevalence of osteoporosis (self-reported) for people aged between 50 and 79 years to 8.5% (3.2% men, 13.1% women) [29]. Little differences with regard to socioeconomic status and an association with age for women were reported, too [29]. On the other hand, considering a study based on routine data of a statutory health insurance, prevalence rates were found to be higher. The BEST study that in addition to a medical diagnosis also included information on osteoporosis-related prescriptions and fractures reported an overall prevalence of 14% (6% men, 24% women) for insured people aged at least 50 years in the year 2009 [30]. Deviating methodical procedures might be responsible for differences in prevalence. Results of studies examining the relationship between smoking and osteoporosis as well as alcohol consumption and osteoporosis including low BMD and fracture risk are inconsistent [33–37]. There was also no

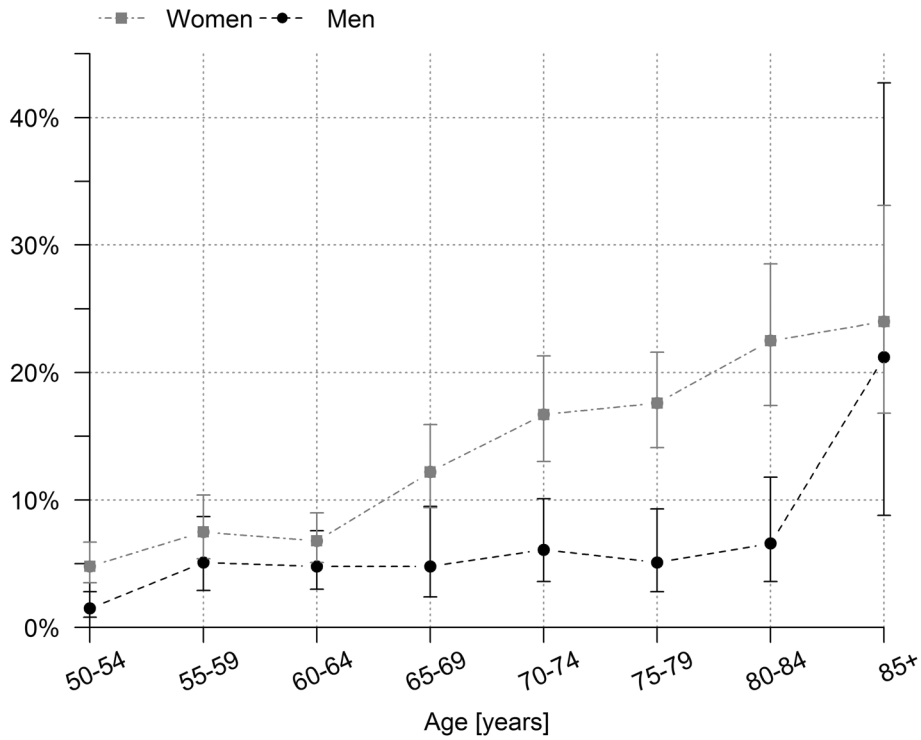

Fig. 1 Age and sex-specific prevalence of osteoporosis with 95% confidence intervals (GEDA 2012)

clear evidence of a relationship between osteoporosis and smoking in the present study. The association between educational level and osteoporosis/BMD remains inconclusive as well [9, 10, 38]. While the prevalence of osteoporosis was significantly lower for higher educated adults in comparison to adults with a low educational level, results of the present regression analysis revealed no significant effects.

Prevalence rates may be biased as a consequence of misclassification as our results are based on self-

Table 2 Associations between osteoporosis and comorbidities with adjusted odds ratios and 95% confidence intervals (GEDA 2012)

Comorbidity	Study population n (%[a]) (*N* = 10,660)	Osteoporosis population n (%[a]) (*N* = 911)	OR[b] (95% CI)
Arthrosis	3541 (34.5)	573 (63.2)	3.3 (2.6-4.1)***
Hypertension	4602 (44.2)	464 (51.3)	1.2 (1.0-1.5)
Chronic low back pain	2656 (26.8)	442 (49.6)	2.8 (2.3-3.5)***
Hypercholesterolemia	3092 (30.1)	334 (38.6)	1.5 (1.2-1.8)**
Coronary heart disease	1278 (13.7)	175 (21.0)	1.5 (1.1-2.0)**
Arthritis	799 (8.3)	171 (20.6)	3.0 (2.2-4.2)***
Any type of cancer	1334 (12.2)	154 (16.0)	1.2 (0.9-1.6)
Depression	911 (8.8)	128 (15.3)	2.3 (1.7-3.1)***
Chronic heart failure	600 (6.1)	110 (14.0)	2.3 (1.6-3.1)***
Diabetes mellitus	1418 (13.7)	122 (13.8)	0.9 (0.7-1.2)
Bronchial asthma	695 (7.1)	106 (12.2)	1.6 (1.2-2.2)**
Chronic bronchitis	701 (7.2)	119 (11.9)	1.6 (1.2-2.2)**
Stroke	437 (4.6)	67 (9.1)	1.8 (1.1-2.8)*
Myocardial infarction	596 (6.2)	59 (7.3)	1.0 (0.7-1.5)
Chronic liver disease	232 (2.1)	36 (3.8)	1.8 (1.0-3.2)*

[a]Weighted results to represent the adult population in Germany
[b]Odds ratio estimated from logistic regression adjusted for age, sex, education, BMI, smoking status and alcohol consumption, *** $p < 0.001$ ** $p < 0.01$ * $p < 0.05$. A separate regression model was fitted for each comorbidity

reported diagnoses that were not clinically verified. Since osteoporosis is not associated with any symptoms prior to a fracture and information on possible fractures were not available within GEDA, prevalence rates may be underestimated by not taking account of yet undiagnosed adults. On the other hand, considering arthritis, for example, prevalence rates may be overestimated as it is known that patients with other joint disorders often falsely state to suffer from rheumatoid arthritis [20, 39].

Using self-reported information on sociodemographic characteristics such as BMI values may lead to biased estimates as well (reporting bias). Moreover, only adults living in private households were contacted, hospitalized adults or adults living in care homes could not be considered. As all interviews were carried out in German, adults had to speak and understand German, thus marginalized groups such as migrants could not be regarded [20]. Low-level educated adults agreed less often to participate in the telephone interview than people with a medium or high level of education [20]. A weighting factor provided by the Robert Koch Institute was used to approach the adult residential population structure in Germany [20].

Osteoporosis represents a major public health concern and its prevention is crucial to the maintenance of health [40]. It is a systemic condition characterized by changes in bone microarchitecture and a reduction of bone mass, both of which lead to decreased bone strength and at the same time to increased fracture risks. As a consequence, treatment at all ages aims at retaining bone mass to prevent any type of fracture (e.g. hip, spine). Fractures with severe complications are serious consequences of osteoporosis that have an influence on morbidity, functional impairment of health, a decrease in quality of life as well as an increase in medical costs [40, 41]. Additionally, at the time of a fracture, comorbidities in osteoporosis patients play a key role. Further, drug-drug interactions may affect the progress of the disease. Regarding osteoporosis, especially the consumption of drugs that have an effect on bone metabolism is of interest. In GEDA however, data on the use of pharmaceuticals were not collected and an evaluation of the use of different drug classes could therefore not be done.

In the present study nearly all adults with osteoporosis reported at least one comorbid condition, but the cross-sectional design did not allow for an analysis of cause and effect. In the GEDA study population participants that stated to suffer from osteoporosis were for example more than twice as likely to also suffer from depression. Drosselmeyer et al. showed that typically depression follows osteoporosis, but not vice versa [42]. Physical disability following fractures affects the capacity for independent living and complicates social participation. Besides, as physical activity is reduced in depressive patients but important to improve or at least stabilize bone mineral density, it would be important to recognize and treat the disease early. Of interest is also the association between arthrosis and osteoporosis. In the present study, participants with osteoporosis showed more than three times higher odds of having arthrosis. However, in most cross-sectional studies [43], arthrosis was negatively connected with osteoporosis in the sense that people with arthrosis showed higher BMD. Despite this negative association, the risk of osteoporotic fractures in patients with arthrosis remains the same [43]. Generally, arthrosis is associated with stiffness and pain in the affected joints, and this may reduce physical activity, which subsequently leads to instability and higher fracture risks. Hence, the relation of osteoporosis and arthrosis appears to be very complex and needs to be analysed further.

Conclusions

The disease burden in adults with osteoporosis is of high relevance. Physicians need to be aware of the high occurrence of multimorbidity in adults with osteoporosis. Health care interventions for affected patients should be expanded by offering early or even preventive care for other diseases that go along with it. Over- or underdiagnosis in different socioeconomic levels has to be further explored.

Abbreviations

ADM: Arbeitskreis Deutscher Markt- und Sozialforschungsinstitute e. V; AUDIT-C: Alcohol Use Disorders Identification Test-Consumption; BMD: Bone Mineral Density; BMI: Body Mass Index; CI: Confidence Intervals; DEGS: German Health Interview and Examination Survey for Adults; EPOS: European Prospective Osteoporosis Study; GEDA: German Health Update; ISCED: International Standard Classification of Education; OR: Odds Ratio; PUF: Public Use File; WHO: World Health Organization

Availability of data and materials

The dataset analysed during the present study is available from the Robert Koch Institute for researchers who meet the criteria for access, [doi: https://doi.org/10.7797/29-201,213-1-1-1] [14].

Authors' contributions

EM and MTP devised the basic idea for the manuscript. MTP performed the statistical analysis, with contributions by EM. MTP and MK drafted the manuscript. EM, KW and MS revised it critically. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Ethics approval and participant consent was not necessary as this study involved the use of a previously-published de-identified database (secondary data analysis) according to national guidelines and recommendations in secondary data analysis [22] .

Competing interests

The authors declare that they have no competing interests.

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Appendix C

Tillmann J, Puth M-T, Weckbecker K, Klaschik M, Münster E: Prevalence and predictors of having no general practitioner - analysis of the German health interview and examination survey for adults (DEGS1). BMC Fam Pract 2019; 20(1): 84
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RESEARCH ARTICLE Open Access

Prevalence and predictors of having no general practitioner - analysis of the German health interview and examination survey for adults (DEGS1)

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Abstract

Background: Although patients in Germany are generally free to choose their primary healthcare provider, this role should mainly be assumed by general practitioners (GPs). While some predictors of the frequency of use of GP services have been reported in international studies, there is still a lack in knowledge what could deter people from contacting a GP in Germany. To improve healthcare, it is important to identify characteristics of people without a GP.

Methods: This cross-sectional analysis was based on the first wave of the "German Health Interview and Examination Survey for Adults" (DEGS1) conducted by the Robert Koch Institute in 2008–2011. Descriptive analyses and multiple logistic regression by gender were performed to analyze the association between having no GP and age, gender, residential area, socioeconomic status (SES), marital status, working hours per week, general state of health, chronic diseases and health insurance.

Results: Overall, 9.5% (95% confidence interval (CI): 8.4–10.7) of the 7755 participants stated to have no GP, more often men (11.4%) than women (7.6%). Life in urban areas (big cities vs. rural: adjusted odds ratio (aOR): 2.9, 95% CI: 2.1–3.9), younger age (18–29 years vs. 65–79 years: aOR: 4.4, 95% CI: 2.5–7.7) and the presence of chronic diseases (yes vs. no: aOR: 0.4, 95% CI: 0.3–0.6) showed significant associations of not having a GP. For men, the type of health insurance (private vs. statutory: aOR: 2.1, 95% CI: 1.5–3.0; other vs. statutory: aOR: 2.1, 95% CI: 1.4–3.1) and for women, SES (low vs. medium: aOR: 1.8, 95% CI: 1.2–2.7; high vs. medium: aOR: 2.1, 95% CI: 1.4–3.0) increased the risk of having no GP.

Conclusions: Our analysis offers new insights into the use of GPs in Germany and revealed differences between men and women. Public health strategies regarding access to a GP have to focus on men and on women with a low SES. Further analyses are needed to determine whether men with private health insurance prefer to consult a specialist rather than a GP. For young adults, improving the transition process from a pediatrician to a GP could fill a gap in health care.

Keywords: General practice utilization, GP, Healthcare, DEGS, Medical care, Family doctor, Public health

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Background

The frequency and predictors of the use of general practice services have rarely been addressed in German research. One of the most important components of the German health care system is characterized by the free choice of a healthcare provider (§ 76 Code of Social Law Volume V) for each of the 82.4 million citizens [1]. It is intended that the GP is the first point of contact for any health problem and acts as a guide at all steps of treatment [2]. GPs are best placed to assess what therapy is necessary or helpful for their patient. Better health outcomes through GP-centered healthcare, especially among older or chronically ill patients, have already been reported [3, 4]. The role of general practitioners (GPs) in Germany is therefore of major importance in the health care system. Although it is advocated that every German citizen should have a GP in case of any possible health problem, research has been limited to the frequency of use of GPs. However, it is important to start research earlier to find out what drives or discourages people from contacting a GP. Thus, knowledge of the effect of various sociodemographic and health characteristics completes the overall picture that is necessary to develop more effective health measures in order to raise awareness of the importance of a GP.

Every employed citizen in Germany is obliged to be insured by a statutory health insurance up to an income of 4350 euros per month and family members who do not earn a living are insured free of charge. Citizens subject to social welfare programs are also covered by statutory health insurance [5]. In total, 87.7% of the German population is covered by statutory health insurance [5]. Citizens with a higher income as well as the self-employed and civil servants have the option of a private health insurance (11.5% of the population) [5]. According to the European Social Survey, a low socioeconomic status (SES) is associated with an increased use of general practice services [6]. In Danish studies, unemployment and a low educational level increased the use of GPs most [7, 8]. According to the "Quality and Costs of Primary Care in Europe" (QUALICOPC) study, financial factors were the main predictors of access to primary health care [9]. In contrast, Hessel et al. reported only a small influence of socioeconomic factors on the number of contacts with GPs among people aged 60 years and over in Germany [10]. Both, in a Danish cohort study (OR: 1.95; 95% CI: 1.85–2.06, aOR: 1.26; 95% CI: 1.09–1.47) [8, 11] and the "German National Health Interview and Examination Survey 1998" (GNHIES98) [8, 11], women were associated with a more frequent use of GPs. In addition, Danish studies showed a clear gender difference in the number of consultations (4.1 per year among women vs. 2.8 among men) [7]. The importance of the residential area remains contradictory: some studies show that people in urban areas use medical care more often than the rural population [11, 12] while others found that there is no impact of the residential area [7]. In a former analysis of a German study, it was also reported that unmarried or married people visited their GPs more often than divorced or widowed ones [7].

Pain medication, a poor individual health status and having one or more health problems were identified as important factors that increased the use of GP services in Australian studies [12]. Jørgensen et al. illustrated that hypertension (OR: 1.63; 95% CI: 1.59–1.67), mental illness (OR: 1.63; 95% CI: 1.61–1.66), diabetes (OR: 1.56; 95% CI: 1.47–1.65) and angina pectoris (OR: 1.28; 95% CI: 1.21–1.34) were associated with the use of GP services [7]. However, comparability of these studies is limited due to methodological differences in health care systems and other characteristics such as age and gender.

The aim of this study was to examine the relationship between a number of sociodemographic and health characteristics and having no GP in Germany.

Methods

This cross-sectional analysis was based on the public use file (PUF) of the "German Health Interview and Examination Survey for Adults" (DEGS) conducted by the Robert Koch Institute [13]. The Robert Koch Institute is a federal institution financed by the German Federal Ministry of Health and is responsible for the research of infectious diseases and, within the framework of health monitoring, for the analysis of national long-term public health trends [14]. The PUF contained interview and examination data from the first wave of the survey (DEGS1) which was conducted between November 2008 and November 2011 with more than 8000 adults. DEGS1 consisted of interviews, self-administered questionnaires, standardized tests and measurements to provide information on various self-reported health conditions, current medications as well as sociodemographic characteristics [15–17]. The target population included people aged 18 to 79 years who lived permanently in Germany. Based on a two-stage stratified cluster sampling procedure, 180 sample points were determined based on a list of nationwide municipalities. Within the sample points, individuals were randomly selected from local population registries two months before the planned study period [15]. Eligible individuals were invited to participate in the survey by letter sent about five weeks prior to the survey visit [15]. DEGS1 included new randomly collected participants (response rate 42%) and former participants (response rate 62%) of the cross-sectional GNHIES98 study, also conducted by the Robert Koch Institute from 1997 to 1999 [18]. The cross-sectional analyses with the PUF were limited to 7987 participants aged between 18 and 79 years. Further

details on the methodological procedures have already been published [15, 18].

The survey collected data on the utilization of different health care services, including information on the use of a GP. Whether or not participants have a GP was used as an outcome measure in the present analysis and was inquired by means of the following question: "Do you have a GP who is usually your first point of contact in case of any health impairment?". If the question was affirmed, it was assumed that the participants had a GP. On the other hand, if the response was negative, it was concluded that these participants did not have a GP.

Potential factors associated with having no GP included in the analysis were age, which was categorized into four different groups: 18–29 years, 30–44 years, 45–64 years and 65–79 years. Four categories were distinguished regarding the residential area depending on the number of inhabitants within a community: rural area (< 5000 inhabitants), small town (5000 - < 20,000 inhabitants), medium-sized town (20,000 - < 100,000 inhabitants) and big city (100,000+ inhabitants). SES was based on a multidimensional index that included information on education, occupation and net household income of the participants. Each of the three dimensions was evaluated on a point scale from 1 to 7, resulting in a range of values from 3 to 21 for the combined index. Based on the distribution of the multidimensional index, it was divided into five equally sized groups (quintiles), which were used to classify low (1st quintile), medium (2nd to 4th quintiles) and high (5th quintile). Further details, such as the classification of the three dimensions, have already been published under [19]. The variable representing marital status was summarized into married (living together or apart), single and divorced/widowed. The availability of information on the usual number of working hours per week was limited to currently employed participants that were younger than 65 years. It was used to generate a variable (long working hours) with a cut-point at 50 h per week. The general state of health was dichotomized into the categories very good/good and average/poor/very poor. The data on the presence of chronic diseases (yes/no) was based on self-reported information for each participant. Health insurance was categorized into statutory health insurance, private health insurance and other (including no insurance, direct payer, foreign health insurance or any other kind of reimbursement).

Statistical analyses included absolute frequencies, percentages and 95% confidence intervals (CI). Differences between adults with and without a GP were examined using Chi-square tests for all categorical variables and a p-value < 0.05 was considered significant. Multiple logistic regression analyses with "having no GP" as dependent variable were performed for the total study population, and separately by gender. Adjustments for age, residential area, SES, marital status, long working hours per week, general state of health, chronic diseases and health insurance were added and adjusted odds ratios (aOR) with 95%-CI were determined. For all covariates, the amount of missing responses did not exceed 5%, so missing responses were allocated to the reference category in the regression analysis. All analyses were weighted according to the standardized weighting factor based on age, gender, federal region of residence, level of education, community class and nationality provided by the Robert Koch Institute in order to correct for any deviations of the DEGS1 study population from the German general population (reference date: 31th December 2010) [18]. For former participants of the GNHIES98, the re-participation rate was also considered within the weighting procedure. IBM SPSS Statistics (version 24) with the complex sample module was used [20].

Results

The total number of participants was 7987. Of those, 232 participants were excluded from the analysis due to missing responses regarding the information on having a GP. Hence, the study population included 7755 participants of which 614 (9.5%) indicated that they did not have a GP (Table 1).

Characteristics of the study population are summarized in Table 1: Having no GP was more prevalent among men (11.4%) than among women (7.6%). Regarding the effect of age, participants aged 18–29 years showed the highest rate to have no GP (17.9%). Participants from urban areas reported more frequently that they had no GP (14.6%) than participants living in rural areas (5.5%). For single participants (15.9%), for people with a low (10.1%) or high (13.8%) SES, and for participants who worked long (13.7%), it was more likely to have no GP. Participants with an average, poor or very poor general state of health as well as participants with chronic diseases stated more often to have a GP. In addition, people with a private (19.6%) or any other type of health insurance (16.0%) were more likely to be without a GP than people with a statutory health insurance (8.3%).

Gender, age, residential area, SES, the presence of chronic diseases and the type of health insurance showed significant associations with the odds of having no GP in multiple logistic regression analysis (Table 2). Not having a GP was more likely in young adults than in men and women in the oldest age group. Adults living in big cities had odds of not having a GP nearly three times higher (men: aOR: 2.7, 95% CI: 1.8–4.2; women: aOR: 3.0, 95% CI: 1.9–4.8) than men and women living in rural areas (Table 2). The presence of chronic diseases for men and women reduced the odds of having no GP (men: aOR: 0.4, 95% CI: 0.3–0.7; women: aOR: 0.5, 95% CI: 0.3–0.8) in comparison to adults without any chronic disease (Table 2).

Table 1 Characteristics of the study population by having no General Practitioner (DEGS1)

	Study population n (%[a])	%[a] with no GP (95% CI)	*p* value[b]
Total	7755 (100)	9.5 (8.4–10.7)	
Gender			< 0.001
Male	3682 (49.7)	11.4 (10.0–13.0)	
Female	4073 (50.3)	7.6 (6.4–9.0)	
Age groups (years)			< 0.001
18–29	1063 (19.1)	17.9 (14.8–21.4)	
30–44	1693 (25.4)	11.8 (9.9–14.1)	
45–64	3051 (36.5)	6.6 (5.5–8.0)	
65–79	1948 (19.0)	3.3 (2.4–4.6)	
Residential area (inhabitants)			< 0.001
Big-city (100,000+)	2179 (31.0)	14.6 (12.3–17.3)	
Medium-sized town (20,000- < 100,000)	2244 (29.5)	8.0 (6.6–9.7)	
Small-town (5000 - < 20,000)	1904 (23.3)	7.3 (5.7–9.2)	
Rural (< 5000)	1428 (16.2)	5.5 (4.2–7.1)	
Marital status			< 0.001
Single	1670 (26.5)	15.9 (13.5–18.6)	
Divorced/widowed	957 (11.2)	6.2 (4.4–8.6)	
Married	5051 (62.3)	7.4 (6.3–8.6)	
Socioeconomic status			< 0.001
Low	1167 (18.9)	10.1 (7.9–12.7)	
Medium	4654 (60.6)	7.9 (6.7–9.2)	
High	1903 (20.4)	13.8 (11.4–16.5)	
Long working hours (≥50 h/week)			< 0.001
Long working hours	592 (8.3)	13.7 (10.8–17.3)	
Non-working/65+ years	3196 (36.9)	6.9 (5.7–8.4)	
No long working hours	3839 (54.9)	10.6 (9.1–12.3)	
General state of health			< 0.001
Very good/good	5723 (75.2)	10.9 (9.6–12.4)	
Average/poor/very poor	2005 (24.8)	5.1 (3.8–6.7)	
Chronic diseases			< 0.001
Any chronic disease	2504 (30.4)	3.7 (2.8–5.0)	
No chronic disease	4875 (69.6)	11.9 (10.4–13.6)	
Health insurance			< 0.001
Private	527 (6.7)	19.6 (15.5–24.5)	
Others[c]	468 (5.4)	16.0 (11.9–21.2)	
Statutory	6749 (87.9)	8.3 (7.2–9.6)	

[a] Weighted results to match the German population structure on 31th December 2010
[b] *P* values: Comparison between adults having a GP and having no GP
[c] "Others" include no insurance at all, direct payer, a foreign health insurance or any other kind of reimbursement
Unweighted n may not add up to total n due to missing responses

Logistic regression analyses stratified by gender showed that, for both men and women, age, residential area and the presence of chronic diseases were associated with not having a GP. Differences between men and women were found in the type of health insurance and SES. For men, the type of health insurance was associated with having no GP (Table 2): Male participants with private (aOR: 2.3, 95% CI: 1.6–3.4) or any other health insurance (aOR: 2.4, 95% CI: 1.5–3.8) were more than twice as likely at risk as men with statutory health insurance. By contrast for

Table 2 Predictors of having no General Practitioner: Adjusted odds ratios (aOR) with 95% confidence intervals (DEGS1)

	Total	Male	Female
	aOR[a] (95% CI)	aOR[b] (95% CI)	aOR[c] (95% CI)
Gender			
Male	1.4 (1.2–1.8)	–	–
Female	ref.	–	–
Age group (years)			
18–29	4.4 (2.5–7.7)	3.4 (1.5–7.6)	5.8 (2.8–12.1)
30–44	3.0 (1.8–4.9)	2.6 (1.3–5.4)	3.2 (1.7–6.1)
45–64	1.9 (1.2–2.9)	1.8 (0.9–3.5)	1.9 (1.0–3.3)
65–79	ref.	ref.	ref.
Residential area (inhabitants)			
Big-city (100,000+)	2.9 (2.1–3.9)	2.7 (1.8–4.2)	3.0 (1.9–4.8)
Medium-sized (20,000- < 100,000)	1.4 (1.0–2.0)	1.2 (0.7–2.0)	1.7 (1.1–2.7)
Small-town (5000 - < 20,000)	1.4 (1.0–2.0)	1.3 (0.8–2.1)	1.4 (0.8–2.5)
Rural (< 5000)	ref.	ref.	ref.
Marital status			
Single	1.2 (0.9–1.7)	1.4 (0.9–2.3)	1.0 (0.6–1.6)
Divorced/widowed	1.1 (0.7–1.6)	1.4 (0.8–2.6)	0.8 (0.5–1.4)
Married	ref.	ref.	ref.
Socioeconomic status			
Low	1.5 (1.1–2.0)	1.3 (0.9–1.9)	1.8 (1.2–2.7)
Medium	ref.	ref.	ref.
High	1.4 (1.1–1.9)	1.1 (0.8–1.6)	2.1 (1.4–3.0)
Long working hours (≥50 h/week)			
Long working hours	1.2 (0.9–1.6)	1.1 (0.8–1.6)	1.5 (0.7–3.3)
Non-working/65+ years	1.1 (0.9–1.5)	1.1 (0.7–1.7)	1.2 (0.8–1.8)
No long working hours	ref.	ref.	ref.
General state of health			
Very good/good	1.2 (0.8–1.7)	1.4 (0.8–2.4)	1.0 (0.6–1.8)
Average/poor/very poor	ref.	ref.	ref.
Chronic disease			
Any chronic disease	0.4 (0.3–0.6)	0.4 (0.3–0.7)	0.5 (0.3–0.8)
No chronic disease	ref.	ref.	ref.
Health insurance			
Private	2.1 (1.5–3.0)	2.3 (1.6–3.4)	1.7 (0.9–3.2)
Others [d]	2.1 (1.4–3.1)	2.4 (1.5–3.8)	1.6 (0.9–2.9)
Statutory	ref.	ref.	ref.

[a] Adjusted odds ratios estimated from logistic regression for the total study population. Nagelkerke's $R^2 = 0.14$, 91% correctly classified
[b] Adjusted odds ratios estimated from logistic regression restricted to male participants. Nagelkerke's $R^2 = 0.13$, 89% correctly classified
[c] Adjusted odds ratios estimated from logistic regression restricted to female participants. Nagelkerke's $R^2 = 0.14$, 92% correctly classified
[d] "Others" include no insurance at all, direct payer, a foreign health insurance or any other kind of reimbursement

women, SES showed a significant effect on the odds of having no GP (Table 2). In particular, female adults with low (aOR: 1.8, 95% CI: 1.2–2.7) or high SES (aOR: 2.1, 95% CI: 1.4–3.0) had higher odds of having no GP than female adults with medium SES. Additional analyses restricted to participants with valid data on all independent variables in regression (complete cases) showed similar results to the main analysis (see Additional file 1: Table S1).

Discussion

Using data of 7755 adults aged between 18 and 79 years in Germany, the overall prevalence of having no GP was

estimated to be 9.5% (men: 11.4%, women: 7.6%). Multiple logistic regression analyses showed that the odds of having no GP significantly decreased with age and the presence of chronic diseases. Odds were higher for adults living in urban areas. For males, the type of health insurance showed a significant association with having no GP: Men with a private or other type of health insurance more often had no GP than men with statutory insurance. By contrast for women, SES was significantly related with having no GP: Females with a high or low SES stated more frequently not to have a GP than females with a medium SES.

The comparison of our results with the existing literature is difficult, since in most studies the frequency of use of GP services instead of having a GP was the main focus of research. Yet, our finding that older and chronically ill participants were more likely to have a GP indicates that those are more often in need of a GP than young and healthier adults, as described in previous literature [7, 12]. Young participants suffer less often from health problems and chronic diseases and are usually not in need to have a GP or another specialized physician [21]. Moreover, older adults may be more familiar with the German health care system and they are used to have a GP as regular point of contact in case of any medical problem. They may also be more often in need to have a GP for e.g. regular health checks due to chronic diseases. On the other hand, participants in early adulthood may not have a GP as result of an insufficient transition process from a pediatrician to a GP. Gender differences in the presence of having a GP were in line with earlier findings and may be explained by a higher health awareness among women [22, 23]. In contrast to findings of the "German Health Update" (GEDA2012), this gender difference cannot be explained by a higher use rate of gynecologists among younger women [23]. Participants living in rural areas stated more frequently to have a GP than participants living in urban areas. One possible explanation might be that medical specialists are rare in rural areas in Germany and people therefore have no choice but to visit a GP [24–26]. On the other hand, people living in big cities may prefer to visit a specialist instead of a GP. A medically unjustified preference of patients to visit specialists instead of GPs would be problematic, as it could lead to misallocations. Such a preference would also lead to longer waiting times at specialists. In addition, this trend could mask a shortage of GPs and hamper the adaptation of medical care to the needs of the population. Further research into the reasons for the lower rate of having a GP in urban areas is needed to determine whether there is a real preference for specialists or whether the use of health care services is generally lower. Another explanation might be the higher work-related fluctuation of city dwellers, which may result in a frequent change of the GP. Although one would expect participants working 50 h or more per week to have less time to get in contact with a GP during regular consultation hours, an effect of the variable was observed in the bivariate analysis. That result may also be related to the often lower health awareness and poorer mental health of this population group, according to present literature [27, 28], and needs further research. Participants aged 65+ or those not in employment were more likely to have a GP, which may be due to a higher age of these participants. Many of them are already retired and may suffer from chronic or age-related diseases. In the present analysis these aspects have been found to be associated with a lower risk of having no GP. In contrast to results reported in most of the literature, not only participants with a low SES but also those with a high SES showed higher odds of having no GP [6–9]. Participants with a medium SES which accounts for about 60% of the DEGS1 study population were most likely to have a GP. Knowledge not only on diseases and symptoms but also on the German health care system may vary in SES groups. Participants of high SES, on the one hand, may prefer to consult medical specialists and thereby avoiding the primary care sector more often than those of medium SES. For adults with a low SES, on the other hand, the obligation to pay a "practice fee" of ten euros could have prevented them from contacting any physician. In Germany, the "practice fee" (in force from 2004 to 2012) was an additional fee payable once a quarter by every adult with a statutory health insurance when visiting a physician and was still in existence at the time of data collection. People with low SES may often not have been in contact with a physician for financial reasons. Especially the fact that SES appears to be a more important factor among female participants indicates the need for further research. A new aspect revealed by the analyses is that every fifth privately insured adult has no GP compared to every twelfth person with statutory health insurance. This difference was more pronounced among men. In Germany, a letter of referral from a GP is not mandatory, so people are free to arrange an appointment with a specialist themselves. Further, waiting times for an appointment with a specialist are significantly shorter for privately insured patients than for statutorily insured patients [29]. Accordingly, in a previous analysis of DEGS1 [21], privately insured adults consulted specialists (especially gynecologists, dermatologists, dentists) more frequently than GPs.

When considering our results, it should be noted that about 90% of the German population do have a GP. But the number of patients going to emergency rooms is growing steadily in Germany [30]. According to the recently published PiNo study, people visiting emergency departments are younger (42 years old on average), rather male (53%) and single (46%) [30]. Our results suggest that these people may be less likely to have a GP. In addition, more than half of the 1175 patients who visited emergency

departments in the PiNo study rated their subjectively perceived treatment urgency as low, and about 35% of them had medical complaints for three days or longer [30]. Instead of going to an emergency department, these patients in particular could have consulted a GP. Hence it is possible that a misallocation of patients is not only due to the fact that the use of specialists is preferred, but also that more emergency departments are used instead of a GP. Further research is therefore necessary to determine whether adults without a GP have a higher number of contacts to emergency departments.

Study limitations

DEGS1 provides a representative sample of the German population aged 18 to 79 years and for the first time, it enables an analysis of prevalence and predictors of not having a GP. Weighted results improve nationally valid conclusions. Still, it is possible that the results are biased, as all the information on the different characteristics is based on self-reported data. As in many other population-based surveys, chronically ill people may be underrepresented due to a potentially lower participation rate of sick people [17]. In addition, the presence of a GP does not mean that a participant actually uses the services of a GP. It only means that they know a doctor to whom they can turn first in the event of a medical problem. GPs as gatekeepers are extremely important in view of the highly relevant problem of over- and underdiagnoses in healthcare. We cannot rule out that participants who have recently moved had difficulties in answering the question of interest. It is possible that these participants used to have a GP in their previous residential area, but not in the new one. Thus, prevalence rates by residential areas may be distorted. Further research is necessary which also takes into account how long participants have been living in their area. Although it is likely that the participants' migration background may have an impact on having no GP, it could not be assessed in this study due to lack of data in the PUF. Research that took the migration background of participants into account was for example considered in [31].

Conclusions

Using a nationally representative sample, DEGS1 offers valuable results and new insights into the prevalence and the effect of different sociodemographic and health characteristics on the presence of having no GP in Germany. Almost every tenth person in Germany has no GP with differences between men and women. Public health strategies especially have to focus in particular on men, and women with a low SES. For men with private health insurance and women with high SES, further analyses are needed to determine whether they prefer to visit a specialist rather than a GP. Improving the transition process from a pediatrician to a GP could fill a gap in health care for young adults.

Additional file

Additional file 1: Table S1. Predictors of having no General Practitioner: Adjusted odds ratios (aOR) with 95% confidence intervals (DEGS1) based on complete data (*n*=7.176). (DOCX 24 kb)

Abbreviations

aOR: Adjusted odds ratio; CI: Confidence interval; DEGS1: German Health Interview and Examination Survey for Adults (first wave); GNHIES98: German National Health Interview and Examination Survey 1998; GP: General practitioner; OR: Odds ratio; PUF: Public Use File; SES: Socioeconomic status

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Authors' contributions

MP and JT mainly devised the basic idea and wrote the manuscript. MP performed the statistical analyses with contributions by JT and EM. JT performed background research on the topic. Methods and results were written by both first authors. KW acted as an advisor with medical and practical knowledge and experience. MK enriched the study with her medical knowledge. EM advised in all important steps. KW, MK and EM revised the manuscript critically. All authors read and approved the final manuscript.

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Availability of data and materials

The dataset analyzed during the present study is available from the Robert Koch Institute for researchers who meet the criteria for access [13, 32].

Ethics approval and consent to participate

Not applicable as the analysis is based on secondary data. However, DEGS1 was approved by the Charité-Universitätsmedizin Berlin ethics committee and participants provided written informed consent prior to the interview and examination [15–17].

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

Appendix D

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Tree-based modeling of time-varying coefficients in discrete time-to-event models

Marie-Therese Puth · Gerhard Tutz · Nils Heim · Eva Münster · Matthias Schmid · Moritz Berger

Abstract Hazard models are popular tools for the modeling of discrete time-to-event data. In particular two approaches for modeling time dependent effects are in common use. The more traditional one assumes a linear predictor with effects of explanatory variables being constant over time. The more flexible approach uses the class of semiparametric models that allow the effects of the explanatory variables to vary smoothly over time. The approach considered here is in between these modeling strategies. It assumes that the effects of the explanatory variables are piecewise constant. It allows, in particular, to evaluate at which time points the effect strength changes and is able to approximate quite complex variations of the change of effects in a simple way. A tree-based method is proposed for modeling the piecewise constant time-varying coefficients, which is embedded into the framework of varying-coefficient models. One important feature of the approach is that it automatically selects the relevant explanatory variables and no separate variable selection procedure is needed. The properties of the method are investigated in several simulation studies and its usefulness is demonstrated by considering two real-world applications.

Keywords Discrete time-to-event data · Time-varying coefficients · Recursive partitioning · Semiparametric regression · Survival analysis

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1 Introduction

Time-to-event models, also referred to as survival models, are a popular tool to analyze data where the outcome variable describes the time to the occurrence of a specific event of interest. In clinical research, for example, one often examines the time to death, the progression of a specific disease, the onset of an infection or the length of stay in hospital (Klein et al., 2016). Further examples from the field of social sciences are the time to re-employment and family developments, like the time to pregnancy or relationship durations (Van den Berg, 2001).

The objective of statistical analyses typically is the modeling of the hazard function $\xi(t) = \lim_{\Delta t \to 0} \{P(t < T \leq t + \Delta t | T > t, \boldsymbol{x})/\Delta t\}$, where T denotes the event time, and to relate ξ to a set of explanatory variables $\boldsymbol{x}^\top = (x_1, \ldots, x_p)$. Traditional methods, like the Cox proportional hazards model (Cox, 1972), usually assume that the event times T are measured on a *continuous scale*. This case has been studied extensively in the literature, see, for example, Kalbfleisch and Prentice (2002) and Klein and Möschberger (2003). Yet, in practice, measurements of time are often intrinsically discrete or the exact (continuous) event times are not recorded, but it is only known that the event occurred between pairs of consecutive points in time, i.e. within pre-specified follow-up visits. Thus, time is measured on a discrete scale $t = 1, 2, \ldots, k$. In the latter case, the event times t refer to mutually exclusive time intervals $[0, a_1), [a_1, a_2), \ldots, [a_{k-1}, \infty)$, with fixed boundaries $a_1, \ldots, a_{k-1}$. A comprehensive treatment of the statistical methodology for discrete time-to-event data has recently been given by Tutz and Schmid (2016) and Berger and Schmid (2018). Generally, a great advantage of discrete time-to-event models is that they can be viewed as regression models with binary outcome variable. This allows to use established tools and standard software packages that have been developed for the analysis of binary outcome data, e.g. logistic regression or probit regression (Willett and Singer, 1993).

In parametric discrete time-to-event models one usually uses simple linear combinations of the explanatory variables, that is, one assumes that the effects of the explanatory variables on the outcome are linear. Moreover, it is often assumed that the effects of the explanatory variables on the outcome are constant over the entire observation time. In many applications, however, this assumption is too restrictive and may produce artefacts, see, for example, Tutz and Binder (2004). An important example constitutes the case where the explanatory variables describe an initial condition like the type of treatment at the beginning of a study. Then, the effect on the hazard at earlier times is expected to be stronger than at later times during the study.

This phenomenon can be addressed by semiparametric regression models that incorporate interactions between the explanatory variables and time. In this class of models one allows the effects of the explanatory variables to vary smoothly over time. A common way to specify smooth functions in t is to use splines, which are represented by a weighted sum of basis functions. In the continuous-time case, smooth time-varying effects, inter alia, have been considered by Sargent (1997), Cai and Sun (2003), Tian et al. (2005), Lambert and Eilers (2005), Groll and Tutz (2017) and Ruhe (2018). In discrete time, the modeling of smooth time-varying has been considered by Fahrmeir and Wagenpfeil (1996), Tutz and Binder (2004) and Groll and Tutz (2017), and, for example, employed by Adebayo and Fahrmeir (2005), Kandala and Ghilagaber (2006) and Djeundje and Crook (2018) in specific applications.

Smoothly time-varying effects are a quite flexible tool but are typically unable to model adequately the effects of explanatory variables that can be constant over a wide range of time though not being constant over the whole range. In particu-

lar, if one is interested in the time points where the strength of effects changes, it is more appropriate to model the variation of effects over time by using *piecewise constant* functions. One should also keep in mind that in discrete survival time points refer to intervals. Thus, smooth variation of effects on the underlying continuous time scale may show jumps of the effect strength on the discrete scale. In our approach the ranges where the effects are constant are identified by the use of *recursive partitioning techniques* or *tree-based modeling*. A tree-based approach for modeling time-varying coefficients in continuous time has been proposed by Xu and Adak (2002). To the best of our knowledge for discrete-time models, no tree-based modeling strategy exists so far.

We propose a tree-based approach for modeling piecewise constant time-varying effects in discrete time-to-event models. Specifically, our method is based on the tree-structured varying coefficients (TSVC) approach that was recently proposed by Berger et al. (2018b). Here we use this approach to allow the effects to be modified by the time t, the so-called *effect modifier*, making use of the fact that regression models incorporating time-varying effects may be seen as varying-coefficient models (Hastie and Tibshirani, 1993). By iterative splitting in one of the explanatory variables the method yields a tree for each variable that shows time-varying coefficients. For each explanatory variable the proposed algorithm determines whether the effect varies across t, is constant over the whole range of t, or if the variable has no effect on the outcome and should therefore be excluded from the model.

The remainder of the article is organized as follows: In Section 2 we give the notation and definitions focusing on right censored data. Details on modeling smooth time-varying coefficients and the proposed tree-structured time-varying coefficient model are introduced in Section 3. Section 4 presents the results of several simulation studies. In these studies we investigated the properties of the TSVC model and compared it to a simple model without time-varying coefficients and a model with smooth time-varying coefficients. In Section 5 we consider two real-world applications dealing with data collected by the Department of Oral and Cranio-Maxillo and Facial Plastic Surgery at the University Hospital Bonn and data from the German Family Panel (pairfam; Brüderl et al. 2018). Section 6 summarizes the main findings of the article.

2 Notation and Methodology

Let in the following T_i denote the event time and C_i the censoring time of an individual i, $i = 1, \ldots, n$, with n individuals given. The times T_i and C_i are assumed to be independent random variables taking discrete values in $\{1, \ldots, k\}$. For right censored data, the time period during which an individual is under observation is denoted by $\tilde{T}_i = \min(T_i, C_i)$, i.e., $\tilde{T}_i$ corresponds to the true event time if $T_i \leq C_i$ and to the censoring time otherwise. The random variable $\Delta_i := I(T_i \leq C_i)$ indicates whether $\tilde{T}_i$ is right-censored ($\Delta_i = 0$) or not ($\Delta_i = 1$). If originally continuous data have been grouped, the discrete event times $1, \ldots, k$ refer to time intervals $[0, a_1), [a_1, a_2), \ldots, [a_{k-1}, \infty)$, where $T_i = t$ means that the event occurred in time interval $[a_{t-1}, a_t)$.

The main tool to describe the stochastic behavior of the discrete random variable T_i is the *hazard function*. For given values of p time-constant explanatory variables $\boldsymbol{x}_i = (x_{i1}, \ldots, x_{ip})^\top$, the discrete hazard function is defined by

$$\lambda(t|\boldsymbol{x}_i) = P(T_i = t | T_i \geq t, \boldsymbol{x}_i), \quad t = 1, \ldots, k\,, \tag{1}$$

which is the conditional probability of an event at time t given that the individual reaches time t. An alternative way to describe the stochastic behavior is to consider

the *survival function* given by

$$S(t|\boldsymbol{x}_i) = P(T_i > t|\boldsymbol{x}_i) = \prod_{s=1}^{t}(1 - \lambda(s|\boldsymbol{x}_i))\,, \tag{2}$$

denoting the probability that an event occurs later than at time t. For further details on the basic concept of discrete time-to-event data, see Tutz and Schmid (2016), Chapter 1. In the following we consider parametric as well as semiparametric regression models for the discrete hazard $\lambda(t|\boldsymbol{x}_i)$.

A class of regression models that relates the discrete hazard function (1) to the explanatory variables $\boldsymbol{x}_i$ is defined by

$$\lambda(t|\boldsymbol{x}_i) = h(\eta(t, \boldsymbol{x}_i)), \quad t = 1, \ldots, k-1\,, \tag{3}$$

where $h(\cdot)$ is a strictly monotone increasing distribution function. Usually it is assumed that the predictor function has the form

$$\eta(t, \boldsymbol{x}_i) = \gamma_{0t} + \boldsymbol{x}_i^\top \boldsymbol{\gamma}\,, \tag{4}$$

which is composed of time-varying intercepts $\gamma_{01}, \ldots, \gamma_{0,k-1}$, referred to as *baseline coefficients*, and a linear function of the explanatory variables with coefficients $\boldsymbol{\gamma} \in \mathbb{R}^p$ that do not depend on t. Using the logistic distribution function for $h(\cdot)$ yields the widely applied *logistic discrete hazard model*, specified by

$$\lambda(t|\boldsymbol{x}_i) = \frac{\exp(\eta(t, \boldsymbol{x}_i))}{1 + \exp(\eta(t, \boldsymbol{x}_i))}\,, \tag{5}$$

which is also known as *proportional continuation ratio model*. The continuation ratio compares the probability of an event at time t to the probability later than t, see, for example, Agresti (2013). As it is the most common model and as the results presented in this paper can easily be extended to other link functions $h(\cdot)$ we reduce our considerations to the logistic model throughout the rest of this article.

By definition, the discrete hazard model (3) has the form of a regression model for binary response data. Therefore, standard estimation techniques for binary regression can be used for deriving estimates of the model parameters. With data $(\tilde{T}_i, \Delta_i, \boldsymbol{x}_i)$, $i = 1, \ldots, n$, the log-likelihood of model (5) is given by

$$\ell = \sum_{i=1}^{n}\sum_{t=1}^{\tilde{T}_i} y_{it}\log(\lambda(t|\boldsymbol{x}_i)) + (1 - y_{it})\log(1 - \lambda(t|\boldsymbol{x}_i))\,, \tag{6}$$

with binary outcome values

$$(y_{i1}, \ldots, y_{i\tilde{T}_i}) = \begin{cases} (0, \ldots, 0, 1), & \text{if } \Delta_i = 1\,, \\ (0, \ldots, 0, 0), & \text{if } \Delta_i = 0\,, \end{cases} \tag{7}$$

see, for example, Berger and Schmid (2018). To construct the log-likelihood (6) and to fit the model with software for binary outcomes, the original data has to be converted into an *augmented data matrix* comprising the binary outcome values (7) beforehand. This results in an augmented design matrix with $\tilde{T}_i$ rows for each individual. The whole data matrix, which is obtained by concatenating the individual augmented matrices together, has $\tilde{n} = \sum_{i=1}^{n}\tilde{T}_i$ rows. For further details on data preparation and the estimation procedure for discrete hazard models, see Tutz and Schmid (2016) and Berger and Schmid (2018).

3 Modeling Time-Varying Coefficients

In common models with predictor (4) it is supposed that the coefficients $\boldsymbol{\gamma}$ do not depend on t. That is, one assumes that the effects of the explanatory variables are constant over the entire observation time. This assumption is typically too restrictive, as, for example, the effect of an explanatory variable on the hazard might be stronger at the beginning of the study than at later times.

3.1 Smooth and Piecewise Constant Time-Varying Coefficients

A general approach that allows the effects to vary over time is a model with predictor

$$\eta(t, \boldsymbol{x}_i) = \gamma_{0t} + \boldsymbol{x}_i^T \boldsymbol{\gamma}(t)\,. \tag{8}$$

The predictor of model (8) contains the vector-valued function $\boldsymbol{\gamma}(t) = (\gamma_1(t), \ldots, \gamma_p(t))$. Each component $\gamma_j(t)$ represents the coefficients of the j-th explanatory variable depending on the time t. The modeling of discrete event times including smooth time-varying coefficients was, for example, considered by Fahrmeir and Wagenpfeil (1996) and Tutz and Binder (2004). A conventional way to specify such a smooth function in t is to use splines, represented by a weighted sum of M basis functions (e.g. Wood, 2017). Then each component $\gamma_j(t)$ has the form

$$\gamma_j(t) = \sum_{m=1}^{M} \phi_m(t)\beta_{jm}\,, \tag{9}$$

where $\phi_1(t), \ldots, \phi_M(t)$ are M fixed basis functions and $\beta_{j1}, \ldots, \beta_{jM}$ are the corresponding parameters to be estimated. Since the explanatory variables all refer to the same period of time (i.e. are measured on the same time scale), the basis functions $\phi_m(t)$ are the same for all variables. With this assumption, the expansion in basis functions yields a model with predictor

$$\eta(t, \boldsymbol{x}_i) = \gamma_{0t} + \sum_{j=1}^{p} \sum_{m=1}^{M} x_{ij}\phi_m(t)\beta_{jm}\,, \tag{10}$$

which constitutes a linear predictor in the parameters $\gamma_{01}, \ldots, \gamma_{0,k-1}, \beta_{11}, \ldots, \beta_{pM}$. A popular class of basis functions are B-splines, which are defined as polynomials of fixed degree d differing from zero in $d+1$ adjacent intervals, see De Boor (1978). In practice one typically uses *P-splines* (Eilers and Marx, 1996), i.e., a relatively large number of B-spline basis functions and an additional penalty term that penalizes differences of adjacent coefficients. Fitting of the model can be done by maximization of the corresponding penalized log-likelihood

$$\ell_p = \ell - \epsilon J\,, \tag{11}$$

where J is the penalty term preventing estimates becoming to wiggly and $\epsilon \in \mathbb{R}^+$ is a penalty parameter that determines the degree of smoothness of the fitted functions $\gamma_j(t)$. For details on spline fitting, see Wood (2011, 2017).

When using P-splines, a smooth variation of the effect strength tends to miss the points where the effect strength changes strongly. Although abrupt changes seem implausible for continuous time data, for discrete time data that refer to intervals of continuous time abrupt changes are to be expected. Therefore, in the following it is assumed that the effects of an explanatory variable do not vary over the whole range of t, but are constant over a certain period of time (or within several

time intervals). That is, one assumes that the time-varying coefficients for the j-th variable are *piecewise constant* and have the form

$$\gamma_j(t) = \sum_{q=1}^{Q_j} \gamma_{jq} I(t \in T_{jq}) \,, \tag{12}$$

where $T_{j1}, \ldots, T_{jQ_j}$ are Q_j time intervals, $\gamma_{j1}, \ldots, \gamma_{jQ_j}$ are the corresponding coefficients, and $I(\cdot)$ denotes the indicator function with $I(a) = 1$ if a is true and $I(a) = 0$ otherwise. More specifically, the observation times are divided by the thresholds $1 = t_{j0} \leq t_{j1} \leq \ldots \leq t_{j,Q_j-1} \leq t_{jQ_j} = k$, and one obtains a partitioning into the time intervals $T_{j1} = \{t_{j0}, ..., t_{j1}\}, T_{jq} = \{t_{j,q-1} + 1, ..., t_{jq}\}, q = 2, ..., Q_j$. Accordingly, the coefficients γ_{jq} are constant over the adjacent time points collected in T_{jq}. The simplest case, a partition of the coefficients of x_j into two time intervals with regard to threshold t_{j1}, yields the function

$$\gamma_j(t) = \gamma_{j1} I(t \in \{1, ..., t_{j1}\}) + \gamma_{j2} I(t \in \{t_{j1} + 1, ..., k\}) \,, \tag{13}$$

where the parameter γ_{j1} denotes the effect of x_j in the first interval until time t_{j1} and γ_{j2} denotes the effect of x_j in the second interval between time $t_{j1} + 1$ and k.

For each explanatory variable, the partitioning into the time intervals T_{jq} can be determined by using recursive partitioning techniques. We propose to adapt the tree-based approach that was recently proposed by Berger et al. (2018b). By iterative splitting in one of the explanatory variables the method yields a tree for each variable that shows time-varying coefficients (see Section 3.2). Thereby, the algorithm itself identifies the coefficients (corresponding to an explanatory variable) that deviate from a constant, and the corresponding thresholds.

Importantly, the use of the tree-based approach by Berger et al. (2018b) (described in detail in Section 3.2 and 3.3) not only achieves the selection of varying and non-varying coefficients, but additionally enforces the selection of variables. More specifically, for each explanatory variable x_j the algorithm determines whether the effect varies across t (by a piecewise constant function), is constant over the whole range of t, or if the variable is influential at all.

3.2 Modeling Piecewise Constant Coefficients by Tree-Based Splits

Assume that we start with the discrete hazard model without time-varying coefficients (4). Then the first split in x_j of a common tree yields a model with predictor

$$\eta(t, \boldsymbol{x}_i) = \gamma_{0t} + x_{ij} \left[\gamma_{j1}^{[1]} I(t \leq t_{j1}^*) + \gamma_{j2}^{[1]} I(t > t_{j1}^*) \right] + \sum_{s \neq j} x_{is} \gamma_s \,. \tag{14}$$

This model just uses an alternative representation of the function in (13), but the two intervals regarding x_j are constructed by a split at split point t_{j1}^* with the two parameters $\gamma_{j1}^{[1]}$ (left interval) and $\gamma_{j2}^{[1]}$ (right interval). For given t_{j1}^*, estimates of the parameters in model (14) can still be obtained by maximizing the log-likelihood function (6), plugging in an augmented data matrix, where the column associated with the j-th explanatory variable is replaced by two new columns containing the values $x_{ij} I(t \leq t_{j1}^*)$ and $x_{ij} I(t > t_{j1}^*)$, see Appendix A.

If the effects of x_j are further modified, a second split (for example in the left interval) with regard to split point t_{j2}^* yields two new intervals

$$I(t \leq t_{j1}^*) I(t \leq t_{j2}^*) \quad \text{and} \quad I(t \leq t_{j1}^*) I(t > t_{j2}^*) \,,$$

and the model with predictor

$$\begin{aligned}\eta(t, \boldsymbol{x}_i) = &\gamma_{0t} + x_{ij}\Big[\gamma_{j1}^{[2]} I(t \leq t_{j1}^*) I(t \leq t_{j2}^*) + \gamma_{j2}^{[2]} I(t \leq t_{j1}^*) I(t > t_{j2}^*) \\ &+ \gamma_{j3}^{[2]} I(t > t_{j1}^*)\Big] + \sum_{s \neq j} x_{is}\gamma_s \,,\end{aligned} \tag{15}$$

where $\gamma_{j1}^{[2]}$, $\gamma_{j2}^{[2]}$, $\gamma_{j3}^{[2]}$ are the new effects in the intervals after the second split. Several splits in the coefficients of x_j, result in a sequence of $Q_j - 1$ selected split points $t_{j1}^*, \ldots, t_{j,Q_j-1}^*$ and coefficients $\gamma_{j1}^{[Q_j-1]}, \ldots, \gamma_{jQ_j}^{[Q_j-1]}$. Ordering the selected split points, such that $1 \leq t_{(j1)}^* < t_{(j2)}^* < \ldots < t_{(j,Q_j-1)}^* < k$, yields the partitioning into the Q_j time intervals

$$T_{j1} = \{1, ..., t_{(j1)}^*\},\, T_{j2} = \{t_{(j1)}^* + 1, ..., t_{(j2)}^*\},\, \ldots,\, T_{jQ_j} = \{t_{(j,Q_j-1)}^* + 1, ..., k\}\,,$$

with the corresponding coefficients $\gamma_{j1}^{[Q_j-1]}, \ldots, \gamma_{jQ_j}^{[Q_j-1]}$ representing the piecewise constant function $\gamma_j(t)$.

In general, the effects of all explanatory variables $x_1, \ldots, x_p$ in model (4) are allowed to vary over time. This results in several tree components $\gamma_j(t)$, i.e. piecewise constant functions, in the predictor $\eta(t, \boldsymbol{x}_i)$ of the model. When fitting the model, the first split is determined by selecting the best model among all the explanatory variables x_j and possible split points $t = 1, \ldots, k-1$ (see Section 3.3 for details on the selection procedure). The second split is either in the coefficients of the same or another explanatory variable. As in later steps the search is the same but for variables that have already been split, one starts from already built time intervals (corresponding to the current nodes of the tree) which are possibly further split in disjoint intervals. If an explanatory variable is never selected for splitting during iteration, it is assumed to simply have a constant effect γ_j on the hazard over time.

After termination of the algorithm (see Section 3.3 for details on stopping criteria), let $V \subseteq \{x_1, \ldots, x_p\}$ denote the subset of explanatory variables that have been selected for splitting and $L \subseteq \{x_1, \ldots, x_p\} \setminus V$ denote the subset of explanatory variables with a constant effect on the hazard (not selected for splitting). If no split is performed at all, V is an empty set and the result is the simple time-constant model with predictor (4). In the other extreme case, where all explanatory variables are selected for splitting at least once, L is an empty set. With this notation, the tree-structured discrete hazard model has the form

$$\eta(t, \boldsymbol{x}_i) = \gamma_{0t} + \sum_{x_j \in V} x_{ij}\gamma_j(t) + \sum_{x_\ell \in L} x_{i\ell}\gamma_\ell \,. \tag{16}$$

In the last step of the algorithm, again following the TSVC approach by Berger et al. (2018b), the time-constant effects γ_ℓ of variables that were not chosen for splitting during iteration are tested for inclusion in the model by using a stepwise elimination scheme. Accordingly the variables are removed from L or kept in the model. If none of the variables is influential at all, the predictor of the model reduces to the baseline coefficients γ_{0t} only.

3.3 Fitting Procedure

In each step of the TSVC algorithm, one selects the best split among all the explanatory variables and possible split points $t = 1, \ldots, k-1$. This is done by testing the equivalence of the two coefficients γ_{jq} and $\gamma_{j,q+1}$ that are associated with the new intervals after splitting. More specifically, one examines all the null hypotheses H_0: $\gamma_{jq} = \gamma_{j,q+1}$ against the alternatives H_1: $\gamma_{jq} \neq \gamma_{j,q+1}$ and chooses the

combination of x_j and t with the smallest p-value of the corresponding likelihood ratio (LR) test.

To decide whether the selected split should be performed, the distribution of the maximally selected LR test statistic, i.e. the maximum of the LR test statistics of the selected variable x_j with regard to t, is investigated. The corresponding p-value provides a measure of the dependence between the outcome values and t at a global level and already takes the number of observation times (i.e., the number of possible split points) into account. Therefore, one explicitly accounts for the involved multiple testing problem. To derive a decision on the null hypothesis we propose to use a permutation test. That means one permutes the values of t in the relevant part of the augmented data matrix, which breaks the relation of t and the outcome values in the selected time interval, and computes the corresponding value of the maximally selected LR test statistic (Berger et al., 2018b). For a large number of permutations, one obtains an approximation of the distribution under the null hypothesis and a corresponding p-value.

To summarize, the following steps are carried out during the fitting procedure:

1. *(Initial Model).* Fit the model without time-varying coefficients (4), yielding the estimates $\hat{\gamma}_{01}, \ldots, \hat{\gamma}_{0,k-1}$ and $\hat{\gamma}_1, \ldots, \hat{\gamma}_p$.
2. *(Tree Building).*
   (a) For all explanatory variables x_j, $j = 1, \ldots, p$, fit all the candidate models with one additional split in one of the already built time intervals.
   (b) Select the best model using the p-values of the LR test statistics.
   (c) Carry out the permutation test for the selected node (defined by a combination of x_j and t) with significance level α. If significant, fit the selected model and continue with Step 2(a), else continue with Step 3.
3. *(Time-Constant Effects).* For all explanatory variables $x_\ell \in L$, examine the null hypotheses $H_0 : \beta_\ell = 0$ by a stepwise backward elimination scheme. Iteratively, the variable with the largest p-value, obtained from LR permutation tests with significance level α, is excluded from L. Stop, if none of the p-values exceeds α anymore.
4. *(Selected Model).* Fit the final model with components $\hat{\gamma}_{0t}$, $\hat{\gamma}_j(t)$ and $\hat{\boldsymbol{\gamma}}_\ell$.

The resulting discrete hazard model is a specific version of a TSVC model as proposed by Berger et al. (2018b) with the time t (treated as an ordinal variable) being the only permitted effect modifier. The main tuning parameter of the algorithm is the error level α which is used as significance level of the permutation tests. As outlined in Berger et al. (2018b) the error level α constitutes an upper bound for the proportion of falsely identified variables with time-varying coefficients.

In R, the augmented data matrix for fitting discrete time-to-event models can be generated by using the function `dataLong()` of the add-on package **discSurv** (Welchowski and Schmid, 2018). The proposed TSVC model can be fitted by applying the function `TSVC()` of the eponymous add-on package (Berger, 2018) with the time t (the only considered effect modifier) specified in the two arguments `effmod` and `only_effmod`.

4 Simulation Study

We considered different simulation scenarios in order to evaluate the performance of the proposed TSVC model and to compare the model to alternative approaches. The different scenarios are described in detail in the following subsections: we assessed the performance in terms of a true model without time-varying effects (Section 4.1), a true model with smooth time-varying effects (Section 4.2) and a true model with piecewise constant time-varying effects (Section 4.3).

Particularly, we compared the fit of the TSVC model to the fit of a simple discrete hazard model given by Equation (4) that did not account for possible time-varying effects (referred to as *NVC model*). In R, simple discrete hazard models without time-varying coefficients were fitted by running `glm()` with family argument `binomial()`. Further, we considered a discrete hazard model allowing for smooth time-varying effects as defined in Equation (9) (referred to as *SVC model*), using a P-spline for each component $\gamma_j(t)$. In R, discrete hazard models with smooth time-varying coefficients can be fitted by applying the function `gam()` in the add-on package **mgcv** (Wood, 2018). The modeling of smooth time-varying coefficients was done by using the function `s()` with the explanatory variables specified in the `by`-argument. The number of basis functions M was set to the default value of **mgcv** with fixed degree $d = 2$. We used a first-order difference penalty J with the optimal smoothing parameter ϵ, see Equation (11), computed by generalized cross-validation (see Wood, 2017).

In all the scenarios we simulated data with constant baseline coefficients $\gamma_{0t} = -2$, $t = 1, \ldots, k-1$, two independent binary explanatory variables, $x_1, x_2 \sim B(1, 0.5)$ and two independent standard normally distributed explanatory variables, $x_3, x_4 \sim N(0, 1)$. The definitions of the respective coefficients of the explanatory variables $\gamma_1, \ldots, \gamma_4$ differed in each scenario, hence they are given in the following subsections.

Each scenario was based on 100 independent samples of size $n = 500$ each and the number of discrete time points was set to $k = 11$. During the estimation procedure, for each permutation test we used 1000 permutations with error level $\alpha = 0.05$ throughout all scenarios. Following a strategy already used in Schmid et al. (2017), the censoring times C_i were sampled independently of T by drawing from a discrete distribution with probability density function $P(C_i = t) = b^{(k+1)-t} / \sum_{j=1}^{k} b^j$, $t = 1, \ldots, k$. Three different censoring rates were considered: the value $b = 0.1$ resulted in low censoring ($\sim 30\%$), a value of $b = 1.0$ was used for a medium level of censoring ($\sim 50\%$), and for strong censoring ($\sim 70\%$) the value b was set to 1.5. This resulted in augmented data matrices with an average number of about $\tilde{n} = 3000$ (low censoring), $\tilde{n} = 2000$ (medium censoring) and $\tilde{n} = 1200$ (strong censoring) rows.

Using the same data-generating process, the performance of the three approaches was assessed by computing the predictive log-likelihood based on new samples with $n = 500$ observations each. Further, to evaluate the performance of the proposed TSVC model, we generated the true positive rate on the covariate level (TPR) and the false positive rate on the covariate level (FPR) that have been introduced in Berger et al. (2018b). The true positive rate describes the amount of all predefined explanatory variables with time-varying effects that have been correctly identified to have an effect that changes over time. Specifically, it is given by

$$TPR = \frac{1}{\#\{j : \vartheta_j = 1\}} \sum_{j:\vartheta_j = 1} I(j : \hat{\vartheta}_j = 1)\,,$$

where $\vartheta_j = 1$ if the explanatory variable x_j, $j = 1, \ldots, 4$, varies over time. In contrast, the false positive rate displays the amount of all prescribed explanatory variables with time constant effects that have falsely been determined to have an effect that varies in the course of time. It is given by

$$FPR = \frac{1}{\#\{j : \vartheta_j = 0\}} \sum_{j:\vartheta_j = 0} I(j : \hat{\vartheta}_j = 1)\,,$$

where $\vartheta_j = 0$ if the explanatory variable x_j, $j = 1, \ldots, 4$, has time-constant effects only.

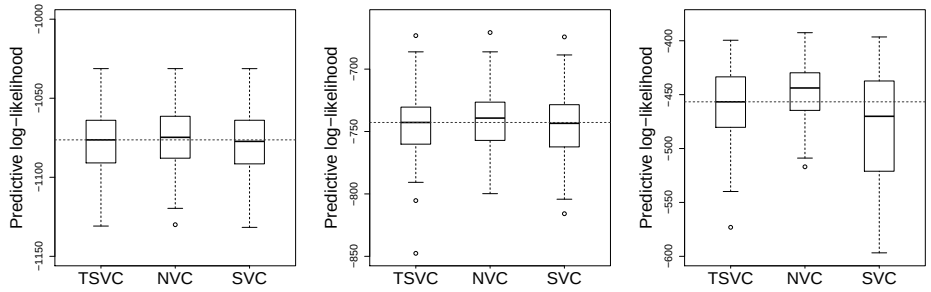

Fig. 1: Results of the simulation study (scenario 1). The figure shows boxplots of the predictive log-likelihood of the TSVC, NVC and SVC model for low (left), medium (center) and strong (right) censoring. The reference line represents the median log-likelihood value of the TSVC model, respectively.

4.1 Model without Time-Varying Effects

In the first scenario, the predictor was given by a linear function of the form

$$\eta(t, \boldsymbol{x}_i) = \gamma_{0t} + x_{i1}\gamma_1 + x_{i2}\gamma_2 + x_{i3}\gamma_3 + x_{i4}\gamma_4$$

with fixed coefficients $\gamma_1 = 0.4$, $\gamma_2 = -0.4$, $\gamma_3 = -0.2$ and $\gamma_4 = 0.2$. Hence, only samples with time-constant coefficients for all explanatory variables were generated. We used this scenario to examine whether the algorithm of the more complex TSVC model was able to identify the simple model with time-constant coefficients only. This was evaluated by the false positive rate which is anticipated to meet the error level α.

In our simulation study, the TSVC model (on average over the 100 replications) yielded false positive rates that approximately met the intended level of $\alpha = 0.05$ regardless of the censoring rate. In detail, the three different settings resulted in false positive rates of 0.050 (low), 0.058 (medium) and 0.073 (strong), respectively. For low censoring, in 82% of all replications none of the four explanatory variables had been selected for splitting during the fitting procedure. For medium and strong censoring, this rate slightly reduced to 79% and 74%, respectively.

Comparing the performance of the three competing approaches with respect to the predictive log-likelihood (see Figure 1), the log-likelihood values of the TSVC model were comparable to the ones of the true model (NVC model) with linear predictor (which was expected to perform best). Further, the TSVC model exhibited higher log-likelihood values than the model allowing for smooth time-varying effects (SVC model), in particular for strong censoring the values of the SVC model showed strong variability. The TSVC algorithm showed a rather good performance, which may partly be due to the fact that it was a simple time-constant discrete hazard model if none of the explanatory variables was selected for splitting (see Section 3.2).

4.2 Model with Smooth Time-Varying Effects

In the second simulation scenario, the underlying model included two explanatory variables with a smooth time-varying effect each while the other effects were kept time-constant. The predictor function had the form

$$\eta(t, \boldsymbol{x}_i) = \gamma_{0t} + x_{i1}\gamma_1 + x_{i2}\gamma_2 + x_{i3}\gamma_3(t) + x_{i4}\gamma_4(t)$$

with fixed coefficients $\gamma_1 = -0.3$ and $\gamma_2 = 0.3$. For the time-varying coefficients of x_3 and x_4 we used two different sigmoid functions given by

$$\gamma_3(t) = (1 + \exp(5 - t))^{-1}, \quad t = 1, \ldots, k,$$

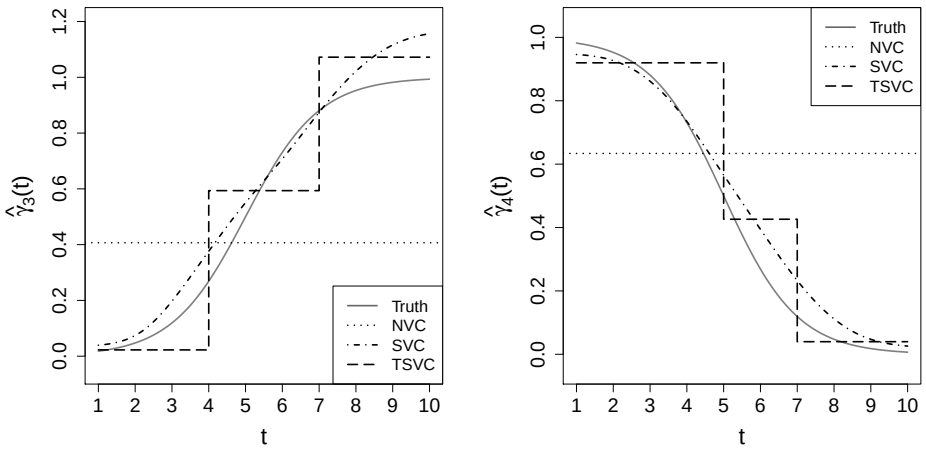

Fig. 2: Results of the simulation study (scenario 2). Estimated coefficients $\hat{\gamma}_3(t)$ of explanatory variable x_3 (left) and $\hat{\gamma}_4(t)$ of explanatory variable x_4 (right) obtained by the three approaches for one randomly chosen sample with low censoring. The true functions are represented by solid lines.

Table 1: Results of the simulation study (scenario 2). Average false positive rates (FPR) and true positive rates (TPR).

Scenario 2	**Censoring**		
	Low	Medium	Strong
FPR	0.060	0.075	0.070
TPR	1.000	0.945	0.395

and

$$\gamma_4(t) = \left(1 + \exp(5-t)^{-1}\right)^{-1}, \quad t = 1, \ldots, k\,.$$

Accordingly, the true data-generating model was a discrete hazard model with smooth time-varying effects. Nevertheless, the TSVC model should still be capable of approximating the functional form of the coefficients of x_3 and x_4 by piecewise constant functions. Figure 2 visualizes the true functions $\gamma_3(t)$ (left panel) and $\gamma_4(t)$ (right panel) and the estimated functions $\hat{\gamma}_3(t)$ and $\hat{\gamma}_4(t)$ obtained by the three approaches for one randomly chosen sample with low censoring. In this example, both the TSVC model and SVC model were well able to approximate the true smooth functions.

Table 1 shows that with increasing level of censoring, the average false positive rate of the TSVC model remained stable while the true positive rate decreased in size. More precisely, for low and medium censoring, the results were similar, with true positive rates higher than 90%. However, for strong censoring the performance of the TSVC model considerably deteriorated. Given all the splits that were generated by the algorithm in any explanatory variable, the proportion of splits in the third or fourth explanatory variable made up 95% for low censoring, 93% for medium censoring and 84% for strong censoring.

For low and medium censoring, the TSVC model and the SVC model provided similar median log-likelihood values whereas the NVC model performed worst (Figure 3). With increasing level of censoring, the NVC model achieved considerably better results and showed a higher median log-likelihood than the SVC model for strong censoring. In this setting, the TSVC model performed best. The SVC model performed worse as there may be only few observations at later points in time,

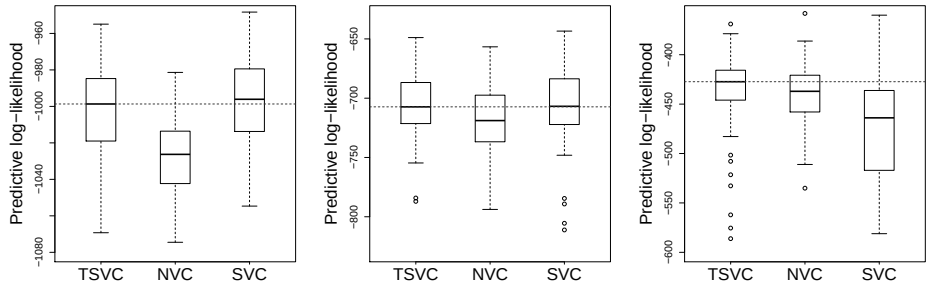

Fig. 3: Results of the simulation study (scenario 2). The figure shows boxplots of the predictive log-likelihood of the TSVC, NVC and SVC model for low (left), medium (center) and strong (right) censoring. The reference line represents the median log-likelihood value of the TSVC model, respectively.

which made it difficult to correctly identify the time-varying effects of an explanatory variable during the fitting procedure. Further of note, when fitting the SVC model, all four explanatory variables were modeled by smooth model terms using the function `s()`. Thus the effects of x_1 and x_2 were not forced to be time-constant, but were also allowed to be fitted as time-varying. This might also be a reason for the high variance of the performance of the SVC model in the strong censoring case.

4.3 Model with Piecewise Constant Time-Varying Effects

The third scenario was based on samples with piecewise constant time-varying effects in two explanatory variables, whereas the effects of the other two explanatory variables were kept constant over time. We defined two splits at different event times: for the binary time-varying explanatory variable x_2, one split was defined at event time $t = 2$. For the standard normally distributed explanatory variable x_4, one split was defined at event time $t = 5$. Hence, the predictor function of the true model was specified by

$$\begin{aligned}\eta(t, \boldsymbol{x}_i) = \gamma_{0t} + x_{i1}\gamma_1 + x_{i2}\Big[\gamma_{21} I(t \leq 2) + \gamma_{22} I(t > 2)\Big] \\ + x_{i3}\gamma_3 + x_{i4}\Big[\gamma_{41} I(t \leq 5) + \gamma_{42} I(t > 5)\Big]\end{aligned}$$

with fixed coefficients $\gamma_1 = 0.3$, $\gamma_3 = -0.3$. The time-varying effects were generated by $\gamma_{21} = -0.3$, $\gamma_{22} = \gamma_{21} - \delta$ and $\gamma_{41} = 0.5$, $\gamma_{42} = \gamma_{41} + \delta$, respectively. In order to analyze how the amount of change in the effect of the explanatory variable over the course of time affects the performance of the approaches, we considered different values of δ. A value of $\delta = 0$ corresponds to a model with time-constant coefficients only, so δ was set to 0.5, 0.8 or 1.0.

The effect of δ is illustrated in Figure 4. Without time-varying effects in the coefficients, the number of events consistently decreased over time (see Figure 4, left panel). Increasing the negative effect of the second explanatory variable resulted in a greater decline of the number of events after time $t = 2$ (see Figure 4, right panel). In the further course, the number of events increased once the positive effect of the fourth explanatory variable at time $t = 5$ had been modified (see Figure 4, right panel).

A summary of the results for the different settings with varying δ and varying censoring rate is given in Table 2. Overall, the false positive rates showed values that were close to the anticipated value of 0.05. Irrespective of the level of censoring, the true positive rate increased for higher values of δ. Further we analyzed the rate

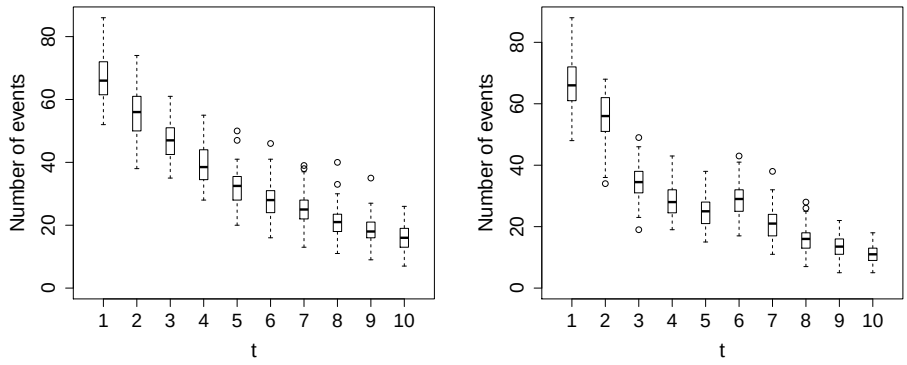

Fig. 4: Results of the simulation study (scenario 3). Illustration of the effect of δ on the number of events. The figure shows boxplots of the number of events over time (observations with $\Delta_i = 1$) for the 100 samples in the setting with low censoring for $\delta = 0.0$ (left) and $\delta = 1.0$ (right). Note the steep decline after $t = 2$ and the increase after $t = 5$ for $\delta = 1.0$.

Table 2: Results of the simulation study (scenario 3). Average false positive rates (FPR) and true positive rates (TPR) for different vaules of δ.

Scenario 3	$\boldsymbol{\delta}$	**Censoring**		
		Low	Medium	Strong
FPR	0.5	0.070	0.050	0.045
	0.8	0.070	0.085	0.075
	1.0	0.055	0.075	0.050
TPR	0.5	0.550	0.330	0.110
	0.8	0.880	0.655	0.295
	1.0	0.950	0.825	0.340

of correctly splitting at the predefined event times. For low censoring, in 68% of all splits (averaged over the three settings with varying δ) the algorithm correctly generated a split at $t = 2$ in x_2 and at $t = 5$ in x_4. This rate reduced to average values of 59% and 45% for medium and strong censoring, respectively. The resulting trees for a randomly chosen sample obtained by the TSVC model showing the estimates for the effects of x_2 and x_4 are presented in Figure 5. The true coefficients in this setting were $\gamma_{21} = -0.3$, $\gamma_{22} = -1.1$ (left panel), and $\gamma_{41} = 0.5$, $\gamma_{42} = 1.3$ (right panel), which were very close to the estimated effects of $\hat{\gamma}_{21} = -0.281$, $\hat{\gamma}_{22} = -1.273$ (left panel) and $\hat{\gamma}_{41} = 0.446$, $\hat{\gamma}_{42} = 1.274$ (right panel), respectively.

Throughout all settings, the median log-likelihood values of the TSVC model were among the highest (Figure 6), whereas the performance of the NVC model and SVC model strongly varied. For medium censoring, the NVC model and the SVC model showed values comparable to those of the TSVC model. However, for low censoring the performance of the NVC model suffered considerably for higher values of δ. Further, the SVC model (as in the previous scenarios) performed very poorly for strong censoring.

4.4 Computational Complexity of the Fitting Procedure

The computational complexity of the TSVC algorithm (in particular the tree building step) is mainly determined by the number of explanatory variables p, the number of time points k and the sample size n. To evaluate this property, we measured the computation time of the fitting procedure in simulation scenarios with time-constant effects in all explanatory variables and a low censoring rate. The specification of the

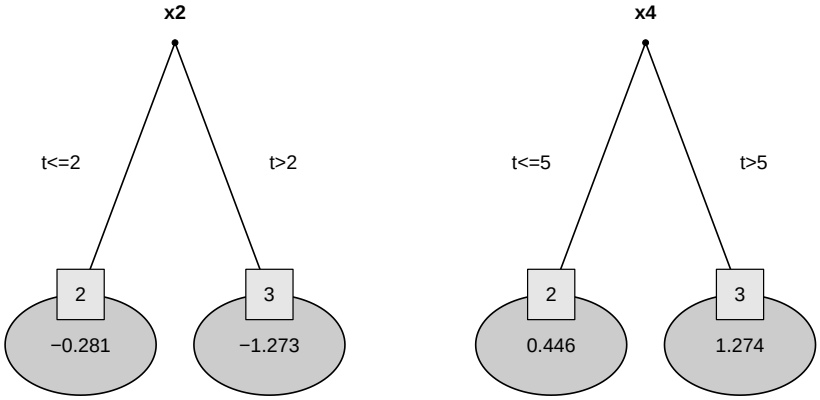

Fig. 5: Results of the simulation study (scenario 3). Estimated trees by the TSVC model for the explanatory variables x_2 (left) and x_4 (right). The results refer to a randomly chosen sample for the setting with $\delta = 0.8$ and low censoring. The estimated time-varying coefficients are given in the leaves of the trees. The true coefficients were $\gamma_{21} = -0.3$, $\gamma_{22} = -1.1$ (left), $\gamma_{41} = 0.5$ and $\gamma_{42} = 1.3$ (right).

predictor was analogous to the first scenario in Section 4.1. We considered scenarios with a varying number of explanatory variables $p = \{4, 8\}$, a varying number of discrete time points $k = \{6, 11, 21\}$ and varying sample size $n = \{100, 500, 1000\}$. In the scenario with $p = 8$ we added two independent binary explanatory variables x_5, x_6, and two independent standard normally distributed explanatory variables x_7, x_8 with coefficients $\gamma_5 = 0.3$, $\gamma_6 = -0.5$, $\gamma_7 = -0.3$ and $\gamma_8 = 0.5$. Depending on k and n, this also led to a varying number of rows in the augmented data matrices. For the lowest dimensional scenario with $p = 4$, $k = 6$ and $n = 100$, the average number of rows was $\tilde{n} = 275$. With increasing number of discrete time points ($p = 4$, $n = 100$), the average number of rows increased to $\tilde{n} = 405$ for $k = 11$ and $\tilde{n} = 620$ for $k = 21$. With increasing sample sizes ($p = 4$, $k = 6$), the average number of rows increased to $\tilde{n} = 1390$ for $n = 500$ and $\tilde{n} = 2775$ for $n = 1000$.
Figure 7 shows the results (computation time in seconds) based on 100 independent samples each. It is seen that a higher number of explanatory variables (left panel), a higher number of discrete time points (middle panel) as well as a larger sample size (right panel) affected the computation time of the fitting procedure. As the permutation test in each iteration evaluates the candidate models with an additional split at all possible time points, the value of k caused the largest rise in time whereas p and n had a smaller influence.

5 Applications

To further illustrate the use of the TSVC model we considered two real-world applications. In those examples, the use of the TSVC model appeared to be appropriate as the model was able to detect important effects that were easy to interpret but were, for example, not found by a more simple model. As in the previous sections we compared the TSVC model to a simple discrete hazard model (NVC model) and to a discrete hazard model allowing for smooth time-varying effects (SVC model).

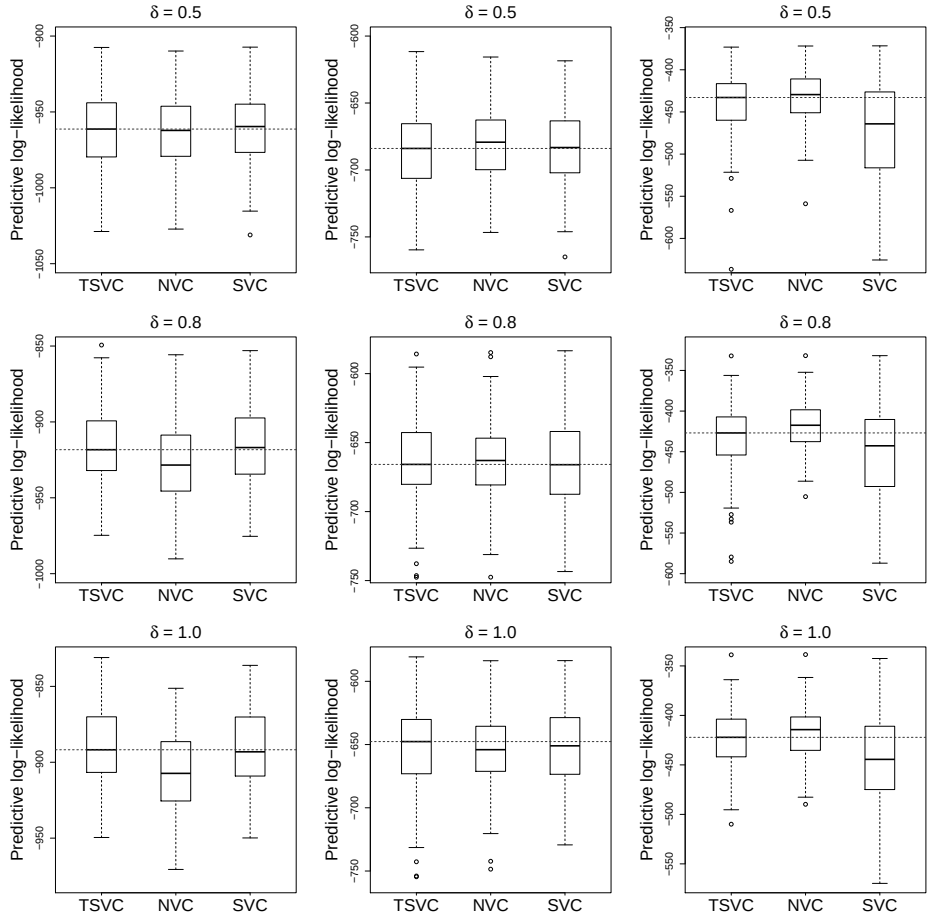

Fig. 6: Results of the simulation study (scenario 3). The figure shows boxplots of the predictive log-likelihood of the TSVC, NVC and SVC model values for low (left), medium (center) and strong (right) censoring. The reference line represents the median log-likelihood value of the TSVC model, respectively.

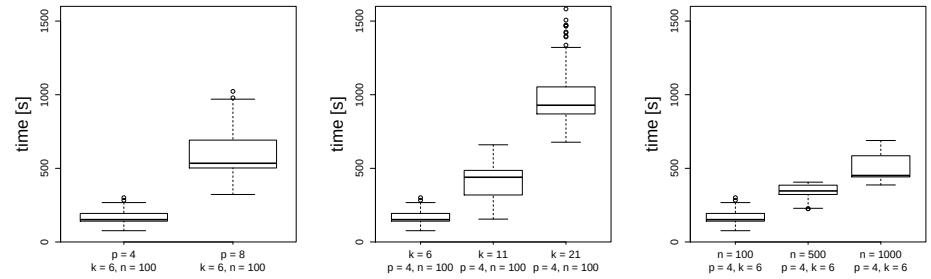

Fig. 7: Results of the simulation study (computational complexity). The figure shows boxplots of the computation time (Hardware: 504 Cores; Opteron 8431 2.4 GHz, Xeon X5650 2.67 GHz, 2.9TB RAM) when running the TSVC algorithm for scenarios with low censoring that differ with regard to the number of explanatory variables p (left), the number of discrete time points k (center) and the sample size n (right).

5.1 Patients with Acute Odontogenic Infection

We considered data of a 5-year retrospective study investigating in-hospital patients with abscess of odontogenic origin conducted between 2012 and 2017 by the

Table 3: Analysis of the odontogenic infection data. Summary statistics of the LOS and the patients characteristics incorporated in the analysis (*n=303*).

Variable	**Summary statistics**					
	x_{min}	$x_{0.25}$	x_{med}	$\overline{x}$	$x_{0.75}$	x_{max}
LOS	1	4	5	5.9	7	18
age	6	31	48	48.6	64	92
gender		0: 146	(48.2%)		1: 157	(51.8%)
spreading		0: 268	(88.4%)		1: 35	(11.6%)
location		0: 263	(86.8%)		1: 40	(13.2%)
antiobiosis		0: 263	(86.8%)		1: 40	(13.2%)
diabetes		0: 278	(91.7%)		1: 25	(8.3%)
remaining focus		0: 118	(38.9%)		1: 185	(61.1%)

Department of Oral and Cranio-Maxillo and Facial Plastic Surgery at the University Hospital Bonn. An acute odontogenic infection is a major burden for patients' health and public health care systems in western countries (Burnham et al., 2011). Practically, every patient suffers from pain, swelling, erythema and hyperthermia. If not treated at an early stage, odontogenic infections are likely to spread into deep neck spaces and cause perilous complications by menacing anatomical structures, such as major blood vessels, the upper airway and even the mediastinum (Biasotto et al., 2004). The main objective of this study was to investigate risk factors (like age, gender, presence of diabetes mellitus type 2) that tend to prolong the length of stay (LOS) in the treatment of severe odontogenic infections. Predicting the LOS may promote transparency to costs and management of patients under inpatient treatment. For this purpose a discrete time-to-event model was considered, where the event of interest was the discharge from the hospital with the hospitalization measured in days ($t = 1, \ldots, 18$).

Here we focused on the data of 303 patients that underwent surgical treatment in terms of incision and drainage of the abscess. Intravenous antibiotics were administered during the operation and for the length of inpatient treatment. For further details on the study we refer to Heim et al. (2018). The LOS of the patients and the patients characteristics considered as explanatory variables in the analysis are summarized in Table 3. These were: age in years (centered around 48), gender (0: female, 1: male), an indicator if the infection spread into other facial spaces (0: no, 1: yes), the location of the infection focus (0: mandible, 1: maxilla), the administered antibiotics (0: ampicillin, 1: clindamycin), the presence of diabetes mellitus type 2 (0: no, 1: yes), and an indicator if the infection was already removed at admission (0: no, 1: yes).

The results of the NVC model and the proposed TSVC model are given in Table 4. The simple NVC model that was recently applied for statistical analysis by Heim et al. (2018) indicated that age and spreading of the infection focus significantly increase the LOS (at the 5% type I error level), while all the other variables showed no evidence for an effect. In particular, diabetes mellitus type 2 revealed no significant increase of the LOS in the present study ($\hat{\gamma} = -0.429$, z value$=-1.699$), although diabetes stands out as a well investigated cause for an increased LOS (Rao et al., 2010).

As seen from the right part of Table 4, the picture changes when fitting the TSVC model. The algorithm performed one split with respect to the risk factor diabetes at split point $t = 4$. According to the estimates, there was a strong negative effect ($\hat{\gamma} = -2.437$) at the beginning of the hospitalization ($t \leq 4$), but the effect vanished for later time points ($t > 4$). This result suggested that patients suffering

Table 4: Analysis of the odontogenic infection data. Overview of the results of the NVC (left) and the TSVC model (right). The algorithm performed one split regarding diabetes at $t = 4$.

Variable	**NVC model**			**TSVC model**	
	Coefficient	Std error	z value	Estimation	Coefficients
age	-0.007	0.003	-2.032	time-constant	-0.008
gender	-0.222	0.139	-1.592	—	—
spreading	-0.970	0.212	-4.566	time-constant	-0.939
location	0.069	0.208	0.332	—	—
antiobiosis	-0.057	0.203	-0.285	—	—
diabetes	-0.429	0.252	-1.699	time-varying	-2.437 0.002
remaining focus	-0.185	0.148	-1.247	—	—

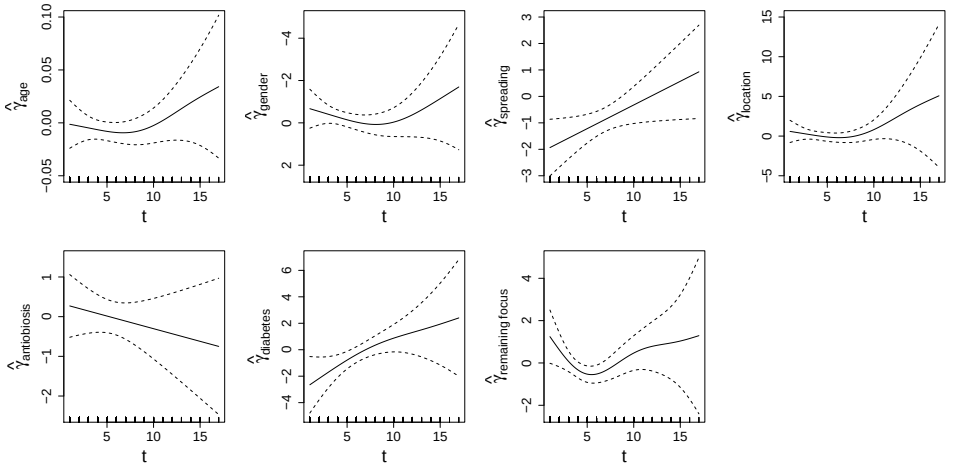

Fig. 8: Analysis of the odontogenic infection data. Estimated effects of the explanatory variables in the SVC model varying over t. Pointwise confidence intervals are drawn by dashed lines, respectively.

from diabetes mellitus type 2 will hardly be released from the hospital before day 4, an important finding that could not be uncovered by the simple NVC model.

The resulting smooth functions $\gamma_j(t)$ when fitting the SVC model, are shown in Figure 8. As in the simulation study we used penalized B-spline basis functions with degree $d = 2$ and a first-order difference penalty. In line with the results of the NVC and the TSVC model, the fitted functions and corresponding confidence intervals showed no evidence for an effect of gender, the location of the infection focus and the administered antibiotics. In contrast to the previous results the SVC model revealed linear time-varying effects for the two risk factors spreading of the infection focus and diabetes. However, the confidence intervals for later time points were very wide. This was also the case for γ_{age} and $\gamma_{\text{remaining focus}}$, which made the effects rather difficult to interpret and strongly suggested that the more parsimonious TSVC model is more appropriate in this analysis.

5.2 Family Developments

In a second application, we evaluated data from the first nine waves of the German Family Panel (*pairfam*: Panel Analysis of Intimate Relationships and Family Dynamics), which provides data on family processes in Germany (Brüderl et al., 2018). The first survey in 2008 collected data from a nationwide random sample

Table 5: Analysis of the pairfam data. Summary statistics of the explanatory variables at the first wave in 2008 (*n=861*).

Variable	**Summary statistics**					
	x_{min}	$x_{0.25}$	x_{med}	$\overline{x}$	$x_{0.75}$	x_{max}
yeduc	8	11.5	13	13.99	17	20
myeduc	8	10.5	11.5	12.18	13	20
fyeduc	8	10.5	11.5	12.76	14.5	20
sat6	0	7	8	7.47	9	10
siblings	0	1	1	1.69	2	16
leisure	1	2	2	1.96	2	4
relstat		0: 460	(53.4%)		1: 401	(46.6%)
casprim		0: 283	(32.9%)		1: 578	(67.1%)

comprising more than 12,000 respondents of the birth cohorts 1971-1973, 1981-1983 and 1991-1993 and their families. In the multi-cohort approach the main focus is on so-called *anchor persons* of a certain birth cohort, who were annually interviewed to get detailed information on topics like the development of partnership, family plans and formation as well as attitudes regarding parenting in general. In addition, information from parents, partner and children of the anchor person was gathered as well. For further details on the study we refer to Huinink et al. (2011).

As all the information was gathered in one-year intervals, the observed duration times of the pairfam study are discrete. The event of interest was defined by the binary outcome whether an anchor woman gave birth to her first child or not. In line with Groll and Tutz (2017), we restricted our consideration to women of the birth cohorts 1971-1973 or 1981-1983 and considered age measured in years as the unit of the discrete hazard model starting with women of at least 25 years. The analysis data set comprised 4077 observations of 861 anchor women who stated to have no children in the initial wave.

As explanatory variables, we included the educational level of the anchor woman measured in years (*yeduc*), the educational levels of the parents of the anchor woman in years (*myeduc* and *fyeduc*), the degree of life satisfaction of the anchor woman (*sat6*, with higher values indicating a higher life satisfaction), the status of relationship of the anchor woman (*relstat*, 0: single, 1: married and/or cohabitation), the employment status of the anchor woman (*casprim*, 0: not employed, 1: employed), the number of siblings of the anchor woman (*siblings*), the amount of leisure time spent for going to bars/cafés/restaurants, doing sport, meeting with friends and/or going to a discotheque of the anchor woman (*leisure*, 1: daily, 2: at least once a week, 3: at least once a month, 4: less often, 5: never). A descriptive overview of all explanatory variables at the first wave in 2008 is summarized in Table 5.

In total, there were 273 observed births in our sample and the amount of censoring was 40%. The distribution of the observed age of the anchor women at the birth of the first child is presented in Figure 9. The median age was 29 years.

The baseline coefficients, which correspond to the effect of age, were fitted by a smooth function as defined in Equation (9), using P-splines of degree $d = 2$ and a second-order difference penalty. The resulting *baseline hazards* when fitting the TSVC, NVC and SVC model are presented in Figure 10. The baseline hazard was respectively obtained by transforming the estimated baseline coefficients using the distribution function $\exp(\hat{\gamma}_{0,\text{age}})/(1 + \exp(\hat{\gamma}_{0,\text{age}}))$ of the logistic model. It can be seen that the baseline hazards were very similar for the NVC and TSVC model. They were found to show a high hazard up to age 35 followed by a strong decline beyond age 35. In contrast the SVC model yielded a steady decline across time.

Fig. 9: Analysis of the pairfam data. Distribution of the observed age of the anchor women at the birth of the first child.

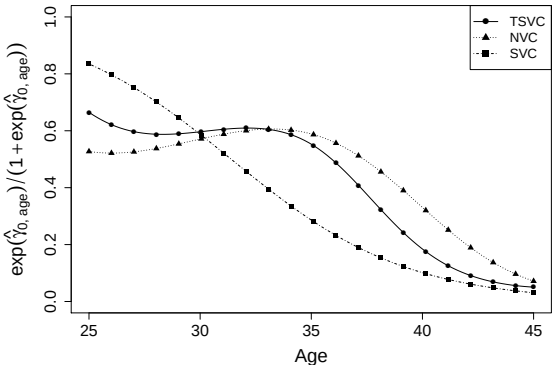

Fig. 10: Analysis of the pairfam data. The figure shows the estimated smooth baseline hazard depending on age for the three models TSVC, NVC and SVC.

Table 6: Analysis of the pairfam data. Overview of the results of the NVC (left) and the TSVC model (right). The algorithm performed one split regarding *yeduc* at $age > 36$ and one split with respect to *sat6* at $age > 28$.

Variable	**NVC model**			**TSVC model**	
	Coefficient	Std error	z value	Estimation	Coefficients
yeduc	0.006	0.026	0.249	time-varying	-0.005 0.044
myeduc	-0.026	0.034	-0.760	—	—
fyeduc	0.011	0.030	0.370	—	—
sat6	0.204	0.047	4.333	time-varying	0.172 0.216
siblings	0.117	0.043	2.697	time-constant	0.123
leisure	0.250	0.111	2.249	time-constant	0.251
relstat	1.696	0.172	9.849	time-constant	1.699
casprim	-0.135	0.156	-0.865	—	—

The estimated coefficients, standard errors and z values obtained by the NVC model are given in Table 6 (left part). There were significant effects for all variables except for the years of education (of the anchor woman and her parents) and the employment status (*casprim*). The estimates indicate that the chance to have a child increased with having a relationship, with the number of siblings, with a higher degree of life satisfaction and a lower amount of leisure time.

Fig. 11: Analysis of the pairfam data. The estimated time-varying coefficients by the TSVC model for explanatory variables yeduc (left) and sat6 (right). The varying coefficients are given in the leaves of the trees.

In the right part of Table 6, the results when fitting the TSVC model are presented. As can be seen there, the algorithm performed two splits with respect to the explanatory variables *yeduc* and *sat6*. Further, there were time-constant effects of the relationship status, the number of siblings and the amount of leisure time. The employment status as well as the educational achievements of the parents were excluded from the model. Figure 11 shows the estimated trees for *yeduc* and *sat6*. In general, the degree of a woman's life satisfaction had a positive effect on the chance of having a child (as already indicated by the NVC model) but got even stronger with age (age $>$ 28 years). The effect of the educational level measured in years of a woman was opposing: while a higher educational level had a positive effect for relatively old women (age $>$ 36 years), the effect was close to zero for younger women (age $\leq$ 36 years). This finding is in line with a previous analysis of the first four waves of the pairfam study which found that half of the women with an academic degree were at least 35 years at the birth of the first child (Huininik, 2014).

Comparing the results of the TSVC model to the NVC model, the TSVC model was able to detect a relevant time-varying effect of *yeduc* which remained undetected by the simple discrete hazard model. For the explanatory variable *sat6*, the NVC model also detected a positive effect, but not the difference over the course of time.

The resulting coefficients when fitting the SVC model allowing for smooth time-varying effects in all explanatory variables are shown in Figure 12. As seen from the fitted functions and the confidence intervals, there was evidence for (i) time-constant effects of the number of siblings and the amount of leisure time, (ii) time-varying effects of a woman's educational level, the degree of life satisfaction and the relationsship status, and (iii) no effects of the parent's educational level and the employment status.

Both, the TSVC and the SVC model showed similar effects for variable *yeduc* on the chances of starting a family, although the function fitted by the SVC model was much more complex. The function also indicated that the effect was close to zero for young women, increased and turned into a constant positive effect for relatively old women (age $>$ 35 years). For the degree of life satisfaction, both models showed a positive effect on the chance for having a child which became slightly stronger with age. Time-constant effects that were similar in magnitude were found for the

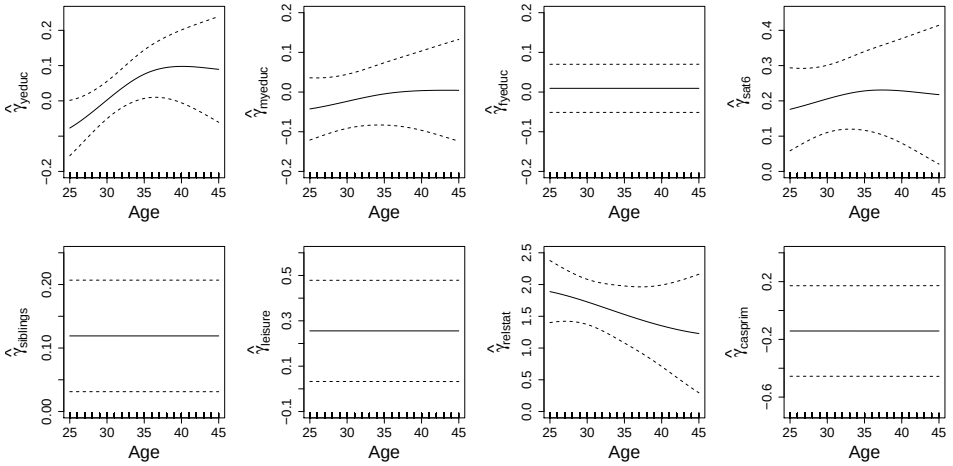

Fig. 12: Analysis of the pairfam data. Estimated effects of the explanatory variables in the SVC model varying over age. Pointwise confidence intervals are drawn by dashed lines, respectively.

explanatory variables *leisure* and *sibilings*. A difference between the models was obtained for the explanatory variable *relstat*, which was estimated to have a time-constant effect by the TSVC model but a time-varying (decreasing) effect by the SVC model. The confidence intervals of the SVC model are very wide making it dubious that the effect is truly time-varying, which favors the more parsimonious TSVC model.

5.3 Choice of the Tuning Parameter α

As described in Section 3.3, the main tuning parameter of the algorithm is the error level α, which was set to $\alpha = 0.05$ in all the previous simulations and the applications. To investigate the dependence of the proposed TSVC model on α, we compared the prediction accuracy for different values of α using the odontongenic infection data analyzed in Section 5.1. We drew 100 subsamples without replacement of size $n_{\text{train}} = 242$ (i.e., 80% of the original sample), fitted the TSVC model using the grid $\alpha = (0.01, 0.05, 0.10, 0.15, 0.20)$ in each of the 100 subsamples and computed the predicitive log-likelihood values from the remaining 100 test sets of $n_{\text{test}} = 61$. Subsampling was stratified by t to ensure a sufficient number of observations per observed event time. It is seen from the boxplots in Figure 13 that the median log-likelihood value was highest for $\alpha = 0.05$, but did only slightly vary for the other values of α. The variance, however, strongly increased for a high error level ($\alpha = 0.20$), which was caused by the fitting of too large trees in some of the replications. These results underline that the algorithm shows the desired behavior and that the use of $\alpha = 0.05$ is a reasonable choice.

6 Concluding Remarks

We propose the use of a tree-based algorithm for the modeling of time-varying coefficients in discrete time-to-event models. The output of the method is a set of piecewise constant functions that are visualized in small trees and are therefore easily accessible. The method constitutes a flexible alternative to models with smooth time-varying coefficients. One of the main features of the algorithm is simultaneous

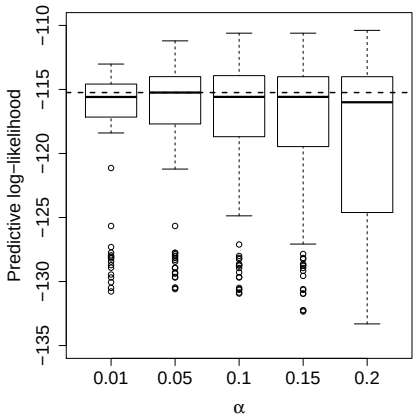

Fig. 13: Analysis of the odontogenic infection data. The boxplots show the predictive log-likelihood values of the TSVC model using different values of α (on the x-axis) based on 100 subsamples of size $n_{\text{train}} = 242$ each. The models were evaluated on the remaining 100 test sets of size $n_{\text{test}} = 61$ each. The reference line represents the median log-likelihood value of the best-performing model.

variable selection (of the explanatory variables to be split and corresponding split points) and model fitting, because all the model parameters are refitted in each iteration.

The simulation study essentially showed that the proposed TSVC model (i) performed well in terms of true positive and false positive rates, (ii) was competitive to the simple NVC model in scenarios without time-varying effects, and (iii) was robust against high censoring rates, where the performance of the SVC model strongly suffered. Obviously, a small number of observations at later time points impedes the reliable detection of time-varying effects fitted by smooth functions. Both applications demonstrated the usefulness of the TSVC model, as the model (i) was well able to identify relevant time-varying effects that could not be detected by the simple NVC model, and (ii) was more parsimonious than the SVC model, which yielded easier interpretations of the model fits.

It is important to note that in the representations of the models in Section 2 and Section 3.2 the explanatory variables for simplicity are considered as being constant over time. This restriction is easily removed by allowing time-dependent values $\boldsymbol{x}_{it}^{\top} = (x_{i1t}, \ldots, x_{ipt})$, $t = 1, \ldots, \tilde{T}_i$, as was already done in the pairfam data. The vectors $\boldsymbol{x}_{it}$ simply need to be inserted in the rows of the augmented data matrices (see also Appendix A) and the analysis can be run in the usual way.

Finally, we restricted our consideration to time-to-event data with a single type of event. An obvious direction for future research is to extend the TSVC model to the competing-risks case with more than one target event that could be realized by embedding the R-package **VGAM** (Yee, 2010, 2017) for fitting vector generalized additive models into the fitting algorithm. Recent extensions of the discrete hazard modeling framework to competing-risks models, allowing for more than one target event, were inter alia considered by Möst et al. (2016), Berger et al. (2018a), Berger et al. (2018c) and Heyard et al. (2018).

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A Augmented Data Matrices of the TSVC model given in Equation (14)

For an individual whose event was observed ($\Delta_i = 1$) at time $\tilde{T}_i$ the augmented data matrix after a split in x_j at split point t^*_{j1} is given by

$$\begin{array}{cc|cccccc} \boldsymbol{y}_i & \boldsymbol{t} & & & & \boldsymbol{X}_i & & \\ \hline 0 & 1 & x_{i1} & \dots & x_{ij} & 0 & \dots & x_{ip} \\ 0 & 2 & x_{i1} & \dots & x_{ij} & 0 & \dots & x_{ip} \\ 0 & 3 & x_{i1} & \dots & x_{ij} & 0 & \dots & x_{ip} \\ \vdots & \vdots & \vdots & & \vdots & \vdots & & \vdots \\ 0 & t^*_{j1} & x_{i1} & \dots & x_{ij} & 0 & \dots & x_{ip} \\ 0 & t^*_{j1}+1 & x_{i1} & \dots & 0 & x_{ij} & \dots & x_{ip} \\ 0 & t^*_{j1}+2 & x_{i1} & \dots & 0 & x_{ij} & \dots & x_{ip} \\ \vdots & \vdots & \vdots & & \vdots & \vdots & & \vdots \\ 1 & \tilde{T}_i & x_{i1} & \dots & 0 & x_{ij} & \dots & x_{ip} \end{array} . \tag{17}$$

For an individual that is censored ($\Delta_i = 0$) at time $\tilde{T}_i$ the augmented data matrix after a split in x_j at split point t^*_{j1} is given by

$$\begin{array}{cc|cccccc} \boldsymbol{y}_i & \boldsymbol{t} & & & & \boldsymbol{X}_i & & \\ \hline 0 & 1 & x_{i1} & \dots & x_{ij} & 0 & \dots & x_{ip} \\ 0 & 2 & x_{i1} & \dots & x_{ij} & 0 & \dots & x_{ip} \\ 0 & 3 & x_{i1} & \dots & x_{ij} & 0 & \dots & x_{ip} \\ \vdots & \vdots & \vdots & & \vdots & \vdots & & \vdots \\ 0 & t^*_{j1} & x_{i1} & \dots & x_{ij} & 0 & \dots & x_{ip} \\ 0 & t^*_{j1}+1 & x_{i1} & \dots & 0 & x_{ij} & \dots & x_{ip} \\ 0 & t^*_{j1}+2 & x_{i1} & \dots & 0 & x_{ij} & \dots & x_{ip} \\ \vdots & \vdots & \vdots & & \vdots & \vdots & & \vdots \\ 0 & \tilde{T}_i & x_{i1} & \dots & 0 & x_{ij} & \dots & x_{ip} \end{array} . \tag{18}$$

The matrices (17) and (18) contain two columns associated with the j-th explanatory variable including the values $\boldsymbol{x}_{ij}^\top I(t \leq t^*_{j1})$ and $\boldsymbol{x}_{ij}^\top I(t > t^*_{j1})$.

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Appendix E

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