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Direct costs in impaired glucose regulation: results from the population-based Heinz Nixdorf Recall study

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ABSTRACT

Objective: For the first time, this population-based study sought to analyze healthcare utilization and associated costs in people with normal fasting glycemia (NFG), impaired fasting glycemia (IFG), as well as previously undetected diabetes and previously diagnosed diabetes linking data from the prospective German Heinz Nixdorf Recall (HNR) study with individual claims data from German statutory health insurances.

Research design and methods: A total of 1709 participants of the HNR 5-year follow-up (mean age (SD) 64.9 (7.5) years, 44.5% men) were included in the study. Age-standardized and sex-standardized healthcare utilization and associated costs (reported as € for the year 2008, perspective of the statutory health insurance) were stratified by diabetes stage defined by the participants' self-report and fasting plasma glucose values. Cost ratios (CRs) were estimated using two-part regression models, adjusting for age, sex, sociodemographic variables and comorbidity.

Results: The mean total direct healthcare costs for previously diagnosed diabetes, previously undetected diabetes, IFG, and NFG were €2761 (95% CI 2378 to 3268), €2210 (1483 to 4279), €2035 (1732 to 2486) and €1810 (1634 to 2035), respectively. Corresponding age-adjusted and sex-adjusted CRs were 1.53 (1.30 to 1.80), 1.16 (0.91 to 1.47), and 1.09 (0.95 to 1.25) (reference: NFG). Inpatient, outpatient and medication costs varied in order between people with IFG and those with previously undetected diabetes.

Conclusions: The study provides claims-based detailed cost data in well-defined glucose metabolism subgroups. CRs of individuals with IFG and previously undetected diabetes were surprisingly low. Data are important for the model-based evaluation of screening programs and interventions that are aimed either to prevent diabetes onset or to improve diabetes therapy as well.

Key messages

- The study combines primary data with health insurance data and thus provides detailed cost data in well-defined glucose metabolism subgroups in Germany.
- Cost ratios of individuals with impaired glucose regulation and previously undetected diabetes compared to those with normal glucose regulation are surprisingly low.
- Data are important for the model-based evaluation of screening programs and interventions to prevent diabetes onset or improve diabetes therapy as well.

INTRODUCTION

Diabetes is a chronic disease associated with substantial individual and societal burden due to increasing healthcare expenditures, reduced productivity at work, premature retirement, or death. The global healthcare expenditure for the treatment of diabetes and its complications has been estimated at US $548 billion for 2013, that is, 10.8% of the total expenditure, and is projected to increase to US $627 billion by 2035.[1] More than 90% of the global healthcare expenditure for diabetes is met by the economically most affluent countries of the world, especially the USA, Germany, and Japan.

In Germany, diabetes is one of the most expensive chronic diseases. Köster *et al*[2] estimated the mean excess diabetes-related costs in a sample of statutorily insured people in 2009 (CoDiM study). After standardization to the German population, the mean total healthcare costs per person with diabetes amounted to €5982. The mean excess diabetes-related costs were €2611, corresponding to total diabetes-related costs of €21.0 billion for all patients with diabetes in Germany.

Although usually considered as diabetes sequelae, diabetes-related comorbidities are frequently present before the diagnosis of diabetes.[3 4] However, costs in the stages before diabetes diagnosis have hardly been researched thus far.[5] The few studies estimating healthcare costs in the years preceding diabetes diagnosis reported significant increases in healthcare costs already 2–8 years

prediagnosis.[4–7] Nevertheless, these studies failed to differentiate between people with impaired fasting glycemia (IFG, a high-risk state for developing diabetes), previously undetected diabetes, or normal glucose regulation who developed diabetes during the study period. In addition, cost data were predominantly not adjusted for socioeconomic position or comorbidity. Knowledge about the costs in different (pre) diabetic stages improves the estimation and prognosis of the total diabetes burden and is essential for the conception of decision analytic models of diabetes prevention, screening, and therapy.[3 8] This is of particular relevance as the global number of 20-year-old to 79-year-old people with impaired glucose tolerance is projected to increase to 471 million by 2035, corresponding to an increase by 49% since 2013.[1]

Therefore, the aim of this population-based study was to analyze the utilization of health services and associated direct costs in people with normal fasting glycemia (NFG), impaired fasting glycemia (IFG), previously undetected diabetes, and previously diagnosed diabetes linking data from the German Heinz Nixdorf Recall study with individual claims data from the main German statutory health insurances. Linking individual data with cost data derived from statutory health insurances enables valid estimates of real-life healthcare costs.

RESEARCH DESIGN AND METHODS

Heinz Nixdorf recall study

Individual characteristics/primary data of the participants were derived from the ongoing Heinz Nixdorf Recall (HNR; 'Risk Factors, Evaluation of Coronary Calcium and Lifestyle') study, a prospective, population-based cohort study evaluating modern risk stratification techniques for coronary outcomes. The study was approved by the responsible local ethics committee. In brief, 9484 inhabitants 45-75-years-old were randomly selected from the mandatory registries of residence of three German cities (Essen, Mülheim and Bochum) located in the northwest of Germany. Between 2000 and 2003, 4814 participants gave their informed consent and took part in the baseline study (recruitment efficacy proportion: 55.8%, response proportion: 53.3%).[9] Further details have been described previously.[10] Of the 4814 participants included in the baseline study, 4157 (86.4%) attended the second examination visit between 2006 and 2008 (5 year follow-up).

Data acquisition

Self-reported data were assessed by a standardized interview. Further clinical data were derived from laboratory and clinical investigations of the participants. In case of participants' approval, the main corresponding health insurances were asked to cooperate with the HNR study. For the current analyses, primary data from the HNR study were individually linked with routine data on healthcare utilization and associated costs from the main statutory health insurances in Germany.

Study population

Health insurance data of the main German statutory health insurances were available from 2184 participants. Of these, 1722 had health insurance data for at least 1 year before the 5 year follow-up and thus were eligible for the analyses. A further 13 participants were excluded because of missing data on their diabetes stage, resulting in 1709 participants for the analyses. Compared with the excluded participants (n=2448), the participants of the final study sample were on average 0.9 years older ($p_{Wilcoxon}<0.001$) and less frequently male (44.5% vs 53.0%, $p\chi^2<0.001$).

Definition of diabetes stages

According to the information provided by the participants and the results of a fasting plasma glucose (FPG) test at follow-up, all participants were divided into four groups of diabetes regulation. 'Previously diagnosed diabetes' was present if the participants reported a physician's diagnosis of diabetes or antihyperglycemic treatment at follow-up. Applying the criteria of the WHO, the International Diabetes Federation (IDF) and the European Diabetes Epidemiology Group (EDEG),[11 12] 'previously undetected diabetes' was assumed if the FPG value was at least 7.0 mmol/L (corresponding to 126 mg/dL) and the participants reported no previous diagnosis of diabetes at follow-up. 'Impaired fasting glycemia' (IFG) was defined as an FPG value between 6.1 mmol/L and <7.0 mmol/L (corresponding to 110–<126 mg/dL) at follow-up. If the FPG value was lower than 6.1 mmol/L, participants were classified as having 'normal fasting glycemia' (NFG).

Sociodemographic and clinical variables

Sociodemographic data included age, sex, country of birth (Germany/other country), living with a partner (yes/no), education, status of employment and quartiles of equivalent income (net income adjusted for household size according to the Luxembourg Income Study[13 14]).

The following clinical variables from the follow-up were included: type of diabetes, diabetes treatment and diabetes duration among people with previously diagnosed diabetes, standardized analyzed glycated hemoglobin value (%, mmol/mol), prevalent hypertension (mean of the second and third systolic/diastolic blood pressure measurement >140/90 mm Hg or antihypertensive medication) since baseline ongoing self-reported previous medical diagnosis of stroke or myocardial infarction (validated by clinical experts) and current body mass index (BMI (kg/m^2)) calculated from standardized measurements of height and weight.

Healthcare utilization and associated costs

Healthcare utilization, associated costs and diagnoses (documented as International Statistical Classification of Diseases and Related Health Problems, German Modification (ICD-10-GM)) or pharmaceutical coding of drugs (Anatomical Therapeutic Chemical (ATC) codes) were derived from the statutory health insurances' data. Numbers and percentages of healthcare utilization per capita as well as resulting costs referred to the four complete quarters before the individual follow-up examination (termed index year). The direct medical costs per capita were determined from the perspective of the statutory health insurance.

Inpatient data included the date of, length and diagnosis for each hospitalization (ICD-10-GM), diagnosis-related group (DRG), and corresponding costs reduced by patients' copayments. In case of missing net costs (10.5%), these costs were estimated using data reported by other statutory health insurances assuming sufficient transferability.

In Germany, costs of outpatient consultations are reimbursed according to the respective German compensation scheme ('Einheitlicher Bewertungsmaßstab' (EBM) reimbursement). Furthermore, extrabudgetary services, costs of dialysis equipment, and material expenses reported by the statutory health insurances were considered.

Information on prescribed medication comprised prescription date, ATC code, and costs of medication adjusted for mandatory drug discounts and copayments. Missing net medication costs (5.1%) were estimated using reported data by other health insurances. Costs of medication are reported as total medication costs, total costs without antihyperglycemic medication, and costs of cardiovascular medication.

Statistical analyses

The description of the data was presented for the total cohort and stratified by diabetes stage. The continuous variables were described using means and SDs. All categorical variables were described using the percentages with 95% CIs. All variables were age-standardized and sex-standardized in order to adjust for potential demographic differences between the diabetes stages (age strata: <65 years, ≥65 years) to the German population using data from the Federal Statistical Office (reference date: 31 December 2006).

Total costs and different cost categories are given as costs per capita in Euro for the last follow-up year 2008 (2008€). Costs of previous years were inflated to 2008 using the German Consumer Price Index.[15] Owing to the right skewed distribution of healthcare utilization data including costs, 95% CIs for the mean values and percentages of health utilization were estimated using bootstrap procedures.[16 17]

The associations between mean total direct healthcare costs, costs of inpatient or outpatient treatment, or medication costs as dependent variables and diabetes stage as main independent variable were estimated using multiple regression analyses. For comparison of the costs between the different diabetes stages, cost ratios (CRs) were estimated adjusting stepwise for age and sex (model 1), additionally country of birth, living with a partner, and equivalent household income (model 2), hypertension, stroke, myocardial infarction, BMI (model 3), and finally healthcare utilization costs of the year before the index year (model 4). Since data contained persons with no healthcare utilization (8.1%), two-part models were used.[18 19] By combining both parts of the model using generalized linear models (1st Poisson regression model with robust error variance,[20 21] 2nd γ regression model), expected CRs for the whole study population were estimated.

RESULTS

Description of the study population

The final study population is described in detail in table 1. A total of 14.6% of the participants (n=250) had been previously diagnosed with diabetes (type 1 diabetes: n=9, type 2 diabetes: n=207, unknown diabetes type: n=34). Mean diabetes duration was 9.6 years. Regarding diabetes therapy, more than half (56%) of the participants were treated with oral antihyperglycemic drugs, about 14% were treated with insulin, and 9% used both oral antihyperglycemic drugs and insulin (data not shown).

Healthcare utilization

Inpatient care

Age-standardized and sex-standardized mean numbers and proportions of healthcare utilization are presented in tables 2 and 3. During the study period, 21.2% (95% CI 19.3 to 23.2) of the participants used hospital services at least once, primarily for inpatient stays (table 3). The mean annual number of hospital stays was 0.3 (0.3 to 0.4; table 2). Every participant spent on average 2.4 (2.1 to 2.8) days per year in hospital. Stratified by diabetes stage, people with diabetes had an increased number of hospitalizations and longer duration per hospitalization compared with people with NFG or IFG.

Outpatient care

Less than 1 in 10 participants did not use any outpatient healthcare service during the year before the 5-year follow-up (index year), while most of the participants used outpatient care throughout all four quarters of the study period. The mean number of outpatient contacts with EBM reimbursement (German compensation scheme) was 9.3 (95% CI 9.0 to 9.6) per year. Stratified by diabetes stage, the number of outpatient contacts ranged between 8.4 (7.2 to 10.4) for people with previously undetected diabetes and 10.9 (10.0 to 11.8) for people with previously diagnosed diabetes. The frequency of ICD diagnoses is presented in the online appendix (as for inpatient care and ATC codes of prescribed medication, online supplementary OSM tables S1–3).

Table 1 Description of the study population

	Full sample (N=1709)	Normal fasting glycemia (N=951)	Impaired fasting glycemia (N=403)	Previously undetected diabetes (N=105)	Previously diagnosed diabetes (N=250)
Sex male % (95% CI)*	44.5 (42.2 to 46.9)	35.7 (32.6 to 38.8)	55.3 (50,3 to 60,3)	57.1 (47.1 to 66.8)	55.6 (49.2 to 61.9)
Mean age (SD)	64.9 (7.5)	63.9 (7.6)	66.0 (7.0)	64.5 (7.9)	66.9 (7.2)
Birth in foreign country % (95% CI)*†‡	7.6 (6.4 to 9.0)	8.2 (6.6 to 10.2)	7.4 (5.1 to 10.5)	6.7 (2.7 to 13.3)	6.0 (3.4 to 9.7)
Living with partner % (95% CI)*‡	74.6 (72.4 to 76.6)	73.3 (70.4 to 76.1)	76.6 (72.2 to 80.7)	75.2 (65.9 to 83.1)	75.6 (69.8 to 80.8)
Education*†‡					
Up to 10 years % (95% CI)	12.9 (11.3 to 14.6)	12.0 (10.0 to 14.3)	12.4 (9.4 to 16.0)	10.5 (5.3 to 18.0)	18.0 (13.4 to 23.3)
11–13 years % (95% CI)	64.9 (61.9 to 68.1)	65.0 (61.9 to 68.1)	64.0 (59.1 to 68.7)	73.3 (63.8 to 81.5)	62.4 (56.1 to 68.4)
14–17 years % (95% CI)	18.2 (16.4 to 20.1)	17.2 (14.8 to 19.7)	21.6 (17.7 to 25.9)	16.2 (9.7 to 24.7)	17.2 (12.7 to 22.5)
At least 18 years % (95% CI)	4.0 (3.2 to 5.1)	5.8 (4.4 to 7.5)	2.0 (0.9 to 3.9)	0.0 (0.0 to 3.5)	2.4 (0.9 to 5.2)
Equivalent household income*‡					
Lowest quartile % (95% CI)	24.6 (22.5 to 26.8)	23.2 (20.5 to 26.1)	24.2 (20.0 to 28.8)	26.5 (18.1 to 36.4)	29.9 (24.0 to 36.2)
2nd quartile % (95% CI)	25.4 (23.3 to 27.6)	27.5 (24.6 to 30.6)	24.7 (20.5 to 29.4)	21.4 (13.8 to 30.9)	19.9 (15.0 to 25.7)
3rd quartile % (95% CI)	23.9 (21.9 to 26.1)	22.8 (20.0 to 25.7)	24.5 (20.3 to 29.1)	25.5 (17.2 to 35.3)	26.8 (21.2 to 33.0)
Highest quartile % (95% CI)	26.1 (23.9 to 28.3)	26.5 (23.6 to 29.6)	26.6 (22.2 to 31.3)	26.5 (18.1 to 36.4)	23.4 (18.1 to 29.4)
Status of employment*‡					
Full-time or part-time employed % (95% CI)	25.8 (23.7 to 27.9)	30.9 (28.0 to 34.0)	21.0 (17.1 to 25.3)	32.7 (23.8 to 42.6)	11.2 (7.6 to 15.8)
Retired % (95% CI)	58.8 (56.5 to 61.2)	52.7 (49.5 to 56.0)	65.1 (60.2 to 69.8)	54.8 (44.7 to 64.6)	73.6 (67.7 to 79.0)
Unemployed % (95% CI)	4.1 (3.2 to 5.1)	3.7 (2.6 to 5.1)	4.2 (2.5 to 6.7)	1.9 (0.2 to 6.8)	6.0 (3.4 to 9.7)
Other % (95% CI)	11.3 (9.9 to 12.9)	12.7 (10.6 to 14.9)	9.7 (7.0 to 13.1)	10.6 (5.4 to 18.1)	9.2 (5.9 to 13.5)
Mean HbA1c % (SD)‡	5.7 (0.8)	5.4 (0.4)	5.6 (0.5)	6.1 (0.9)	6.8 (1.2)
Mmol/mol (SD)	38.9 (8.6)	35.8 (4.5)	37.7 (5.4)	43.3 (9.6)	50.8 (12.8)
Hypertension % (95% CI)*‡§	67.3 (65.0 to 69.5)	56.8 (53.6 to 60.0)	74.7 (70.1 to 78.9)	81.9 (73.2 to 88.7)	89.2 (84.7 to 92.8)
Stroke % (95% CI)*‡§	1.6 (1.1 to 2.4)	1.0 (0.4 to 1.8)	2.0 (0.9 to 3.9)	1.0 (0.0 to 5.2)	4.0 (1.9 to 7.2)
Myocardial infarction % (95% CI)*§	1.2 (0.7 to 1.8)	1.2 (0.6 to 2.1)	0.7 (0.2 to 2.2)	2.9 (0.6 to 8.1)	1.2 (0.2 to 3.5)
Mean BMI (kg/m²) (SD)‡¶	28.6 (4.9)	27.5 (4.4)	29.0 (4.9)	30.7 (5.5)	31.0 (5.1)
Weight status*‡¶					
Underweight % (95% CI) (BMI <18.5 kg/m²)	0.3 (0.1 to 0.7)	0.4 (0.1 to 1.1)	0.3 (0.0 to 1.4)	0.0 (0.0 to 3.5)	0.0 (0.0 to 1.5)
Normal weight % (95% CI) (BMI 18.5–<25.0 kg/m²)	22.4 (20.4 to 24.4)	27.9 (25.1 to 30.9)	17.7 (14.1 to 21.8)	18.3 (11.4 to 27.1)	10.5 (7.0 to 15.0)
Overweight % (95% CI) (BMI 25.0–<30.0 kg/m²)	44.1 (41.7 to 46.5)	48.0 (44.7 to 51.2)	44.9 (39.9 to 49.9)	26.0 (17.9 to 35.5)	35.5 (29.5 to 41.8)
Obesity I % (95% CI) (BMI 30.0–<35.0 kg/m²)	23.4 (21.4 to 25.5)	17.7 (15.3 to 20.3)	26.9 (22.7 to 31.6)	40.4 (30.9 to 50.5)	32.3 (26.5 to 38.5)
Obesity II % (95% CI) (BMI 35.0–<40.0 kg/m²)	7.1 (5.9 to 8.4)	4.2 (3.0 to 5.7)	6.2 (4.1 to 9.1)	9.6 (4.7 to 17.0)	18.2 (13.6 to 23.5)
Obesity III % (95% CI) (BMI≥40.0 kg/m²)	2.8 (2.1 to 3.7)	1.8 (1.0 to 2.9)	4.0 (2.3 to 6.4)	5.8 (2.1 to 12.1)	3.6 (1.7 to 6.8)

HNR study, follow-up examination (2006–2008), Germany.
Data are given as means with SDs (SD) or proportions with CIs (CIs).
*95% CI calculated using the exact method proposed by Clopper and Pearson.
†Baseline data.
‡Number of missing values: birth in foreign country: 2, living with partner: 4, education: 2, equivalent household income: 117, status of employment: 6, extent of employment: 6, HbA1c: 33, hypertension: 2, BMI: 7.
§Classified according to the American Society of Hypertension and the International Society of Hypertension guidelines (available from http://ish-world.com/news/a/New-ISH-Hypertension-Guidelines-published-in-December-2013-together-with-the-American-Society-of-Hypertension-ASH-./).[29]
¶Classified according to the WHO classification scheme. http://apps.who.int/bmi/index.jsp?introPage=intro_3.html.[30]
BMI, body mass index; HbA1c, glycated hemoglobin.

Table 2 Healthcare utilization, HNR study, Germany*

	Full sample (N=1709)	Normal fasting glycemia (N=951)	Impaired fasting glycemia (N=403)	Previously undetected diabetes (N=105)	Previously diagnosed diabetes (N=250)
Inpatient care per person and year (mean†, 95% CI‡)					
Mean number of hospitalizations	0.32 (0.29 to 0.37)	0.29 (0.25 to 0.34)	0.30 (0.24 to 0.38)	0.51 (0.24 to 1.33)	0.42 (0.33 to 0.55)
Mean duration per hospitalization	2.41 (2.09 to 2.81)	2.12 (1.74 to 2.64)	2.20 (1.65 to 3.00)	2.62 (1.38 to 5.65)	3.94 (2.86 to 5.54)
Outpatient care per person and year					
Number of quarters with at least one outpatient utilization %† (95% CI‡)					
0	8.9 (7.6 to 10.4)	9.8 (7.8 to 12.0)	8.6 (6.1 to 11.9)	9.5 (4.7 to 16.4)	7.8 (4.9 to 12.2)
1	4.3 (3.4 to 5.5)	4.9 (3.6 to 6.5)	4.0 (2.3 to 6.5)	6.0 (2.3 to 12.5)	1.6 (0.4 to 4.8)
2	7.5 (6.3 to 8.9)	8.0 (6.3 to 10.0)	9.8 (7.2 to 13.3)	5.7 (2.4 to 10.9)	2.7 (1.0 to 5.8)
3	13.3 (11.8 to 15.0)	14.7 (12.6 to 17.3)	14.9 (11.5 to 18.8)	14.8 (8.5 to 22.7)	3.2 (1.3 to 6.7)
4	66.0 (63.7 to 68.2)	62.6 (59.5 to 65.7)	62.7 (57.8 to 67.4)	64.1 (54.6 to 73.1)	84.8 (79.2 to 89.3)
Mean number of outpatient contacts (multiple answers possible)† (95% CI‡)	9.29 (8.99 to 9.60)	8.99 (8.61 to 9.37)	9.08 (8.49 to 9.77)	8.40 (7.17 to 10.38)	10.89 (9.97 to 11.86)
Outpatient contacts with EBM reimbursement (German compensation scheme)	9.27 (8.97 to 9.57)	8.97 (8.59 to 9.35)	9.08 (8.48 to 9.77)	8.38 (7.16 to 10.36)	10.85 (9.93 to 11.81)
Outpatient contacts associated with costs for dialysis equipment	0.008 (0.002 to 0.024)	0.005 (0.000 to 0.026)	0.026 (0.000 to 0.095)	0.0	0.0
Outpatient contacts with extrabudgetary services	0.79 (0.72 to 0.87)	0.76 (0.68 to 0.87)	0.72 (0.58 to 0.88)	0.62 (0.38 to 0.96)	1.05 (0.81 to 1.36)
Other outpatient services	4.42 (4.21 to 4.62)	4.05 (3.81 to 4.31)	4.26 (3.86 to 4.72)	3.71 (2.92 to 5.19)	6.10 (5.44 to 6.83)
Medication per person and year (mean†, 95% CI‡)					
Mean number of total drugs	11.59 (11.02 to 12.20)	9.83 (9.18 to 10.55)	10.45 (9.53 to 11.56)	12.01 (9.42 to 16.96)	19.82 (17.90 to 22.11)
Mean number of cardiovascular drugs	4.06 (3.80 to 4.34)	3.22 (2.90 to 3.60)	3.97 (3.49 to 4.53)	4.83 (3.81 to 5.98)	7.25 (6.38 to 8.31)
Mean number of total drugs without antihyperglycemic drugs (ATC A10)	10.96 (10.41 to 11.52)	9.83 (9.18 to 10.55)	10.45 (9.53 to 11.56)	12.01 (9.42 to 16.96)	15.51 (13.89 to 17.50)

*Study period: four complete quarters before the follow-up examination (ie, 1 year).
†Age-standardized and sex-standardized; standard: German population 31 December 2006 (http://www.destatis.de).
‡BCA-method using bootstrap procedure.
ATC, anatomical therapeutic chemical; EBM, einheitlicher bewertungsmaßstab; HNR, Heinz Nixdorf Recall study.

Table 3 Description of costs, HNR study, Germany*

	Age-standardized and sex-standardized† proportions of persons with healthcare in % (95% CI‡)					Age–sex standardized† mean costs per person in €(95% CI‡)				
	Full sample (N=1709)	Normal fasting glycemia (N=951)	Impaired fasting glycemia (N=403)	Previously undetected diabetes (N=105)	Previously diagnosed diabetes (N=250)	Full sample (N=1709)	Normal fasting glycemia (N=951)	Impaired fasting glycemia (N=403)	Previously undetected diabetes (N=105)	Previously diagnosed diabetes (N=250)
Inpatient care per person and year										
Hospitalization	21.2 (19.3 to 23.2)	20.8 (18.3 to 23.5)	19.9 (16.1 to 24.0)	19.7 (12.6 to 28.2)	26.6 (21.3 to 32.9)	845 (741 to 975)	784 (652 to 954)	806 (593 to 1078)	1128 (487 to 3169)	1186 (879 to 1600)
Outpatient care per person and year										
Total outpatient contacts	91.1 (89.6 to 92.4)	90.2 (88.0 to 92.2)	91.4 (88.1 to 93.9)	90.5 (83.6 to 95.3)	92.2 (87.8 to 95.1)	782 (734 to 865)	720 (664 to 862)	847 (717 to 1152)	741 (591 to 963)	934 (844 to 1037)
Outpatient contacts with EBM reimbursement (German compensation scheme)	91.1 (89.6 to 92.4)	90.2 (88.0 to 92.2)	91.4 (88.1 to 93.9)	90.5 (83.6 to 95.3)	92.2 (87.8 to 95.1)	645 (616 to 678)	610 (573 to 652)	653 (594 to 728)	645 (520 to 832)	749 (676 to 841)
Outpatient contacts associated with costs for dialysis equipment	0.2 (0.0 to 0.4)	0.1 (0.0 to 0.5)	0.4 (0.0 to 1.6)	0.0	0.0	40 (13 to 116)	32 (0 to 169)	108 (0 to 393)	0.00	0.00
Outpatient contacts with extrabudgetary services	27.0 (25.0 to 29.1)	27.5 (24.8 to 30.4)	27.4 (23.0 to 31.9)	21.8 (14.0 to 30.3)	26.2 (20.6 to 32.2)	25 (20 to 32)	24 (18 to 35)	23 (15 to 43)	23 (8 to 81)	27 (18 to 54)
Other outpatient services	76.7 (74.6 to 78.7)	75.4 (72.5 to 78.2)	77.9 (73.5 to 82.0)	73.2 (63.5 to 80.7)	78.1 (71.9 to 83.3)	73 (64 to 83)	54 (44 to 67)	62 (47 to 91)	73 (41 to 131)	158 (134 to 187)
Medication per person and year										
Intake of drugs	84.8 (83.0 to 86.5)	83.7 (81.2 to 86.2)	83.6 (79.7 to 87.2)	83.9 (75.3 to 90.2)	89.4 (84.6 to 93.0)	379 (339 to 455)	305 (271 to 381)	382 (297 to 641)	342 (234 to 585)	641 (559 to 750)
Intake of drugs without antihyperglycemic drugs (ATC A 10)	84.6 (82.7 to 86.2)	83.7 (81.2 to 86.2)	83.6 (79.7 to 87.2)	83.9 (75.3 to 90.2)	87.8 (82.9 to 91.7)	352 (314 to 429)	305 (271 to 381)	382 (297 to 641)	342 (234 to 585)	457 (390 to 546)
Intake of cardiovascular drugs (ATC C)	54.4 (51.9 to 56.7)	47.5 (44.3 to 50.7)	55.8 (51.0 to 60.6)	61.3 (52.0 to 70.6)	75.6 (69.7 to 81.0)	109 (101 to 118)	86 (76 to 99)	110 (95 to 129)	111 (87 to 147)	201 (172 to 236)
Total direct healthcare per person and year										
Total direct healthcare	91.9 (90.3 to 93.1)	91.1 (89.0 to 93.0)	92.0 (88.9 to 94.5)	90.5 (83.6 to 95.3)	93.6 (89.5 to 96.2)	2006 (1859 to 2175)	1810 (1634 to 2035)	2035 (1732 to 2486)	2210 (1483 to 4279)	2761 (2378 to 3268)

*Study period: four complete quarters before the follow-up examination (ie, 1 year).
†Age-standardized and sex-standardized; standard: German population 31 December 2006 (http://www.destatis.de).
‡BCA-method using bootstrap procedures.
ATC, anatomical therapeutic chemical; BCA, bias corrected and accelerated; EBM, einheitlicher bewertungsmaßstab; HNR, Heinz Nixdorf Recall study.

Prescribed medication

More than four in five participants (84.8%; (83.0 to 86.5)) had at least one prescription during the study period. The mean annual number of prescriptions varied with diabetes stage (range NFG 9.8 (9.2 to 10.6) to previously diagnosed diabetes 19.8 (17.9 to 22.1); table 2). However, CIs between the previously diagnosed diabetes group and the other groups overlapped after exclusion of antihyperglycemic medication (previously diagnosed diabetes: 15.5 (13.9 to 17.5)). In the total study population, drugs for the cardiovascular system (ATC C) were prescribed by far most frequently (35.7%) as described in online supplementary OSM table S3.

Direct healthcare costs

Total direct healthcare costs (table 3) ranged between €1810 (1634 to 2035) for NFG and €2761 (2378 to 3268) for people with previously diagnosed diabetes.

Regarding the subcategories of healthcare costs, costs were consistently highest among people with previously diagnosed diabetes and lowest among people with NFG. Moreover, after the exclusion of antihyperglycemic drugs, medication costs remained highest among people with previously diagnosed diabetes. The order of costs between people with previously undetected diabetes and IFG varied; however, CIs were large and overlapping.

Results from regression analyses

Since differences between crude and age-adjusted and sex-adjusted CRs were marginal, crude CRs were not presented. Table 4 summarizes CRs as results from multiple regression analyses. Considering participants with NFG as the reference group, age-adjusted and sex-adjusted CRs of the other diabetes stages were comparatively higher. They were consistently increased among people with previously diagnosed diabetes compared with those with NFG. Among people with IFG, costs of outpatient care and medication were also significantly increased compared with people with NFG. However, no difference was seen with regard to costs of inpatient care and total costs. Furthermore, there was no statistically significant difference between people with previously undetected diabetes versus NFG regarding all cost categories.

Further adjustment resulted in smaller CRs for all diabetes stages. In the fully adjusted models, CRs remained significantly increased only among people with previously diagnosed diabetes compared with NFG (exception: inpatient care). In contrast, among people with IFG and previously undetected diabetes, there were no significant differences compared with NFG. The exception was medication costs, which were even significantly lower among people with previously undetected diabetes than among people with NFG (CR previously undetected diabetes vs NFG 0.70 (0.51 to 0.95)). A restriction of all regression analyses on the subgroup of participants with complete information regarding all included variables (n=1265) resulted in similar CRs (data not shown).

DISCUSSION

Stratifying healthcare utilization and related costs by diabetes stage, this population-based study enables for the first time multiple, extensively adjusted comparisons within and between the different healthcare sectors. On the basis of individually matched data from the statutory health insurance, total direct healthcare costs were most increased in people with previously diagnosed diabetes. Of interest and surprisingly, regarding the existing literature, excess costs in previously undetected diabetes and IFG (if any) were low compared with NFG.

Comparison with other studies

International comparisons are limited because of differences between healthcare systems and diabetes therapy, differences in the study design, cost analysis, and characteristics of the study population.

To the best of our knowledge, there is no study analyzing and comparing total healthcare costs and costs in different healthcare sectors stratified by diabetes stage including IFG and previously undetected diabetes. Furthermore, costs were predominantly reported in absolute figures without presenting adjusted CRs.

As early as 2000, Nichols *et al*[6] estimated direct excess medical care costs in the USA (reference: without impending diabetes) up to 8 years preceding type 2 diabetes diagnosis. Mean total excess costs (1998 $1205, ie, €1112), as well as inpatient (1998 $639, ie, €593), outpatient (1998 $390, ie, €363), and medical costs (1998 $177, ie, €164) reported by Nichols *et al*, were remarkably higher than for people with IFG and unknown diabetes in the present study. In addition, Zhang *et al*[4 5] reported excess costs (expressed as cost differences) for people with IFG and unknown diabetes, however, without presenting absolute costs in the groups. Again, the mean excess costs for people with previously undetected diabetes were remarkably higher (2007 $1745, ie, €1303) than in the HNR study, but excess costs for people with IFG (2009 $443, ie, €321) were lower than reported by Nichols *et al* and slightly higher than in the HNR study (2008 €225). The corresponding unadjusted total CR of people with IFG compared with those without diabetes in the studies of Nichols would be 1.5, that is, higher than in the HNR study. Maybe the lower CR in the HNR study is due to a high healthcare use in people with NFG, which could be explained by the relatively older population, and a high level of healthcare seeking in Germany in general.[22]

Previous analyses of drug prescriptions in Germany during the years preceding diabetes diagnosis (1993–2002) showed 21%/28% higher prescription costs for men/women before diabetes diagnosis.[7] Recently, medication costs by glucose tolerance stage were estimated in the southern German population-based KORA (Cooperative Health Research in the Region of Augsburg) follow-up study.[16 23] The higher age-adjusted and sex-adjusted medication CRs (when compared with the results of this study) may be explained by differences

Table 4 Multivariate CRs of healthcare costs—results of the two-part models

	Impaired vs normal fasting glycemia	Previously undetected diabetes vs normal fasting glycemia	Previously diagnosed diabetes vs normal fasting glycemia
Inpatient care per person and year			
Model 1	0.97 (0.69–1.36)	1.31 (0.73–2.35)	1.49* (1.05–2.11)
Model 2	0.90 (0.63–1.28)	1.31 (0.73–2.36)	1.45 (1.02–2.06)
Model 3	0.95 (0.67–1.35)	1.07 (0.58–1.95)	1.53* (1.06–2.22)
Model 4	0.87 (0.59–1.30)	1.15 (0.57–2.35)	1.41 (0.92–2.17)
Outpatient care per person and year			
Model 1	1.14* (1.02–1.28)	1.03 (0.85–1.26)	1.29* (1.12–1.47)
Model 2	1.02 (0.91–1.14)	1.07 (0.88–1.30)	1.28* (1.12–1.47)
Model 3	1.01 (0.90–1.14)	1.11 (0.91–1.35)	1.31* (1.14–1.52)
Model 4	1.05 (0.94–1.19)	1.00 (0.81–1.23)	1.37* (1.18–1.59)
Medication per person and year			
Model 1	1.28* (1.09–1.51)	1.01 (0.77–1.35)	2.03* (1.68–2.45)
Model 2	1.14 (0.96–1.35)	0.83 (0.62–1.11)	1.99* (1.63–2.42)
Model 3	1.08 (0.91–1.29)	0.69* (0.52–0.93)	1.72* (1.40–2.11)
Model 4	0.93 (0.78–1.12)	0.70* (0.51–0.95)	1.52* (1.23–1.89)
Total direct healthcare per person and year			
Model 1	1.09 (0.95–1.25)	1.16 (0.91–1.47)	1.53* (1.30–1.80)
Model 2	1.00 (0.87–1.15)	1.12 (0.88–1.43)	1.51* (1.27–1.79)
Model 3	1.00 (0.87–1.15)	0.98 (0.76–1.26)	1.49* (1.25–1.78)
Model 4	0.94 (0.80–1.09)	1.01 (0.77–1.34)	1.37* (1.13–1.66)

*p<0.05.
Model 1: adjusted for age and sex (N=1709, thereof N_{NFG}=951 (55.6%), N_{IFG}=403 (23.6%), $N_{undetected\ diabetes}$=105 (6.1%), $N_{diagnosed\ diabetes}$=250 (14.6%)).
Model 2: Model 1+additional adjustment for birth in a foreign country (baseline study), living with a partner, equivalent income (N=1589, thereof N_{NFG}=877 (55.2%), N_{IFG}=383 (24.1%), $N_{undetected\ diabetes}$=98 (6.2%), $N_{diagnosed\ diabetes}$=231 (14.5%)).
Model 3: Model 2+additional adjustment for hypertension, stroke, myocardial infarction, BMI (N=1581, thereof N_{NFG}=874 (55.3%), N_{IFG}=381 (24.1%), $N_{undetected\ diabetes}$=97 (6.1%), $N_{diagnosed\ diabetes}$=229 (14.5%)).
Model 4: Model 3+additional adjustment for total direct healthcare costs in the four complete quarters before the index year (N=1265, thereof N_{NFG}=693 (54.8%), N_{IFG}=311 (24.6%), $N_{undetected\ diabetes}$=76 (6.0%), $N_{diagnosed\ diabetes}$=185 (14.6%)).
CRs, cost ratios; NGV, normal fasting glycemia; IFG, impaired fasting glycemia.

in the definitions of IFG and previously undetected diabetes (based on oral glucose tolerance tests in the KORA study vs fasting glucose in the HNR study) associated with different susceptibility to diseases,[24 25] differences in the assessment of medication (KORA: inclusion of non-prescription medication) and regional differences in drug therapy.[26 27]

Study limitations and strengths

Several limitations have to be considered. First, the generalizability of the analyzed data may be limited because severely ill or disabled people as well as institutionalized people were not included in the HNR study. This may explain the relatively low absolute costs. Furthermore, health insurance data were available only for a subsample of the HNR study participants and participants with claims data differed from those without claims data according to age and sex. This finding was expected, since statutory health insurances in Germany contract different population groups.[28] However, the analyses were based on data from statutory health insurances from various areas and it is not likely that CRs between the diabetes stages are affected. Moreover, CRs were adjusted for age, sex, socioeconomic status, and a number of additional variables. Second, since the date of diabetes onset was not known for people with newly diagnosed diabetes at follow-up, misclassification regarding the diabetes stage of these participants during the study period cannot be ruled out. In addition, missing repeated measurement of fasting plasma glucose values may have diluted differences between people with IFG and unknown diabetes. Third, the cost estimates and CRs are uncertain as reflected by large CIs. Additionally, healthcare costs may have been underestimated, because the costs of remedies, adjuvants, transportation, and dentistry care were not available.

The strengths of the study are the population-based sample of participants, the link and joint analysis of clinical data and data from the main German statutory health insurances enabling more valid estimates of healthcare utilization and costs than by using self-reported data, and the presentation of results stratified by diabetes stage which has been identified by fasting plasma glucose testing.

In conclusion, using data from various German statutory health insurances supplemented by individual data

from a population-based study, healthcare utilization and associated costs were quantified for the first time in people with normal fasting glycemia, impaired fasting glycemia, previously undetected diabetes, and previously diagnosed diabetes. Although age-standardized and sex-standardized direct medical costs were highest for people with previously diagnosed diabetes, the remarkable increase in healthcare costs for people with IFG or previously undetected diabetes reported in the USA was not reproduced in Germany. Given the increasing prevalence of diabetes and its precursors, these data provide useful information for the model-based evaluation of screening programs and interventions to prevent diabetes onset or improve diabetes therapy.

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Contributors CB. designed the study, assisted in the analyses, and wrote the manuscript. HC. processed the data and conducted the statistical analysis. SA. contributed to the data acquisition, assisted in the data processing, and reviewed the manuscript. MB. assisted in the data processing and reviewed the manuscript. CMD. contributed to the monetary evaluation and reviewed the manuscript. US. and UR. managed the data and assisted in the data processing and analysis. SM and KHJ. are members of the investigative groups of the HNR study; they contributed to the data acquisition and reviewed the manuscript. AI. is the principal investigator of the study and contributed to every aspect of this article. AI is the guarantor of this work and, as such, takes responsibility for the work as a whole, including the study design, access to the data, and the decision to submit and publish the manuscript.

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