ROBERT KOCH INSTITUT

PROJEKT BURDEN 2020

Methodological report on the quantification of burden of disease indicators in the project BURDEN 2020 – disease frequencies, severities, durations, disability weights and sensitivity analyses

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1. Introduction

Under the leadership of the Robert Koch Institute (RKI) the "BURDEN 2020 Project - The Burden of Disease in Germany at the national and regional level" was dedicated to the development of a national Burden of Disease study for Germany. Cooperation partners were the Federal Environmental Agency (UBA) and the Scientific Institute of AOK (WIdO). The project term extended from April 2018 to June 2021. BURDEN 2020 was funded by the Innovation Fund at the Federal Joint Committee (G-BA) (funding code: 01VSF17007). The demographic change and the increasing need for care and prevention in the population require a reliable data base to comprehensively and comparably map the burden of disease in the population on a national and regional level.

To fill this gap, the BURDEN 2020 project developed a Burden of Disease study for Germany and at the national and regional level, that include the health measures Years of life lost (YLL) and Years lived with disability (YLD). This information on mortality and morbidity can be combined in the summary measure DALY (Disability adjusted life years) to the overall burden of disease. The method for calculating the burden of disease is based on the Global Burden of Disease (GBD) study, who's origin lies with the World Health Organisation (WHO) and that is conducted by the Institute for Health Metrics and Evaluation (IHME).

With respect to mortality, BURDEN 2020 included all ICD-10-coded causes of death while in the domain of morbidity, it is initially limited to a selection of important diseases. The main aim is a transparent information system that supports a demand-oriented, expedient and economical decision-making in politics and the health care system (https://www.daly.rki.de/). In addition, the methods and results are described in detail in scientific publications [1-15].

This document is to be understood as a methodological companion to the article "The Burden of Disease in Germany at the National and Regional Level-Results in Terms of Disability–Adjusted Life Years (DALY) from the BURDEN 2020 Study" [7]. It provides deeper insight into various sub-aspects of the morbidity-related burden of disease in the context of the BURDEN 2020 project and allows the interested reader to fully obtain information on the genesis of all variables included in the calculation of Years lived with disability (YLD). These "input variables" include prevalence, incidence or rates, severity distributions, disease durations, and disability weights. Further steps were necessary to calculate the input variables, which are seen as preliminary work in the course of presenting the results.

In the BURDEN 2020 project, it was only possible to include a selection of diseases (see Table 1) that can be found on the so-called level 3 of the nomenclature of the GBD study [16]. A grouping on level 2 and higher is not possible for the field of morbidity, because not all diseases belonging to the respective level could be included. For example, only diabetes mellitus (level 3) was selected for the project but not chronic kidney disease (level 3), which are, however, jointly assigned to the entity diabetes mellitus and chronic kidney disease (level 2). A detailed overview of the level hierarchy is given in Table 2. Some of the entities can be further subdivided to level 4 or, for the purpose of calculation, to level 5. In the latter presentation, results will be reported up to level 4 at most.

Table 1: Selected burden of disease causes used to calculate years lived with disability (YLD); listed by proportion of all DALYs in 2017

Ranking	burden of disease causes (level 3)	share and DALY total for Germany (in %)
1	ischemic heart disease	9,3
2	low back pain	6,6
3	tracheal, bronchus, and lung cancer	4,0
4	stroke	4,0
5	chronic obstructive pulmonary disease (COPD)	3,9
6	Alzheimer's disease and other dementias	3,6
7	diabetes mellitus	2,9
8	headache	2,7
9	neck pain	2,3
10	depressive disorders	2,2
11	colon and rectum cancer	2,1
12	anxiety disorders	1,9
13	breast cancer	1,7
14	alcohol use disorders	1,3
15	road injuries	1,3
16	lower respiratory infections	1,2
17	prostate cancer	1,0
18	hypertensive heart disease	1,0
	Total	**53**

[1] The results fluctuate due to methodological adjustments within the GBD study and are also recalculated for earlier vintages with each wave; the exact values reported here can therefore no longer be found in the information systems of the GBD study.
[2] From the use of road injuries statistics, the operationalization of "road traffic accidents" (level 3) also resulted in the group of "other transport injuries" (level 3). These are not explicitly listed here because they are a residual category and were not originally selected as an entity for the project. For the operationalization of road injuries, see chapter 3.18.

Section 2 of the methodological report presents a procedure for disaggregating epidemiological measures (prevalence, incidences, or rates) from larger age ranges into 5-year age groups. The metrics in the larger age ranges are available at www.krankheitslage-deutschland.de [2, 3], which then form the basis of the YLD calculation after disaggregation.

In *section 3*, further detailed definitions and data sources are given for each disease or injury (in short, burden of disease cause) selected in the project and for each input variable in the context of so-called disease models. For some burden of disease causes, it was necessary to consult additional, external sources or to perform our own calculations. The reader is also provided with tables on severity distributions, disability weights and disease durations.

In this methodological report, the uncertainty concept is presented in *section 4*. Uncertainty intervals in the estimation occur both in the redistribution of ill-defined causes of death to valid ones and in the merging of different epidemiological measures such as prevalence or incidences, severities, and episode durations. This

section also discusses how to combine these intervals into the DALY. A stochastic simulation was used to calculate the uncertainty intervals for the outcomes YLD and DALY.

Section 5 presents a procedure (microsimulation) that addresses the problem of multimorbidity in estimating the morbidity-related burden of disease component YLD. Because individuals may suffer from multiple conditions, a correction must be made when determining the years of life spent with health limitations. This prevents overestimation of YLD. *Section 6* discusses the diagnostics of the simulation in more detail. A comparison of the results between the unadjusted and adjusted YLD is given in *Section 7*.

Furthermore, results of a sensitivity analysis on the YLD are presented and discussed in *section 8*. In calculating the input variables, decisions have to be made about the definition and estimation of the individual components. In the sensitivity analysis, two variants of the system are contrasted, based on different assumptions regarding disease durations.

Table 2: Overview about the diseases under consideration within the level hierarchy (morbidity component)

level 1	level 2	level 3	level 4
communicable, maternal, neonatal, and nutritional diseases	respiratory infections and tuberculosis	lower respiratory infections	→ lower respiratory infections
		[...]	
	[...]		
Non-communicable diseases	neoplasms	colon and rectum cancer	→ colon and rectum cancer
		tracheal, bronchus, and lung cancer	→ tracheal, bronchus, and lung cancer
		breast cancer	→ breast cancer
		prostate cancer	→ prostate cancer
		[...]	
	cardiovascular diseases	ischemic heart disease	→ ischemic heart disease
		stroke	ischemic stroke
			intracerebral hemorrhage
			subarachnoid hemorrhage
		hypertensive heart disease	→ hypertensive heart disease
		[...]	
	chronic respiratory diseases	chronic obstructive pulmonary disease	→ chronic obstructive pulmonary disease
		[...]	

level 1	level 2	level 3	level 4
	neurological disorders	Alzheimer's disease and other dementias	→ Alzheimer's disease and other dementias
		headache disorders	migraine
			tension-type headache
		[...]	
	mental disorders	depressive disorders	major depressive disorder
			dysthymia
		anxiety disorders	→ anxiety disorders
		[...]	
	substance use disorders	alcohol use disorders	→ alcohol use disorders
		[...]	
	diabetes and kidney diseases	diabetes mellitus	diabetes mellitus Typ 1
			diabetes mellitus Typ 2
		[...]	
	musculoskeletal disorders	low back pain	→ low back pain
		neck pain	→ neck pain
		[...]	
	[...]		
injuries	transport injuries	road injuries	pedestrian road injuries
			cyclist road injuries
			motorcyclist road injuries
			motor vehicle road injuries
			other road injuries
		other transport injuries	→ other transport injuries
	[...]		

2. Disaggregation of the epidemiological indicators used and modeling of the uncertainty interval

2.1. Procedure for disaggregation of epidemiological indicators into 5-year age groups

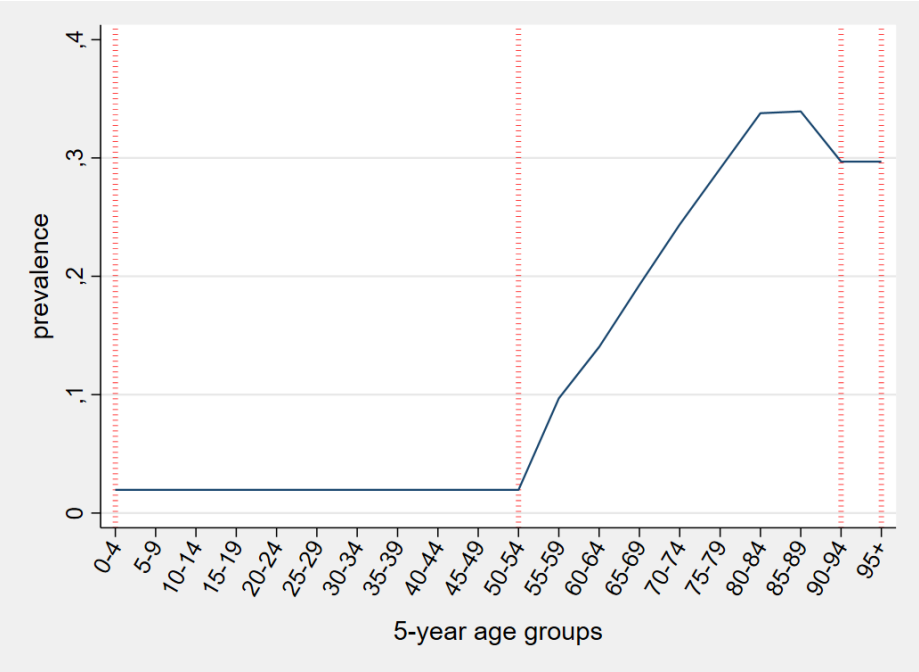
An essential input variable of the YLD calculation is the disease frequency in the form of epidemiological measures such as prevalence, incidences or rates. In the BURDEN 2020 project, both survey data from the RKI and routine health insurance data from the AOK were used to estimate these indicators. For the routine health insurance data, it must be taken into account that the insured persons of the AOKs is not a representative sample of the population [1]. Therefore, for the generation of the epidemiological measures used in the BURDEN 2020 project, the routine health insurance data were extrapolated to the population according to age, gender and morbidity structure, starting from the insured persons of the AOKs [1].

Due to low case numbers in some cases, this method requires age groups to be aggregated into age ranges (see horizontal lines Figure 1). In the survey data, the results in higher age groups were also subject to high uncertainty due to the small sample size. The goal of the BURDEN 2020 project was to provide results on the burden of disease in 5-year age groups. To achieve this, a procedure was developed to allow simple disaggregation of epidemiological measures starting from aggregated age ranges of 5-year age groups. This procedure was also used to model prevalence in the older age groups from the survey data.

The disaggregation procedure involves four steps:

A. Assumption of a "true" age distribution and calculation of growth rates along the age groups
B. Localization of the ranges of values to be disaggregated and identification of (initial) "valid" values
C. Application of the growth rates in the respective age groups
D. (Marginal)adjustment of the disaggregated outcomes to the overall estimator of the age range from the original, morbidity-adjusted extrapolation of the AOK routine data or from the survey data, respectively

Figure 1: Exemplary age distribution of type 2 diabetes with the aggregated age ranges (AOK routine data morbidity-adjusted [1], both sexes, Germany), the value ranges to be adjusted are marked in red (shown as vertical lines).



The procedure (step A) uses as an assumption a previously defined "true" age distribution (see Figure 2 for the example of type 2 diabetes). The term "true" is intended to express that the distribution of prevalence, incidence, or rate across age groups is known and thus given. The disaggregation of epidemiological measures is thus dependent on the choice of the "true" age curve. In the figures, this is exemplified by GBD prevalence[2]. In the actual analysis for the calculation of the YLD, the non-morbidity-adjusted progressions of the AOK insured persons were used[3], which are included in the procedure in a gender-specific manner. On the basis of the "true" histories of prevalence, incidences or rates (in short, outcome), growth rates are calculated, whereby a fundamental distinction is made as to whether a calculation is in higher or younger age groups. The calculation is based on the following formulas:

Table 3: Formulas for calculating the growth rates

Growth rates for the younger age groups	Growth rates for the older age groups
$\Delta_j = \frac{Outcome_{w,j} - Outcome_{w,j-1}}{Outcome_{w,j-1}}$	$\Delta_j = \frac{Outcome_{w,j} - Outcome_{w,j+1}}{Outcome_{w,j+1}}$

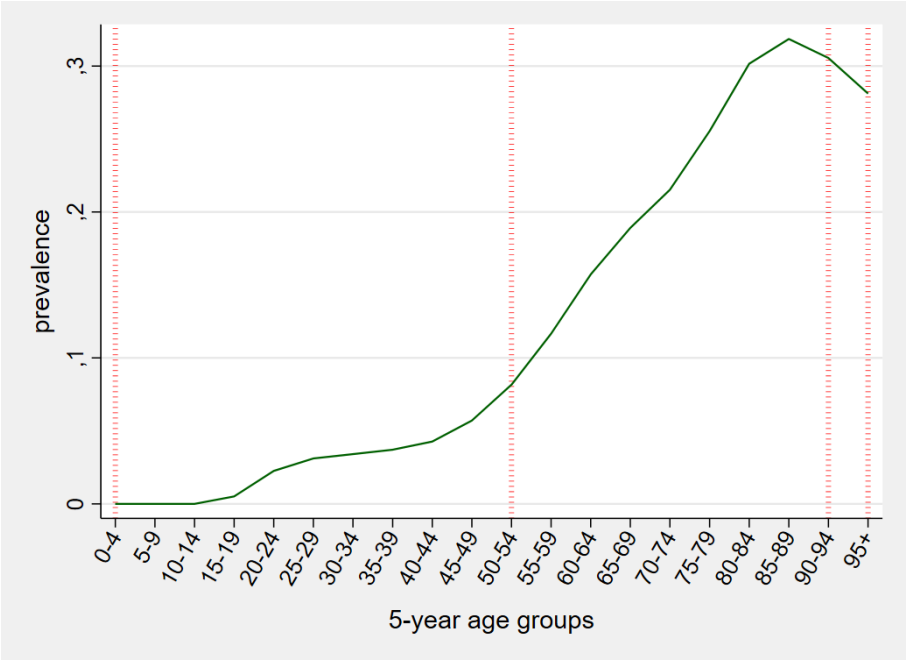
Where the index w indicates the "true" age distribution and j indicates the age group.

[1] Available at *krankheitslage-deutschland.de.*

[2] Taken from the 2017 GBD study. The data are no longer available in this form via the website https://vizhub.healthdata.org/gbd-results/, as all previous years are recalculated with each update of the GBD results (most recent study: GBD 2019). 17. Institute for Health Metrics and Evaluation (IHME). *Global Health Data Exchange. GBD Results Tool*. 2022 21.01.2022)]; Available from: http://ghdx.healthdata.org/gbd-results-tool.

[3] Due to data protection requirements, these results are not shown here.

Figure 2: Exemplary representation of a "true" age distribution for the prevalence of type 2 diabetes; the prevalence are taken from the GBD Study 2017 for Germany (reporting year 2017, both sexes, Germany).



In the next step (B), the value ranges for which the calculation of prevalence (5-year-age groups) is to be performed are localized. The localization is necessary for the direction, thus for the disaggregation in younger or higher age groups. The calculation itself is then performed using so-called "valid" values, where the term "valid" here means age-group-specific estimates of prevalence, incidences, or rates (see Figure 1, in the range between 55-59 and 85-89 years of age, the values are already available in "valid" 5-year age groups). Based on these "valid" values, in the next step (C) the growth rates are then applied to the aggregated ranges (see Figure 1, ranges between 0-4 and 50-54 and between 90-94 and 95+) to model a possible age curve. The following formulas were used for this purpose:

Table 4: Application of the growth rates to the aggregated value ranges

Extrapolation to younger age groups	**Extrapolation to higher age groups**
$Outcome_{d,j} = Outcome_{g,j+1} + (\Delta_j * Outcome_{g,j+1})$	$Outcome_{d,j} = Outcome_{g,j-1} + (\Delta_j * Outcome_{g,j-1})$

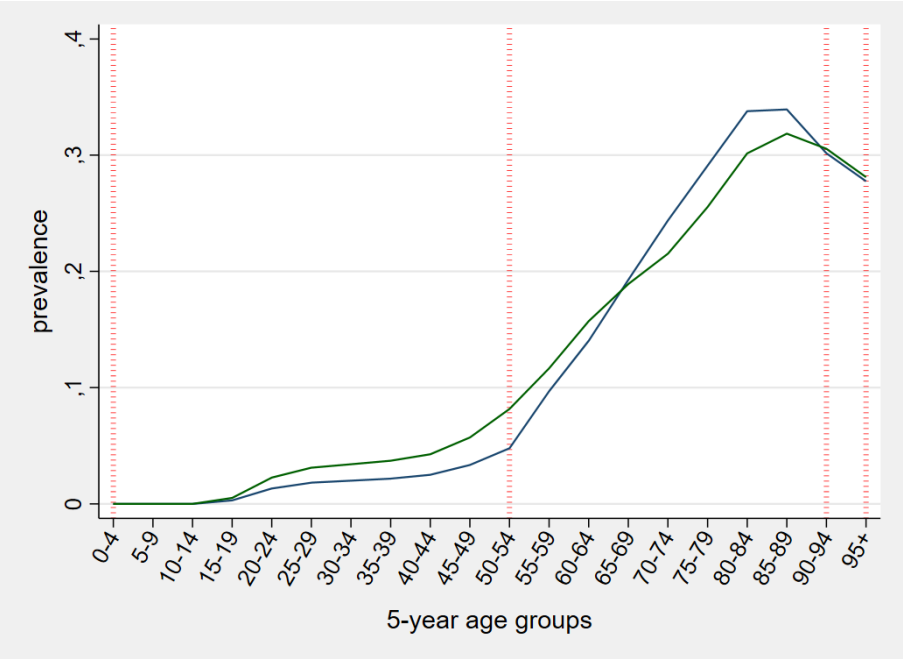
Where index d represents disaggregated outcomes, g represents "valid" values, and j represents age group.

The age distributions are extrapolated step by step: Starting from the last "valid" value (in the example, the prevalence estimates in the 55-59 and 85-89 age groups), the formulas in Table 4 are applied to both the higher and younger age groups until all values have been disaggregated. The resulting values are again considered "valid" in the stepwise approach and applied to each subsequent age group. Since an overall morbidity-adjusted estimate of the outcome is available for the aggregated value ranges, a (marginal)adjustment (step D) of the individual disaggregated values ($Outcome_{d,j}$) can be made to the overall estimator. This is done by multiplying these values by a sex-specific, age-group constant factor, which is the quotient of the overall estimator ($Outcome_{m,\hat{j}}$) and the sum of the disaggregated values ($\sum_{j=1}^{\hat{j}} Outcome_{d,j}$), for the respective age range ($\hat{j}$). In summary, the following formula was applied:

$$\text{Outcome}_{c,j} = \text{Outcome}_{d,j} * \frac{\text{Outcome}_{m,\hat{j}}}{\sum_{j=1}^{\hat{j}} \text{Outcome}_{d,j}}$$

Where index c represents the (margin-)adjusted estimate of the outcome, d represents the disaggregated, non (margin-)adjusted values, m represents the original morbidity-adjusted values, j represents the age group, and ĵ represents the aggregated age group ranges.

Figure 3: Result of disaggregation (blue curve: disaggregated WIdO prevalence; green: "true" age curve taken from the GBD study 2017).



As a result (see Figure 3), the procedure models the shape of an alternative curve, but equally ensures that the sum of the individual age-group-specific (disaggregated) point estimates is equal to the value for the age range from the morbidity-adjusted estimate (adjusting the level of the curve).

In a few cases, there were no specific values for a 5-year age group (so to speak no "valid" values) in the morbidity-adjusted age distributions. This can be attributed to the fact that the number of cases in the 5-year age groups was always too low for extrapolation and therefore age groups had to be combined for the entire age range. As a result, the described procedure could not be fully implemented. As a solution, the "true" trajectories were fully applied to the outcomes. The "true" values (alternative age progression, $\text{Outcome}_{w,j}$) were scaled via a factor to the overall estimates ($\text{Outcome}_{m,\hat{j}}$) of the morbidity adjustment as follows:

$$\text{Outcome}_{c,j} = \text{Outcome}_{w,j} * \frac{\text{Outcome}_{m,\hat{j}}}{\sum_{j=1}^{\hat{j}} \text{Outcome}_{w,j}}$$

Where index c represents the (margin-)adjusted estimate of the outcome, m represents the original morbidity-adjusted values, j represents the age group, and ĵ represents the aggregated age group ranges.

Furthermore, using survey data resulted in uncertain point estimates in the older age groups. A prediction of the point estimates was solved with the procedure described above using the four steps outlined. The GBD survey data were used as the "true" trajectories. The age-unspecific overall estimators based on the survey data were used as a (marginal) adjustment.

2.2. Modeling the uncertainty interval (UI)

In addition to the point estimates for the 5-year age groups (see 2.1), a simple procedure was also used to derive a 95% uncertainty interval (UI). The basis of this modeling is both the UIs from the AOK measures extrapolated to the population and those from the survey data. Analogous to the procedure already outlined for calculating the point estimates, "valid" values (in this case bounds) were first identified, which are used as the basis for the modeling. In the first step (A), the variability of the UI at these "valid" points is first determined by calculating the deviation α_i as the relative distance of the lower or upper bound of the UI from the point estimator:

lower bound	upper bound
$\alpha_{lb} = \frac{\hat{\mu}_g - \hat{\mu}_{g,lb}}{\hat{\mu}_g}$	$\alpha_{ub} = \frac{\hat{\mu}_{g,ub} - \hat{\mu}_g}{\hat{\mu}_g}$

The deviation α_i is applied to all disaggregated points. The index i takes the value lb (lower bound) or ub (upper bound) and the index g refers to the "valid" values.

These so-called base deviations α_i were adjusted in the second step (B) using two assumptions: (B.1) The higher the prevalence, incidence or rate (for short, outcome) seen relative to the population, the more certain the point estimate. This weighting factor δ_j was calculated over the point estimates from the first modeling (after disaggregation, $\text{Outcome}_{c,j}$) by age (index j) and sex. By subtracting 1, the following statement can be made in the overall formula: The lower (rarer) the outcome, the closer δ_j is to 1, and thus the estimated bound becomes larger.

$$\delta_j = 1 - \text{Outcome}_j$$

(B.2) The larger the (relative) population, the more certain the point estimate. This weighting factor $\theta_j$was determined over the population of each age group in the total population. By subtracting 1, the following statement can be made in the overall formula: The lower the population proportion, the closer θ_j is to 1, and thus the larger the estimated bound.

$$\theta_j = 1 - \text{share population}_j$$

Both assumptions combined can be interpreted as follows (C): The higher (more frequent) the outcome and the larger the population, the lower the bound. This combined weight $\hat{\alpha}_{i,j}$ was derived via a multiplicative formula from all the above parameters $\alpha_{i,j}$, δ_j and θ_j as follows:

$$\hat{\alpha}_{i,j} = 1 - ((1 - \alpha_{i,j}) * (1 - (\alpha_{i,j} * \delta_j * \theta_j)))$$

In the following table, assumption (C) is illustrated by a calculated example. The following parameters were assumed (for α_{lb}= 0.5):

Outcome high: δ = 0.6 (prevalence = 0.4).
Outcome low: δ = 0.95 (prevalence = 0.05).
Share of population high: θ = 0.77 (proportion = 0.23)
Share of population low: θ = 0.95 (proportion = 0.05).

This leads to the following exemplary deviations for $\hat{\alpha}_{lb}$:

$\hat{\alpha}_{lb}$	Share population high; θ low: 0,77	Share population low; θ high: 0,95
Outcome often; δ low: 0,6	0,6155	0,6425
Outcome rare; δ high: 0,95	0,6829	0,7256

It can be seen that the deviation $\hat{\alpha}_{i,j}$ is lower for a high prevalence as well as a high population proportion than for a low prevalence and a low population proportion. In all cases, however, the variances are larger than the baseline variance. Thus, modeling uncertainty across the above parameters is not determined additively, but converges to the limit 1 (= level is identical to the baseline deviation α_i). By assumption, the deviation $\hat{\alpha}_{i,j}$ is necessarily larger than $\alpha_{i,j}$, since δ_j and θ_j never reach the value 1, but are always below it, depending on the value.

From the formula for the base deviation α_i (A), the upper and lower bounds at the respective disaggregated point can now be derived via transformation by replacing the result for α_i in the first equation for $\hat{\alpha}_{i,j}$ and using the age-group-specific point estimators $\hat{\mu}_{c,j}$ (see section 2.1) for the "valid" outcome ($\hat{\mu}_g$). For the upper bound, addition is used, and for the lower bound, subtraction of the weighted variance from $\hat{\alpha}_{i,j}$ and $\hat{\mu}_{c,j}$.

$$\hat{\mu}_{c,i,j} = \hat{\mu}_{c,j} +/- (\hat{\alpha}_{i,j} * \hat{\mu}_{c,j})$$

The described methodology was chosen in order to be able to provide results during the BURDEN 2020 project despite the limited human and time resources. For future developments, it would be necessary to affirm the calculation of the point estimators and their 95% UIs via alternative methods.

3. Disease Models – Profiles

3.1. Hypertensive heart disease

level	disease/cause
3	hypertensive heart disease

3.1.1. Prevalence

- Age restriction: no calculation for under 25-year-olds (both sexes, expert opinion from the RKI)
- Data source: WIdO [2]
- Definition: see indication profile hypertensive heart disease [3]
- Temporal definition: 12-month prevalence
- Age distribution adjusted (see 2)

3.1.2. Severity distribution

- Data source: WIdO [2]
- Definition: indication profile hypertensive heart disease [3]

3.1.3. Disability Weights

- Data source: GBD-Study [16]

3.1.4. Duration

- N/A

3.1.5. Input variables

Disease / cause	Severity	Severity distribution and disability weights					
		sev	95% UI		dw	95% UI	
			down	top		down	top
hypertensive heart disease (HHD)	Mild heart failure due to hypertensive heart disease	61.3%	61.1%	61.4%	0.041	0.026	0.062
	Moderate heart failure due to hypertensive heart disease	18.3%	18.1%	18.4%	0.072	0.047	0.103
	Severe heart failure due to hypertensive heart disease	20.5%	20.4%	20.6%	0.179	0.122	0.251

3.2. Ischemic heart disease

level	disease/cause
3	ischemic heart disease
5	myocardinal infarction (MI)
5	angina pectoris (AP)
5	heart failure (HF)

3.2.1. Prevalence

- Ischemic heart disease is composed of three diseases, namely myocardial infarction (MI), angina pectoris (AP) and heart failure (HF)
- Age restriction: no calculation for MI < 25 years and for HF < 25 years; for AP no age restriction
- Data source: WIdO [2]
- Definition of disease: see indication profiles for myocardial infarction, angina pectoris, and heart failure [3]
- Temporal definition: MI is 12-month case rate per 100,000 population (was converted to prevalent cases by adding population numbers), AP is 12-month prevalence, HF is 12-month prevalence
- Age distribution adjusted (see 2.)

3.2.2. Severity distribution

- Data source: MI and HF based on data from WIdO [2], distribution for AP based on GBD study [18]
- Definition: indication profiles for myocardial infarction and heart failure [3], angina pectoris in the GBD study [16]
- The severity of myocardial infarction is a special case in the method, since it does not correspond to a classical distribution that can be summed up to 100%. In myocardial infarctions, mortality, and thus the burden of disease due to morbidity, is highly dependent on the time in days after an infarction. To adequately reflect the burden of disease due to morbidity, each case passes through both degrees of severity, which should be viewed and interpreted in a temporal sequence. The respective percentage corresponds to the proportion of patients with myocardial infarction who were still alive within the time window considered (within the first 2 days or between 3 and 28 days) and thus spent time with health impairment. The temporal sequence is evident from this, as the proportion of cases in which patients survived the infarction event decreases with time. Cases in which patients were alive after more than 28 days of the myocardial infarction event are considered asymptomatic [see 16].

3.2.3. Disability Weights

- Data source: GBD-Study [16]

3.2.4. Duration

- To adequately reflect the time spent with health impairment due to a myocardial infarction, the average number of days with impairment were further determined for the respective severity level. For the severity level "acute myocardial infarction (first 2 days)" an average duration of 2 days per

year and for the severity level "acute myocardial infarction (3 to 28 days)" an average duration of 26 days per year was assumed [3].

3.2.5. Input variables

Disease / cause	Severity	Severity distribution and disability weights					
		sev	95% UI		dw	95% UI	
			down	top		down	top
myocardinal infarction	Acute myocardial infarction (first 2 days)	96.0%	95.8%	96.1%	0.432	0.288	0.579
	Acute myocardial infarction (3 to 28 days)	89.5%	89.3%	89.8%	0.074	0.049	0.105
angina pectoris	Asymptomatic angina due to ischemic heart disease	30.5%	27.9%	33.0%	0	0	0
	Mild angina due to ischemic heart disease	24.0%	16.7%	30.9%	0.033	0.02	0.052
	Moderate angina due to ischemic heart disease	12.6%	8.9%	16.7%	0.08	0.052	0.113
	Severe angina due to ischemic heart disease	33.0%	27.3%	39.2%	0.167	0.11	0.24
heart failure	Mild heart failure due to ischemic heart disease	63.8%	63.7%	63.9%	0.041	0.026	0.062
	Moderate heart failure due to hypertensive heart disease	18.1%	18.0%	18.2%	0.072	0.047	0.103
	Severe heart failure due to hypertensive heart disease	18.1%	18.0%	18.2%	0.179	0.122	0.251

3.3. Stroke

level	disease/cause
3	stroke
4	ischemic stroke
4	intracerebral hemorrhage
4	subarachnoid hemorrhage

3.3.1. Prevalence

- The disease stroke is composed of three types of stroke, namely ischemic stroke, intracerebral hemorrhage and subarachnoid hemorrhage
- There is no differentiation between acute and chronic strokes
- Age restriction: none
- Data source: (1) estimate of stroke prevalence overall and (2) proportion of the three stroke types in the overall estimate, WIdO [2]
- Definition of the disease: see indication profiles on stroke [3]
- Temporal definition: 10-year prevalence (from acute and chronic strokes).
- Age distribution adjusted (see 2.)

3.3.2. Severity distribution

- Data source: GBD study [16, 18]
- Definition: GBD study [16, 18]

3.3.3. Disability Weights

- Data source: GBD study [16, 18]

3.3.4. Duration

- N/A

3.3.5. Input variables

Disease / cause	Severity	Severity distribution and disability weights					
		sev	95% UI		dw	95% UI	
			down	top		down	top
intracerebral hemorrhage	asymptomatic	10.4%	0.0%	46.4%	0	0	0
	severity level 1	42.1%	12.5%	71.4%	0.019	0.01	0.032
	severity level 2	22.8%	0.0%	53.3%	0.07	0.046	0.099
	severity level 3	20.1%	0.0%	44.7%	0.316	0.206	0.437

	severity level 4	3.9%	0.0%	22.2%	0.552	0.377	0.707
	severity level 5	0.8%	0.0%	11.1%	0.588	0.411	0.744
ischemic stroke	asymptomatic	18.6%	9.5%	29.9%	0	0	0
	severity level 1	42.8%	32.4%	52.8%	0.019	0.01	0.032
	severity level 2	22.7%	14.4%	31.5%	0.07	0.046	0.099
	severity level 3	11.7%	5.0%	19.4%	0.316	0.206	0.437
	severity level 4	1.6%	0.0%	4.6%	0.552	0.377	0.707
	severity level 5	2.5%	0.7%	5.4%	0.588	0.411	0.744
subarachnoid hemorrhage	asymptomatic	10.4%	0.0%	46.4%	0	0	0
	severity level 1	42.1%	12.5%	71.4%	0.019	0.01	0.032
	severity level 2	22.8%	0.0%	53.3%	0.07	0.046	0.099
	severity level 3	20.1%	0.0%	44.7%	0.316	0.206	0.437
	severity level 4	3.9%	0.0%	22.2%	0.552	0.377	0.707
	severity level 5	0.8%	0.0%	11.1%	0.588	0.411	0.744

3.4. Diabetes mellitus

level	disease/cause
3	diabetes mellitus
4	diabetes mellitus type 1 (DT1)
4	diabetes mellitus type 2 (DT2)

3.4.1. Prevalence

- The disease diabetes mellitus is further subdivided into type 1 and type 2 diabetes
- Age restriction: DT1 none, DT2 none calculation < 10 years (expert opinion)
- Data source: WIdO [2]
- Disease definition: see indication profile for diabetes mellitus [3]
- Temporal definition: 12-month prevalence.
- Age distribution adjusted (see 2.)

3.4.2. Severity distribution

- Data source: WIdO [2]
- Definition: indication profiles for diabetes mellitus [3]
- The health state "Diabetic neuropathy and amputation with treatment due to diabetes mellitus type 1/type 2 without treatment with a prosthesis" is not considered in the analysis. It is assumed that every amputation in Germany is treated.

3.4.3. Disability weights

- Data source: GBD-Study [16, 19, 20]
- In the table accompanying the original article, the weights for (1) neuropathy and diabetic foot and (2) neuropathy and amputation were missing. These were calculated independently using the multiplicative method from the respective individual weights [16, 19, 20].

3.4.4. Duration

- N/A

3.4.5. Input variables

Disease / cause	Severity	Severity distribution and disability weights					
		sev	95% UI		dw	95% UI	
			down	top		down	top
diabetes mellitus Typ 1	Uncomplicated diabetes mellitus	66.5%	66.2%	66.9%	0.049	0.031	0.072

	Diabetic neuropathy without diabetic foot or amputation	19.1%	18.8%	19.3%	0.133	0.089	0.187
	Diabetic foot due to neuropathy	13.8%	13.6%	14.1%	0.15	0.075	0.224
	Diabetic neuropathy and amputation with treatment	0.4%	0.3%	0.4%	0.166	0.093	0.24
	Moderate vision impairment due to diabetes mellitus retinopathy	0.2%	0.2%	0.2%	0.031	0.019	0.049
	Severe vision impairment due to diabetes mellitus retinopathy	0.1%	0.1%	0.1%	0.184	0.125	0.259
	Blindness due to diabetes mellitus retinopathy	0.7%	0.7%	0.8%	0.187	0.124	0.26
diabetes mellitus Typ 2	Uncomplicated diabetes mellitus	73.3%	73.2%	73.3%	0.049	0.031	0.072
	Diabetic neuropathy without diabetic foot or amputation	15.6%	15.6%	15.7%	0.133	0.089	0.187
	Diabetic foot due to neuropathy	10.7%	10.7%	10.7%	0.15	0.075	0.224
	Diabetic neuropathy and amputation with treatment	0.3%	0.3%	0.3%	0.166	0.093	0.24
	Moderate vision impairment due to diabetes mellitus retinopathy	0.1%	0.1%	0.1%	0.031	0.019	0.049
	Severe vision impairment due to diabetes mellitus retinopathy	< 0.1%	< 0.1%	< 0.1%	0.184	0.125	0.259
	Blindness due to diabetes mellitus retinopathy	0.1%	0.1%	0.1%	0.187	0.124	0.26

3.5. Lower respiratory infections

level	disease/cause
3	lower respiratory infections

3.5.1. Incidence

- Age restriction: none
- Data source: WIdO [2]
- Definition of disease: see indication profiles for lower respiratory infections [3]
- Temporal definition: 12-month case rate per 100,000 population (was converted to prevalent cases by adding population numbers).
- Age distribution adjusted (see 2.)

3.5.2. Severity distribution

- Data source: GBD study [21]
- Definition: see GBD study [16, 21]

3.5.3. Disability weights

- Data source: GBD study [16, 21]

3.5.4. Duration

- Data source: average duration of disease from GBD study [16, 21]

3.5.5. Input variables

Disease / cause	Severity	Severity distribution, disability weights and duration								
		sev	95% UI		dw	95% UI		dur	95% UI	
			down	top		down	top		down	top
lower respiratory infections	moderate	84.9%	83.1%	86.7%	0.051	0.032	0.074	7.79	6.2	9.64
	severe	15.1%	13.3%	16.9%	0.133	0.088	0.19	7.79	6.2	9.64

3.6. Chronic obstructive pulmonary disease (COPD)

level	disease/cause
3	chronic obstructive pulmonary disease

3.6.1. Prevalence

- Age restriction: no calculation < 35 years (expert opinion)
- Data source: WIdO [2]
- Definition of disease: see indication profiles for COPD [3]
- Temporal definition: 12-month-prevalence
- Age distribution adjusted (siehe 2.)

3.6.2. Severity distribution

- Data source: own calculation, estimation from prevalent cases of an former GBD round (GBD 2013) [22], assumption here is time-constant severity distributions across GBD rounds [23]
- Definition: see GBD-Study [16]

3.6.3. Disability weights

- Data source: GBD-Study [16]

3.6.4. Duration

- N/A

3.6.5. Input variables

Disease / cause	Severity	Severity distribution and disability weights					
		sev	95% UI		dw	95% UI	
			down	top		down	top
chronic obstructive pulmonary disease (COPD)	asymptomatic	35.3%	28.1%	42.9%	0	0	0
	mild	42.4%	34.2%	50.8%	0.019	0.011	0.033
	moderate	9.9%	6.6%	13.5%	0.225	0.153	0.31
	severe	12.4%	4.2%	19.3%	0.408	0.273	0.556

3.7. Alzheimer's disease and other dementias

level	disease/cause
3	Alzheimer's disease and other dementias

3.7.1. Prevalence

- Age restriction: no calculation < 40 years (expert opinion).
- Data source: WIdO [2]
- Definition of the disease: see indication profiles for Alzheimer's disease and other dementias [3]
- Temporal definition: 12-month prevalence
- Age distribution adjusted (see 2.)

3.7.2. Severity distribution

- Data source: GBD-Study [18]
- Definition: see GBD-Study [16]

3.7.3. Disability weights

- Data source: GBD-Study [16]

3.7.4. Duration

- N/A

3.7.5. Input variables

Disease / cause	Severity	Severity distribution and disability weights					
		sev	95% UI		dw	95% UI	
			down	top		down	top
Alzheimer's disease and other dementias	mild	71.7%	63.3%	78.6%	0.069	0.046	0.099
	moderate	20.2%	16.1%	25.6%	0.377	0.252	0.508
	severe	8.1%	5.1%	12.5%	0.449	0.304	0.595

3.8. Headache disorders

level	disease/case
3	headache disorders
4	Migraine
5	definite migraine (without medication overuse)
5	probably migraine
5	migraine with medication overuse
4	tension-type headache
5	tension-type headache with medication overuse
5	tension-type headache

3.8.1. Prevalence

- Headache disorders are divided into migraine and tension headache. This includes a separate consideration of each of those groups of persons who have developed medication-overuse headache (MOH) as a result of a primary headache disorder [6, 16].
- Age restriction: no calculation < 18 years (restriction by telephone survey)
- Data source: study on headache, backache, and neck pain in Germany (2019/2020) (add-on survey) [6]
- Definition of disorder: see operationalization of primary headache types [6]
- Temporal definition: 12-month prevalence
- Age distribution adjusted (see 2.) on the basis of the progression of primary headache disorders in the GBD study for those cases in which the estimate of prevalence for the 5-year age groups on the basis of the survey was too uncertain (Coefficient of Variation (CV) > 33).
- Special case MOH: The overall estimator of MOH was split between migraine and tension type headache at a ratio of 70% to 30%, which follows the procedure of the GBD study [16]. In addition, the age distribution of the MOH was modeled based on the gender and age distribution of the respective primary headache disorder.

3.8.2. Severity distribution

- Data source: Study on headache, back pain and neck pain in Germany (2019/2020) [6]
- Definition: average proportion of days within one year (denominator: 365.25 days) spent with symptoms by sufferers, corresponds to “time symptomatic” in the GBD study [16]

3.8.3. Disability weights

- Data source: GBD-Study [16]

3.8.4. Duration

- Measured via the question "How many days with headaches have you had in the past 12 months?" Proxy for the average time in days that sufferers spent with symptoms.

- Data source: study on headache, back pain, and neck pain in Germany (2019/2020) [6]

3.8.5. Input variables

Disease / cause	Severity	Severity distribution and disability weights					
		sev	95% UI		dw	95% UI	
			down	top		down	top
definite migraine without medication overuse	time symptomatic as proportion of the year with symptoms	12.3%	9.5%	15.1%	0.441	0.294	0.588
probably migraine	time symptomatic as proportion of the year with symptoms	9.5%	7.8%	11.1%	0.441	0.294	0.588
migraine with medication overuse	time symptomatic as proportion of the year with symptoms	74.7%	61.0%	88.4%	0.223	0.146	0.313
tension-type headache	time symptomatic as proportion of the year with symptoms	6.7%	5.7%	7.6%	0.037	0.022	0.057
tension-type headache with medication overuse	time symptomatic as proportion of the year with symptoms	74.7%	61.0%	88.4%	0.223	0.146	0.313

3.9. Depressive disorders

level	disease/cause
3	depressive disorders
4	major depressive disorder (MDD)
4	dysthymia (DY)

3.9.1. Prevalence

- Age restriction: MDD and DY no calculation < 15 years (expert opinion).
- Data source: WIdO [2]
- Definition of the disorder: see indication profiles for major depression and dysthymia [3]
- Temporal definition: 12-month prevalence
- Age distribution adjusted (see 2.)

3.9.2. Severity distribution

- Data source: distribution for DY based on the GBD study [18], distribution for MDD based on WIdO data [2]
- Definition: see GBD-Study [16] and for operationalization see WIdO [2, 3]

3.9.3. Disability weights

- Data source: GBD-Study [16]

3.9.4. Duration

- Mean duration of impairment for major depression was estimated from the Mental Health Module in DEGS1 (DEGS1-MH, 2009-2012) [24, 25]. The number of days with mental impairment in the last 4 weeks was extrapolated to provide yearly data and used as a proxy.
- Data source: DEGS1-MH (2009-2012) [24, 25]

3.9.5. Input variables

Disease / cause	Severity	Severity distribution and disability weights								
		sev	95% UI		dw	95% UI		dur	95% UI	
			down	top		down	top		down	top
major depressive disorder	asymptomatic	8.8%	8.7%	8.8%	0	0	0	0.0	0.0	0.0
	mild	19.7%	19.6%	19.7%	0.145	0.099	0.209	59.6	46.1	73.1
	moderate	49.6%	49.5%	49.6%	0.396	0.267	0.531	59.6	46.1	73.1
	severe	22.0%	22.0%	22.1%	0.658	0.477	0.807	59.6	46.1	73.1

dysthymia	proportion of the year with symptoms	35.0%	29.6%	39.7%	0.145	0.099	0.209	.	.	.

3.10. Anxiety disorders

level	disease/cause
3	anxiety disorders

3.10.1. Prevalence

- Age restriction: none
- Data source: WIdO [2]
- Definition of the disease: see indication profile for anxiety disorders [3]
- Temporal definition: 12-month prevalence
- Age distribution adjusted (see 2.)

3.10.2. Severity distribution

- Data source: GBD study [18]
- Definition: see GBD study [16]

3.10.3. Disability weights

- Data source: GBD study [16]

3.10.4. Duration

- No calculation of an average duration/days with restrictions. The assumption is that anxiety disorders have a high degree of chronicity [26].

3.10.5. Input-variables

Disease / cause	Severity	Severity distribution and disability weights					
		sev	95% UI		dw	95% UI	
			down	top		down	top
anxiety disorders	asymptomatic	28.3%	26.8%	29.6%	0	0	0
	mild	40.9%	33.0%	47.2%	0.03	0.018	0.046
	moderate	18.5%	13.8%	23.8%	0.133	0.091	0.186
	severe	12.3%	8.2%	17.4%	0.523	0.362	0.677

3.11. Alcohol use disorders

level	disease/cause
3	alcohol use disorders

3.11.1. Prevalence

- Alcohol use disorders according to DSM-IV criteria (*Diagnostic and Statistical Manual of Mental Disorders*) include both alcohol abuse and alcohol dependence [27]
- Age restriction: no calculation < 18 and > 64 years (restriction by Survey).
- Data source: Epidemiological Survey of Substance Abuse in Germany [28]
- Definition of the disorder: see operationalization of alcohol use disorders [29]
- Temporal definition: 12-month prevalence
- Age distribution adjusted (see 2.) on the basis of the progression of alcohol use disorders in the GBD study for those cases in which the estimation of prevalences for the 5-year age groups on the basis of the survey was too uncertain (*Coefficient of Variation* (CV) > 33)

3.11.2. Severity distribution

- Data source: GBD study [18]
- Definition: see GBD study [16]

3.11.3. Disability weights

- Data source: GBD study [16]

3.11.4. Duration

- N/A

3.11.5. Input variables

Disease / cause	Severity	Severity distribution and disability weights					
		sev	95% UI		dw	95% UI	
			down	top		down	top
alcohol use disorders	asymptomatic	36.8%	32.2%	41.8%	0	0	0
	very mild	53.4%	49.0%	58.5%	0.123	0.082	0.177
	mild	3.8%	2.2%	5.8%	0.235	0.160	0.327
	moderat	3.4%	1.6%	5.3%	0.373	0.248	0.508
	severe	2.6%	0.9%	5.7%	0.570	0.396	0.732

3.12. Low back pain

level	disease/cause
3	low back pain
5	low back pain with leg pain
5	low back pain without leg pain

3.12.1. Prevalence

- Low back pain is further subdivided according to whether the pain also extends into the leg [16].
- The localization of the pain is determined by whether the back pain was in the upper back, i.e. at the level of the thoracic spine, or in the lower back, i.e. at the level of the lumbar spine, in the buttocks or in the hip. It was also possible to indicate both the upper and lower back [12]. These people were counted as prevalent cases in both groups.
- Age restriction: no calculation < 18 years (restriction due to telephone survey).
- Data source: study on headache, back pain and neck pain in Germany (2019/2020) (add-on survey) [6, 12]
- Disease definition: see operationalization lower back pain [12]
- Temporal definition: 12-month prevalence.
- Age distribution adjusted (see 2.) based on the distribution of low back pain prevalence in the GBD study for those cases in which the estimate of prevalence for the 5-year age groups based on the survey was too uncertain (*Coefficient of Variation* (CV) > 33)

3.12.2. Severity distribution

- Data source: study on head, back and neck pain in Germany (2019/2020) [6, 12]
- Definition: the lay descriptions of severity in the GBD study [16] were translated into German and queried by telephone in the study [12]

3.12.3. Disability weights

- Data source: GBD study [16]

3.12.4. Duration

- Measured via the question "How many days with back pain did you have in the last 12 months?"; proxy for the average time in days that sufferers spent with symptoms/pain.
- Data source: study on headache, back pain, and neck pain in Germany (2019/2020) [6, 12]

3.12.5. Input variables

Disease/cause	Severity	Severity distribution and disability weights								
		sev	95% UI		dw	95% UI		dur	95% UI	
			down	top		down	top		down	top

low back pain with leg pain	asymptomatic	18.8 %	15.3%	23.0 %	0	0	0	0.0	0.0	0.0
	mild	14.2 %	11.3%	17.7%	0.02	0.011	0.035	161.6	146.3	177.0
	moderate	21.3%	17.6 %	25.5%	0.054	0.035	0.079	161.6	146.3	177.0
	severe	19.5 %	16.0 %	23.4 %	0.325	0.219	0.446	161.6	146.3	177.0
	most severe	26.3 %	21.7 %	31.4%	0.384	0.256	0.518	161.6	146.3	177.0
low back pain without leg pain	asymptomatic	34.9 %	31.0 %	39.0 %	0	0	0	0.0	0.0	0.0
	mild	25.2 %	21.8 %	29.0 %	0.02	0.011	0.035	78.6	68.4	88.8
	moderate	20.2 %	17.0 %	23.7 %	0.054	0.035	0.079	78.6	68.4	88.8
	severe	13.9 %	10.6 %	17.9 %	0.272	0.182	0.373	78.6	68.4	88.8
	most severe	5.8%	3.9%	8.6%	0.372	0.25	0.506	78.6	68.4	88.8

3.13. Neck pain

level	disease/cause
3	neck pain

3.13.1. Prevalence

- Age restriction: no calculation < 18 years (restriction due to telephone survey).
- Data source: study on headache, back pain and neck pain in Germany (2019/2020) (add-on survey) [6, 12]
- Definition of the disease: see indication profile for neck pain [12]
- Temporal definition: 12-month prevalence
- Age distribution adjusted (see 2.) based on the distribution of neck pain prevalence in the GBD study for those cases in which the estimate of prevalence for the 5-year age groups based on the survey was too uncertain (*Coefficient of variation* (CV) > 33)

3.13.2. Severity distribution

- Data source: study on head, back and neck pain in Germany (2019/2020) [6, 12]
- Definition: the lay descriptions of severity in the GBD study [16] were translated into German and queried by telephone in the study [12]

3.13.3. Disability weights

- Data source: GBD study [16]

3.13.4. Duration

- Measured via the question "How many days with neck pain have you had in the past 12 months?"; proxy for the average time in days that sufferers spent with symptoms/pain.
- Data source: study on headache, back pain and neck pain in Germany (2019/2020) [6, 12]

3.13.5. Input variables

Disease / cause	Severity	Severity distribution and disability weights								
		sev	95% UI		dw	95% UI		dur	95% UI	
			down	top		down	top		down	top
neck pain	asymptomatic	17.2%	14.8%	19.9%	0	0	0	0.0	0.0	0.0
	mild	57.2%	53.6%	60.8%	0.052	0.036	0.074	87.9	78.6	97.3
	moderate	13.1%	10.9%	15.8%	0.112	0.079	0.162	87.9	78.6	97.3
	severe	2.1%	1.3%	3.6%	0.226	0.147	0.323	87.9	78.6	97.3

	most severe	10.3%	8.1%	13.0%	0.3	0.199	0.434	87.9	78.6	97.3

3.14. Breast cancer

level	disease/cause
3	breast cancer

3.14.1. Prevalence

- Age restriction: no calculation < 20 years.
- Additional restriction: no estimate for men
- Data source: WIdO [2]
- Definition of the disease: see indication profile for breast cancer [3]
- Temporal definition: 10 years prevalence
- Age distribution adjusted (see 2.)

3.14.2. Severity distribution

- Data source: WIdO-Data [2]
- Definition: see GBD study [16] and for the operationalization see WIdO [2, 3]

3.14.3. Disability weights

- Data source: GBD study [16]
- Additional weight for the health state "Controlled phase with mastectomy". Application of the multiplicative formula based on the weights for (1) "Controlled phase" and (2) "Mastectomy".

3.14.4. Duration

- The duration of the disease phases is included in the calculation of the severity distributions [2, 3]. Thus, these are not shown separately here.

3.14.5. Input variables

Disease / cause	Severity	Severity distribution and disability weights					
		sev	95% UI		dw	95% UI	
			down	top		down	top
breast cancer	diagnosis and primary therapy phase	3.3%	3.2%	3.4%	0.288	0.193	0.399
	controlled phase, without mastectomy	46.7%	46.5%	46.8%	0.049	0.031	0.072
	controlled phase, with mastectomy	38.8%	38.6%	38.9%	0.082	0.045	0.122
	metastatic phase	10.8%	10.7%	10.9%	0.451	0.307	0.6
	terminal phase	0.5%	0.5%	0.5%	0.54	0.377	0.687

3.15. Prostate cancer

level	disease/cause
3	prostate cancer

3.15.1. Prevalence

- Age restriction: no calculation < 40 years
- Gender-specific cancer, so results are only available for men
- Data source: WIdO [2]
- Definition of the disease: see indication profile for prostate cancer [3]
- Temporal definition: 10 years prevalence
- Age distribution adjusted (see 2.)

3.15.2. Severity distribution

- Data source: WIdO-data [2]
- Definition: see GBD stud [16] and for the operationalization see WIdO [2, 3]
- Addition of a health state, namely "Controlled phase with incontinence and impotence"

3.15.3. Disability weights

- Data source: GBD study [16]
- Additional weight for the health state "Controlled phase with incontinence"; application of the multiplicative formula based on the weights for (1) "Controlled phase" and (2) "Incontinence".
- Additional weight for health state "Controlled phase with impotence"; application of multiplicative formula based on weights for (1) "Controlled phase" and (2) "Impotence"
- Additional weight for the health state "Controlled phase with incontinence and impotence"; application of the multiplicative formula based on the weights for (1) "Controlled phase," (2) "Incontinence," and (3) "Impotence"

3.15.4. Duration

- The duration of the disease phases is included in the calculation of the severity distributions [2, 3]. Thus, these are not shown separately here.

3.15.5. Input variables

Disease / cause	Severity	Severity distribution and disability weights					
		sev	95% UI		dw	95% UI	
			down	top		down	top
prostate cancer	diagnosis and primary therapy phase	3.2%	3.1%	3.3%	0.288	0.193	0.399
	controlled phase, without impotence or incontinence	67.3%	67.1%	67.5%	0.049	0.031	0.072

	controlled phase, with impotence	0.8%	0.8%	0.8%	0.065	0.031	0.099
	controlled phase, with incontinence	17.2%	17.1%	17.4%	0.18	0.104	0.257
	controlled phase, with impotence and incontinence	1.1%	1.1%	1.2%	0.194	0.119	0.269
	metastatic phase	9.7%	9.6%	9.8%	0.451	0.307	0.6
	terminal phase	0.7%	0.7%	0.7%	0.54	0.377	0.687

3.16. Colon and rectum cancer

level	disease/cause
3	colon and rectum cancer

3.16.1. Prevalence

- Age restriction: no calculation < 20 years
- Data source: WIdO [2]
- Definition of the disease: see indication profile for colon and rectum cancer [3]
- Temporal definition: 10 years prevalence
- Age distribution adjusted (see 2.)

3.16.2. Severity distribution

- Data source: WIdO-data [2]
- Definition: see GBD stud [16] and for the operationalization see WIdO [2, 3]
- Addition of a health state, namely "Controlled phase with incontinence and impotence".

3.16.3. Disability weights

- Data source: GBD study [16]
- Additional weight for health state "Controlled phase with stoma"; application of multiplicative formula based on weights for (1) "Controlled phase" and (2) "Stoma".

3.16.4. Duration

- The duration of the disease phases is included in the calculation of the severity distributions [2, 3]. Thus, these are not shown separately here

3.16.5. Input variables

Disease / cause	Severity	Severity distribution and disability weights					
		sev	95% UI		dw	95% UI	
			down	top		down	top
colon and rectum cancer	diagnosis and primary therapy phase	4.1%	4.0%	4.2%	0.288	0.193	0.399
	controlled phase, without stoma	76.8%	76.6%	76.9%	0.049	0.031	0.072
	controlled phase, with stoma	5.1%	5.0%	5.2%	0.139	0.083	0.193
	metastatic phase	13.1%	12.9%	13.3%	0.451	0.307	0.6
	terminal phase	0.9%	0.9%	1.0%	0.54	0.377	0.687

3.17. Tracheal, bronchus, and lung cancer

level	disease/cause
3	tracheal, bronchus, and lung cancer

3.17.1. Prevalence

- Age restriction: no calculation < 25 years
- Data source: WIdO [2]
- Definition of the disease: see indication profile for tracheal, bronchus, and lung cancer [3]
- Temporal definition: 10 years prevalence
- Age distribution adjusted (see 2.)

3.17.2. Severity distribution

- Data source: WIdO-data [2]
- Definition: see GBD study [16] and for the operationalization see WIdO [2, 3]

3.17.3. Disability weights

- Data source: GBD study [16]

3.17.4. Duration

- The duration of the disease phases is included in the calculation of the severity distributions [2, 3]. Thus, these are not shown separately here.

3.17.5. Input variables

Disease / cause	Severity	Severity distribution and disability weights					
		sev	95% UI		dw	95% UI	
			down	top		down	top
tracheal, bronchus, and lung cancer	diagnosis and primary therapy phase	4.3%	4.2%	4.5%	0.288	0.193	0.399
	controlled Phase	60.2%	59.8%	60.6%	0.049	0.031	0.072
	metastatic phase	32.6%	32.2%	33.0%	0.451	0.307	0.6
	terminal phase	2.9%	2.8%	3.1%	0.54	0.377	0.687

3.18. Transport injuries

level	disease/cause
3	road injuries
4	pedestrian road injuries
4	cyclist road injuries
4	motorcyclist road injuries
4	motor vehicle road injuries
4	other road injuries
3	other transport injuries

3.18.1. Prevalence

- Age restriction: none
- Data source: Road traffic accident statistics (STVU for short), injured in accidents with personal injury reported to the police [30],GEDA 2010 [31], KiGGS wave 2 [32]
- Definition of disease/cause: assignment of traffic accidents according to type of traffic accident involvement via key numbers [for definition see Table 5]

Table 5: Assignment of traffic involvement type from STVU and RKI survey data to traffic accidents (level 4)

Cause by level			Code number "Type of traffic involvement" according to STVU [30]	Assignment to RKI survey data [31, 32]
level 2	level 3	level 4		
transport injuries	road injuries	pedestrian road injuries	81, 84, 93	pedestrian
		cyclist road injuries	71, 72	cyclist
		motorcyclist road injuries	01-03, 06-12, 14-15	car
		motor vehicle road injuries	04, 13, 21, 22, 31-34, 35, 40-52	car
		other road injuries	61, 82, 83, 91, 92	other
	other transport injuries		53, 54, 55, 57, 58, 59, 62	car

- Temporal definition: STVU: 12-month prevalence for the reporting year 2017; GEDA 2010: 2009-2010 survey period; KiGGS Wave 2: 2014-2017 survey period
- Correction of the prevalence estimate: Road traffic accident statistics record accidents with personal injury or property damage reported by the police, which leads to an under-reporting of accidents in

the population that are not registered by the police. In this context, it can be assumed that unregistered road traffic accidents also lead to injuries and thus cause disease burden among those affected. The results of the GEDA 2010 survey and the KiGGS wave 2 survey on road traffic injuries show that a certain degree of underreporting is to be expected in road traffic accident statistics, which varies according to accident type (Table 6). While the share of under-reporting is lowest for motor vehicle accidents according to the survey, the majority of accidents involving pedestrians are less frequently recorded (in the 20+ age group 93%, see Table 6). The injury figures from the STVU were therefore corrected for the portion of accidents that were not recorded. Since there were no significant differences by age and gender in the survey studies with regard to the proportion of accidents recorded by the police, adjustments were made for gender in only three age groups. Since information was available from both surveys for the 15 to 19 age group, the mean value was assumed here. Differentiation between the burden of disease groups "motorcyclists," "motor vehicle occupants," and "other traffic accidents" was not possible with the survey data, so the same values were assumed (motor vehicles).

Table 6: Proportion of police-recorded accidents in all accidents by type of accident and age group - determined from RKI survey data, 95% confidence interval in parentheses

Type of accident	Age group		
	0-14	15-19	20+
pedestrian	8,7 (3,3-21,0)	7,8 (3,0-19,2)	7,0 (2,6-17,4)
cyclist	13,6 (5,7-28,9)	21,7 (12,2-36,3)	29,7 (18,8-43,7)
motorcyclist, motor vehicle occupants, other transport injuries (car)	58,1 (37,8-76,0)	57,5 (41,4-72,1)	57,0 (45,1-68,1)
other road injuries (other)	2,7 (0,4-17,1)	3,3 (0,9-13,9)	4,0 (1,4-10,7)
source:	KiGGS Welle 2	AM	GEDA 2010

AM: Arithmetic mean from KiGGS Welle 2 and GEDA10

3.18.2. Severity distribution

- Data source: GBD study [16, 17]
- Definition: With regard to the topic of accidents, the GBD study follows its own methodology, which differs slightly from the health state designations presented [20]. In summary, a variety of injuries (nature of injury) are assigned to each cause of accident (cause of injury). Depending on which cause is considered, the injuries differ in nature (nature of injury) and number. In the context of road injuries, the GBD methodology distinguishes at a higher level (group of nature of injury) between amputations, burns, fractures, head injuries, spinal injuries, minor injuries, and other injuries [16]. A case is assigned to only one of the nature of injuries. A given nature of injury is further differentiated into more specific injuries, to which the individual weights and durations are linked [20].

- The severity thus corresponds to the age- and gender-specific proportions of cases per superordinate injury type (nature of injury group) within an accident type (cause of injury) estimated for Germany.
- The injury figures according to road injuries statistics were divided according to this distribution key.

3.18.3. Disability weights

- Data source: GBD study [17]
- Definition: Since the distribution of individual weights and durations cannot be accessed, only average weights, so-called average disability weights (abbreviated av_{dw}), are used in the course of the project. These express the average impairment of the respective group of the nature of injury over all individual weights.
  The following formula was used for this purpose:

$$av_{dw,i,j} = \frac{YLD_{i,j}}{prevalence_{i,j}}$$

  Where i is the cause of injury and j is the nature of injury group. The input data on YLD and prevalences were taken from the GBD study for Germany in 2017 [17].
- Further explanation: in the YLD formula, av_{dw} replace the individual weights dw and durations.

3.18.4. Duration

- N/A

3.18.5. Input variables

Disease / cause	Severity	Severity distribution and disability weights					
		sev	95% UI		av_{dw}	95% UI	
			down	top		down	top
pedestrian road injuries	amputation	21.7%	17.8%	25.6%	0.022	0.016	0.028
	burns	7.5%	5.9%	9.3%	0.025	0.02	0.03
	fractures	43.0%	35.9%	49.9%	0.051	0.04	0.064
	head injuries	8.0%	6.8%	9.8%	0.147	0.117	0.167
	injuries of the spine	1.0%	0.8%	1.2%	0.276	0.229	0.311
	minor injuries	14.3%	11.4%	17.3%	0.009	0.005	0.014
	other injuries	4.5%	3.9%	5.1%	0.078	0.061	0.095
cyclist road injuries	amputation	24.7%	19.6%	31.5%	0.011	0.008	0.015
	burns	6.8%	5.2%	8.7%	0.027	0.022	0.03
	fractures	45.0%	37.8%	54.1%	0.053	0.041	0.064

	head injuries	8.2%	7.2%	9.4%	0.146	0.116	0.174
	injuries of the spine	1.2%	1.0%	1.5%	0.277	0.229	0.312
	minor injuries	10.7%	8.6%	13.3%	0.009	0.005	0.014
	other injuries	3.5%	3.0%	3.9%	0.081	0.062	0.098
motorcyclist road injuries	amputation	17.9%	14.8%	21.2%	0.022	0.016	0.029
	burns	4.4%	3.6%	5.4%	0.035	0.029	0.042
	fractures	46.2%	39.4%	53.4%	0.048	0.037	0.062
	head injuries	9.4%	8.2%	11.0%	0.149	0.117	0.181
	injuries of the spine	1.3%	1.1%	1.6%	0.28	0.231	0.318
	minor injuries	16.2%	13.4%	19.3%	0.009	0.005	0.015
	other injuries	4.5%	4.1%	5.1%	0.073	0.056	0.089
motor vehicle road injuries	amputation	17.6%	14.5%	22.2%	0.018	0.014	0.023
	burns	5.0%	3.9%	6.1%	0.022	0.017	0.028
	fractures	44.8%	37.9%	53.7%	0.056	0.044	0.067
	head injuries	11.7%	10.1%	13.4%	0.147	0.118	0.177
	injuries of the spine	2.2%	1.7%	2.8%	0.275	0.234	0.301
	minor injuries	13.0%	10.7%	16.7%	0.009	0.005	0.014
	other injuries	5.8%	5.2%	6.7%	0.077	0.06	0.091
other road injuries	amputation	30.0%	24.5%	37.0%	0.011	0.008	0.016
	burns	5.5%	4.2%	7.2%	0.018	0.013	0.024
	fractures	50.8%	42.9%	60.5%	0.056	0.043	0.067
	head injuries	4.5%	3.8%	5.4%	0.144	0.117	0.176
	injuries of the spine	1.1%	0.9%	1.3%	0.27	0.227	0.301
	minor injuries	5.7%	4.8%	6.9%	0.008	0.004	0.014

	other injuries	2.5%	2.1%	2.9%	0.084	0.063	0.109
other transport injuries	amputation	35.2%	28.0%	43.0%	0.024	0.019	0.029
	burns	7.1%	5.4%	9.4%	0.022	0.018	0.027
	fractures	29.0%	24.4%	33.9%	0.05	0.039	0.061
	head injuries	8.0%	6.8%	9.2%	0.147	0.117	0.178
	injuries of the spine	2.7%	2.3%	3.2%	0.266	0.213	0.299
	minor injuries	11.8%	9.6%	14.1%	0.009	0.005	0.014
	other injuries	6.1%	5.4%	7.0%	0.071	0.055	0.086

4. Uncertainty concept

4.1. Years of life lost (YLL)

Redistribution of non-informative ICD-10 codes and resulting uncertainties

In 2017, 25.8% of deaths in the cause-of-death statistics had an ICD-10 code that was non-informative - in the sense of a burden-of-disease assessment - as to the cause of death [13]. Non-informative ICD codes may be those describing, for example, sequelae, symptoms of disease, or non-specific causes of death. In order to be able to use these deaths for the calculation of the YLL as well, non-informative ICD codes are redistributed to informative ICD codes. This is done following the methodology of the GBD study [33-35]. Thus, for all deaths with a non-informative ICD code, assumptions are made about actual causes of death and so-called target codes are defined.

For a non-informative ICD-10 code in the cause-of-death statistics, various informative ICD-10 codes are thereby available as target codes that can be used as actual causes of death for statistical purposes [14]. For example, nonspecific stroke can be assigned to ischemic stroke, intracerebral hemorrhage, or subarachnoid hemorrhage [see 15]. In this context, the distribution of target codes or causes of death vary by age and sex in the population, so redistribution is performed separately by age, sex, and regional groups accordingly. The assumption is made that the cause of death was correctly documented for deaths with an informative ICD code.

For each death with a non-informative ICD-10 code, the process of redistribution (to informative ICD-10 codes) is repeated 1000 times [see 14]. This is to represent the variation of different possible causes of death. The 1000 values formed allow for the calculation of an uncertainty interval for each cause of death, within which 95% of the repetitions lie. In summary, the uncertainty interval thus represents the range of death case numbers or YLL within which the true value lies, given the assumptions made.

Imputation of blocked case numbers

In order to depict death events on a regional level, the data used in the cause-of-death statistics were processed and evaluated at the Research Data Center (FDZ) [36]. Unlike the freely available federal level data [37], the FDZ data allow a state-specific redistribution of non-informative ICD codes to informative ICD codes due to additional information regarding the place of residence of the deceased person [see 14]. The analysis of the data (YLL and deaths) was performed at the level of the 96 spatial planning regions. To exclude re-identification of persons, fields with less than three cases are blocked during data transmission (primary suppression according to the rule of minimum case numbers). In addition, so-called secondary suppression may occur if addition or subtraction using these fields allows conclusions to be drawn about blocked cells with fewer than three cases (secondary suppression according to the rule of margin).

At the highest level of detail (by age, sex, spatial planning region, and cause of death), 16.2% of all deaths were blocked, which were distributed across 77.5% of all cells (out of a total of 203,199). At the lowest level of detail (total age, both sexes, federal level, by cause of death), less than 0.001% of deaths were blocked, which were distributed across 7 cells (out of 131). Imputation must therefore consider several marginal distributions. First, the all-cause mortality is given, which was 932,269 deaths in absolute terms in Germany in 2017. In addition, based on the mortality tables of the Federal Statistical Office [38], values are also known by gender (474,512 women and 457,757 men), age and space (here: spatial planning regions, ROR for short).

The imputation is performed at the respective aggregation levels by space, sex and age as follows: First (1), the dataset with the number of deaths per cause of death is imputed for Germany (total age and total sex). Then

(2), the dataset is imputed by cause of death and spatial planning region (total age, total sex). The distributions of cases across causes of death known from the freely available federal level data [37] are used. This makes it possible to estimate how the cases to be imputed (difference between existing cases and 932,269) are distributed across the blocked causes of death. The imputation is iterative: first, the cases to be imputed (see difference) are distributed proportionally (according to the federal proportions) among the blocked causes of death. This is followed by (3) a comparison with the all-cause mortality and, if necessary, a correction of the imputation.

Thus, at the level with the lowest level of detail (total age, both sexes, federal government, by cause of death), for example, 11.4 deaths are distributed across 7 fields (see above). The 11.4 cases are not evenly distributed, but rather the distribution of deaths across these causes of death in the freely available federal level data [37] is taken into account. At this lowest level of detail, it is only important to reach 932,269 total deaths. At more detailed levels, e.g., by sex, the respective all-cause mortality must be considered as well (474,512 women and 457,757 men). The adjustment then becomes correspondingly more complex. After a distribution of the cases to be imputed according to the federal distribution (steps 1 and 2 above), the imputation is thus adjusted with respect to all-cause mortality (step 3).

4.2. Years lived with disability (YLD)

The calculation of the 95% uncertainty interval (UIs) is discussed in detail below using a stochastic simulation, which is also often known as the Monte Carlo simulation [39]. The calculations were performed in STATA 17 using the software package *psimulate2* [40].

Basis of YLD calculation (adjustment for multimorbidity, see section 5).
To calculate the point estimates and UIs across the dimensions of age (a), sex (s), region (r), and cause (c), the simplified formula [see 7, formula [2]] was expanded to the following equation:

$$YLD_{a,s,r,c} = \sum_{j=1}^{k} p^*_{a,s,r,c,j} * t^*_{a,s,c} * dw_{c,j} \qquad [2.1]$$

where k can range from one to eight depending on the cause (c) and corresponds to the number of severities. For the selection of burden of disease causes reported here, a maximum of eight severities were observed.

For each cause (c), information on the prevalence or incidence (p^*), the (average) duration of the cause in days within a year (t), the severity distribution (j), and the disability weight (dw) is used. The duration plays a role for causes that occur only in isolated, short-lived episodes within a year. Examples include migraine or tension-type headache, from which affected only suffer for a certain proportion of the year [6]. For these disorders, the point prevalence (p) is calculated by weighting the 12-month prevalence (p^*) with a time factor $t^* = \frac{t}{365{,}25}$ [2.2] via $p = p^* * t^*$ [2.3]. It follows that for chronic conditions such as type 2 diabetes, which by assumption causes health impairment every day of the year, the weighting is $t^* = 1$, and thus $p^* = p$.

The point estimates and 95% confidence intervals (CI) per cause and input variable were estimated based on multiple data sources and using different methods. Furthermore, these are to some extent taken from previously published GBD study results and are thus only used secondarily in the calculation [16]. As a result, depending on which burden of disease cause and input variable is considered, the CI addresses a different source of uncertainty. For example, whereas the estimation of prevalence based on claims data corrected for possible selection effects by collectives of insured persons, the uncertainty in the RKI survey data reflects both

the selection probability of individuals into the sample and the adjustment for population structure [1, 6]. As a result, pooling the CIs into the YLD changes their meaning, as multiple sources of uncertainty are combined. Therefore, we refer to uncertainty intervals (UIs) when calculating the outcome.

Stochastic simulation

To approximate the UIs, a possible distribution of the outcome (YLD) is simulated by using an algorithm. On the one hand, classical Monte Carlo methods, which are often used in numeric for the calculation of integrals, provide orientation. An arbitrary real number q is approximated by randomly drawing n times from independent, identically distributed (usually equally distributed) random variable with expected value q [see 39]. The larger the number of repetitions, the more accurately the real number q can be replicated. On the other hand, application fields of bootstrapping come into play, which provides an alternative to inferential statistics for computing standard errors by asymptotic formulas. Based on this procedure, we assume that the distribution of our random variables corresponds to that of the population (N) and we can draw n samples (so-called bootstrap samples) from it. After n repetitions we get a bootstrap sample distribution as a result, which is a good approximation of our original targeted distribution [for the procedure see 41].

Starting from this, the simulation is based on the following algorithm: (1) All input variables (p^*, t^*, j, dw) are considered random variables with a known mean and standard deviation, which are written in capital letters below. (2) A value is then randomly and independently drawn from the input variables using a random number generator and (3) substituted into equation [2.1] to calculate the YLD, which is assumed to be deterministic, i.e., with no other random component [42]. (4) This procedure is repeated n = 1,000 times, resulting in 1,000 possible outcomes and thus an approximation of a possible distribution of the YLD [see 16]. (5) The 95% UI is calculated based on this distribution over the 2.5th percentile (lower bound) and 97.5th percentile (upper bound). The distribution assumption for each input variable in the simple form is the log-normal distribution [43]:

$$P^*_{a,s,r,c,j} \sim LN(\hat{\mu}_{a,s,r,c,j}, \hat{\sigma}_{a,s,r,c,j})$$
$$T^*_{a,s,c} \sim LN(\hat{\mu}_{a,s,c}, \hat{\sigma}_{a,s,c})$$
$$J_{k,a,s,c} \sim LN(\hat{\mu}_{k,a,s,c}, \hat{\sigma}_{k,a,s,c})$$
$$DW_{c,j} \sim LN(\hat{\mu}_{c,j}, \hat{\sigma}_{c,j})$$
$$YLD_{a,s,r,c} = \sum_{J_{a,s,c}=1}^{k} P^*_{a,s,r,c,j} * T^*_{a,s,c} * DW_{c,j}$$

Because the point estimates are not symmetric in the 95% CI or 95% UI in some cases, the mean $\hat{\mu}$ is approximated using $\hat{\mu} = \frac{\hat{\mu}_{lb}+\hat{\mu}_{ub}}{2}$, resulting in a more accurate representation of the bounds of the CI or UI. From the 95% CIs ($\hat{\mu}_{lb}$; $\hat{\mu}_{ub}$), the standard deviation $\hat{\sigma}$ is derived from the formula $\hat{\sigma} = \frac{\hat{\mu}_{ub} - \hat{\mu}_{lb}}{3{,}92}$ [2.4] [by transformation 44, p. 43]. The simulation also takes into account a constraint: Since the severity distribution usually adds up to 100%, the realizations from $J_{k,a,s,c}$ ($J_{1,a,s,c,1}$, $J_{2,a,s,c,1}$, … , $J_{l,a,s,c,1}$) are scaled to the denominator $\sum_{k=1}^{l} j_{a,s,c}$ using the point estimators.

4.3. Disability-adjusted life years (DALY)

The disability-adjusted life years (DALY) are the sum of YLL and YLD. The same algorithm was used to calculate the 95% UI as outlined in the section on YLD. For this purpose, both input variables (YLL, YLD) are considered random variables with a known mean and standard deviation. The point estimate $\hat{\mu}$ is approximated by $\hat{\mu} = \frac{\hat{\mu}_{lb}+\hat{\mu}_{ub}}{2}$ and the standard deviation $\hat{\sigma}$ is in turn derived from the formula $\hat{\sigma} = \frac{\hat{\mu}_{ub} - \hat{\mu}_{lb}}{3{,}92}$. The distribution assumption for each input variable is the log-normal distribution.

$$YLL_{a,s,r,c} \sim LN(\hat{\mu}_{a,s,r,c}, \hat{\sigma}_{a,s,r,c})$$
$$YLD_{a,s,r,c} \sim LN(\hat{\mu}_{a,s,r,c}, \hat{\sigma}_{a,s,r,c})$$
$$DALY_{a,s,r,c} = YLL_{a,s,r,c} + YLD_{a,s,r,c}$$

The 95% UI is again calculated using the distribution of 1,000 possible DALY outcomes across the 2.5th percentile (lower bound) and 97.5th percentile (upper bound). As with the merging of the input variables to determine the YLD, the source of uncertainty in the DALY can no longer be accurately inferred because the merging with the YLL adds another source of uncertainty.

5. Multimorbidity adjustment

When quantifying YLD, a correction for multimorbidity or comorbidity is necessary, otherwise the morbidity-related part of the burden of disease is overestimated [16, 45]. Studies for Germany indicate that a large proportion of the population over 50 years of age suffers from more than one disease, the number of burden of disease causes increases steadily with age, and can occur simultaneously in affected individuals [46-48]. The term multimorbidity is often used here, which should be distinguished from the term comorbidity [49]. In the case of comorbidity, it is assumed that one of the burden of disease causes is to be seen as the index disease and that the comorbidities as such are only added [49, 50].

Multimorbidity, on the other hand, is defined as the presence of two or more health conditions without defining a so-called index disease, where all health conditions are equivalent to each other. In the following, we define the presence of two or more health conditions as multimorbidity and consider all health conditions as equivalent in the simulation. Unlike the GBD study, we therefore use the term multimorbidity adjustment, or MUMO, rather than comorbidity adjustment, or COMO [16].

A microsimulation is used to correct for YLD, since the adjustment is not performed at the population level but at the individual level [16]. Microsimulation is used, among other things, to evaluate (health) policy measures and interventions. In these methods, a synthetic dataset is usually generated using statistical methods to predict effects of (health) policy measures or interventions on, for example, the behavior of individuals (or simulants) [51]. Burden-of-disease studies often use static models that refer to only one point in time [16].

The following outlines the microsimulation framework, which was aligned with the GBD study.

Framework of the microsimulation

For each combination of age (a), sex (s), and region (r), a synthetic dataset of 40,000 pseudo-individuals (also called simulants) is generated. Using the information on prevalence ($P_{a,s,r,c}$) per cause (c), each simulant is assigned a vector of burden of disease causes based on (independent) Bernoulli experiments where $P_{a,s,r,c} \sim B(p)$ holds. For this purpose, prevalence is considered as probability and $E[P_{a,s,r,c}] = p$. It should be noted that burden of disease causes whose prevalence in the population is less than 0,0025 % cannot be assigned via the Bernoulli experiment and thus no adjustment is possible under these conditions.

The assignment of the burden of disease causes was independent, which means that the presence of one disease ($P_{a,s,r,1}$) does not influence the presence of another disease ($P_{a,s,r,2}$). However, study results on multimorbidity in the elderly have shown that clusters of burden of disease causes are often apparent and thus some dependence or correlation is to be expected [47, 48]. Since such a procedure requires a much larger amount of data, which could not be generated in the present study, only independent assignments are applied in this version of the simulation, as in the GBD study. As a consequence, the amount of YLD is still overestimated even with an independent MUMO adjustment [45].

MUMO adjustment procedure

The calculation (or algorithm) of the microsimulation is outlined below. The adjustment takes place at the level of individuals and disability weights (DW) by calculating an adjusted contribution of each disease-specific weight to the individual combined DW (or individual YLD). After generating the synthetic dataset, which contains a vector of burden of disease causes per simulant, so-called average DW (hereafter referred to as avdw) are mapped for this purpose, which express the average impairment of an individual due to a disease. These can be described by the following formula:

$$avdw_{a,s,c} = \sum_{j=1}^{k} dw_{c,j} * t^*_{a,s,c} * j_{a,s,c} \quad [2.5]$$

First the sum of all individual avdw is calculated via $\sum_{c=1}^{v} \text{avdw}_{\text{sim,c}}$, where sim is the index for the simulant and c is the number of assigned causes. Then the cumulative avdw (hereafter referred to as cavdw), which expresses a corrected total impairment, is calculated using the following multiplicative formula:

$$cavdw_{sim} = 1 - ((1 - avdw_{sim,1}) * (1 - avdw_{sim,2}) * \ldots * (1 - avdw_{sim,c})) \quad [2.6]$$

From a mathematical point of view, it is guaranteed that the individual, cumulative impairment does not reach the value 1, but merely converges to it [52]. In the context of burden of disease studies, it is therefore assumed that the loss of quality of life cannot simply be "added up" for people suffering from more than one disease. Disability weights reflect the impairment of the respective disease on a scale from 0 (no impairment) to less than 1 (1 would be equivalent to death) [16]. If a simple summation of avdw were applied, in some cases a value much greater than 1 would result, meaning that a living but diseased person in a cross-sectional year would have a greater loss of life years for that year than a person who died from that disease. Therefore, each avdw is further scaled relative to the denominator $\text{cavdw}_{\text{sim,u}}$ using the following formula:

$$avdw_{adj,sim,c} = \frac{avdw_{sim,c}}{\sum_{c=1}^{v} avdw_{sim,c}} * cavdw_{sim} \quad [2.7]$$

In the final step, the adjusted YLD are extrapolated from the synthetic population to the population (denoted $b_{a,s,r,c}$ below) by age, sex, and region using the following formula:

$$YLD_{adj,a,s,r,c} = \left(\frac{1}{n}\sum_{sim=1}^{n} avdw_{adj,sim,c}\right) * b_{a,s,r,c} \quad [2.8]$$

where $n = 40{,}000$.

Uncertainty interval of adjusted YLD

The uncertainty interval of the adjusted YLD is derived from the microsimulation just outlined in conjunction with the stochastic simulation described in section 4 on the uncertainty concept. For this purpose, all input variables (p^*, t^*, j, dw) are considered as log-normally distributed random variables with known mean and standard deviations, from which one value is randomly and independently generated a thousand times and used in the microsimulation algorithm just described. This results in 1,000 outcomes and thus a possible distribution of the adjusted YLD. The 95% UI is generated by this distribution over the 2.5th percentile (lower bound) and 97.5th percentile (upper bound).

6. Stochastic simulation: convergence diagnostics

To determine the 95% uncertainty intervals (UI) for YLD and DALY, a stochastic simulation was applied, which additionally includes a microsimulation when calculating the adjusted YLD (see sections 4 and 5). In what follows we discuss to what extent the (micro-)simulation achieves its goal of generating a sufficiently accurate replication of the distributions of all input variables (prevalences, incidences, severity distributions, disability weights and durations) as well as the number of iterations needed to do so. This is because, when calculating the outcome (YLD, DALY), all input variables are considered as random variables with a given mean and a given dispersion (calculated over the lower and upper 95% confidence and uncertainty intervals, respectively). The distributions that can be derived for the individual input variables are then used to simulate the distributions of the target variables, since these are not known. More specifically, we determine the number of repetitions from which the distribution of a random variable, measured at the mean value as well as lower and upper bound (output values), can be replicated under the assumption of log-normal distribution. The independent Bernoulli experiments represent an additional source of variability (microsimulation).

As an example, the method was applied for an undefined disease with a prevalence of 0.3468 [95%-UI: 0.3161-0.3765]. The following steps were performed in the diagnostic procedure:

(1) Determination of all parameters assuming log-normal distribution.

(2) Random (log-normally distributed) drawing of a possible prevalence from the 95% UI. Generation of a synthetic dataset with 40,000 (pseudo) individuals. Using the prevalence as a (Bernoulli distributed) random variable to predict a disease indicator (1/0) among the 40,000 (pseudo) individuals.

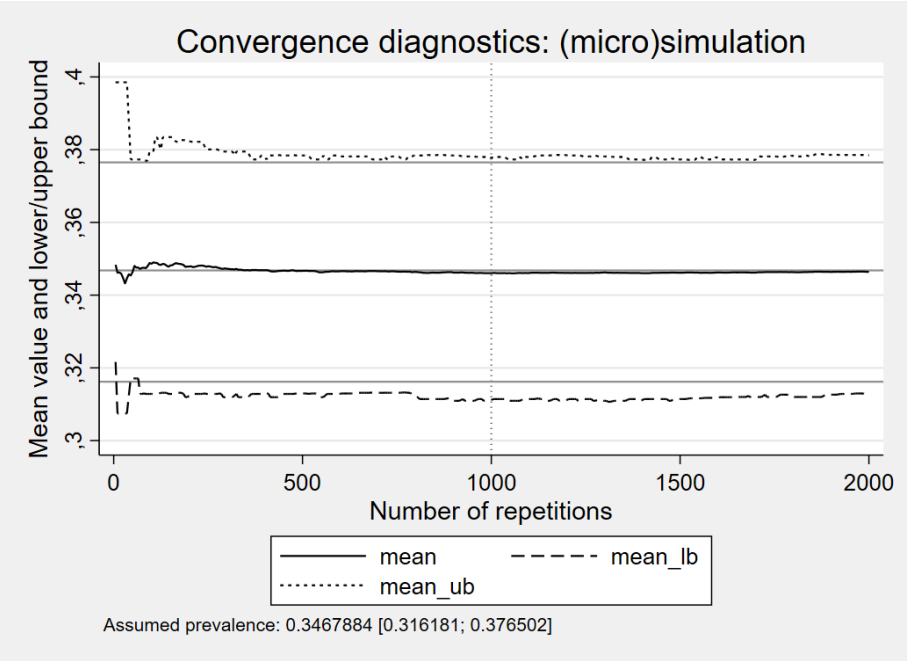
(3) Calculating and storing the prevalence from the Bernoulli experiment among the (pseudo) individuals.

(4) Repeat the process up to 2,000 times.

(5) Stepwise calculation (steps of 5) of the (average) prevalence and the lower and upper bounds (2.5th percentile and 97.5th percentile of the distribution, respectively).

Figure 4 shows the results of the convergence diagnostics. As the number of repetitions increase, the development of the mean, as well as the lower and the upper bound can be seen. The gray horizontal lines indicate the initial values. On the one hand, it is clear that at the beginning of the simulation the distribution of the outcome cannot be replicated with sufficient stability. Only after increasing the number of repetitions do the parameters converge to their initial values. For the present analysis, a number of 1,000 repetitions (vertical gray dotted line) was chosen, since the accuracy of the replication does not improve significantly beyond that (up to 2,000). Similarly, the duration of the simulation as well as the available computing capacities have to be considered. For example, the calculation of 1,000 repetitions took about 21-24 days for a matrix of 19 diseases and injuries at level 3, given the project-specific hardware and software resources available. The replication of the outcome would be somewhat more accurate with 2,000 or more repetitions, but could not be implemented under the given restrictions.

Figure 4: Convergence diagnostics for (micro)simulation (adjusted YLD).



Source: BURDEN 2020, own calculations

7. Results of MUMO-adjustment: comparison of non-adjusted and adjusted *YLD*

In the course of calculating the YLD, a correction for multimorbidity is necessary (for the procedure, see section 5). This is done under the central assumption that each person, regardless of their number of causes, can spend a maximum of one year with health limitations. In other words, the individual YLD must not exceed 1, but only approach it [52]. Consequently, in the context of burden of disease studies, it is assumed that the loss of quality of life cannot simply be "added up" for individuals suffering from more than one disease.

Disability weights reflect the magnitude of impairment by a health state on a scale from 0 (no impairment) to less than 1 (1 would be equivalent to death) [16]. If a simple summation of the weights were applied, it would result in some cases in a value much greater than 1. This would mean that a living but diseased person in a cross-sectional year would have a loss of years of life for that year equivalent to more than one year of life due to death. To correct for such implausible scenarios, the adjustment for multimorbidity (MUMO) is performed using multiplicative rather than additive correction of the weights.

More specifically, the adjustment of the weights (or individual YLD) is proportional to the level of the respective individual weight. Thus, the adjustment for individual YLD is higher for those conditions that are assumed to have higher impairment or are very common in the population. Table 7 compares the adjusted and unadjusted YLD, showing a reduction in YLD in all cases. While the YLD is most adjusted for Alzheimer's disease and other dementias at 5.6%, hypertensive heart disease at 4.7%, and prostate cancer at 4.6%, the MUMO adjustment is lowest for lower respiratory infections at 0.6%. The question whether the assumption of a proportional adjustment is correct remains unanswered for the time being.

Table 7: Comparison of adjusted to unadjusted YLD at level 3 of burden of disease causes (total, both sexes).

Burden of disease cause (level 3)	$YLD_{unadjusted}$	$YLD_{adjusted}$	*Reduction (in %)*
ischemic heart disease	212.080,9	202.781,5	-4,4%
lower back pain	1.485.972,0	1.434.132,0	-3,5%
tracheal, bronchus, and lung cancer	35.045,9	33.464,0	-4,5%
stroke	106.608,7	102.268,8	-4,1%
chronic obstructive pulmonary disease	311.586,8	301.819,1	-3,1%
Alzheimer's disease and other dementias	249.555,4	235.566,2	-5,6%
diabetes mellitus	541.972,2	526.822,9	-2,8%
headache disorders	878.128,4	853.028,3	-2,9%
neck pain	486.411,4	473.412,9	-2,7%
depressive disorders	478.367,4	469.767,3	-1,8%
colon and rectum cancer	62.269,5	59.502,2	-4,4%
anxiety disorders	510.356,2	500.130,3	-2,0%
breast cancer	105.120,2	101.444,9	-3,5%
alcohol use disorders	215.066,2	208.714,8	-3,0%
road injuries	65.375,6	64.581,3	-1,2%
lower respiratory infections	13.117,3	13.041,5	-0,6%
prostate cancer	73.377,0	69.976,4	-4,6%
hypertensive heart disease	77.827,6	74.197,5	-4,7%

Source: BURDEN 2020, own compilation

8. Sensitivity analyses: Duration of illness

In the course of defining and estimating individual input variables for calculating YLD, assumptions are made at several points, especially regarding disease durations. In this sensitivity analysis, results of YLD calculations are compared that refer to different statistical measures of the central tendency with respect to disease durations. In all cases considered, the distribution of disease durations is positively skewed due to a mostly small proportion of affected individuals with very high values (outliers). Thus, the mean value is larger than the median. The question for the sensitivity analysis was whether and to what extent the use of the median compared to the mean influences the results of YLD. Disease durations were estimated for the burden of disease causes lower back pain, neck pain, headache disorders, and major depression using survey data.

Table 8 compares the results of YLD based on mean values (YLD_{mean}) with those based on the median (YLD_{median}). On the one hand, it is clear that the above-mentioned causes result in significantly less burden of disease when the median is considered. While major depressive disorder as part of depressive disorders decreases in YLD most significantly with 57.9%, YLD for lower back pain only decreases by 33.7%. On the other hand, YLD usually increase for the other burden of disease causes, which is due to the proportional method of MUMO adjustment. In summary, it is clear that the calculation of YLD is highly sensitive to change in assumptions regarding disease durations. In the course of the project, the mean values were ultimately used for the disease durations, since it is generally desirable to draw conclusions about the average burden caused by a disease. In addition, the values using the mean were closer to the results of the GBD study, assuming their use as reference values despite clear methodological differences.

Table 8: Comparison of YLD based on the mean values for disease durations versus YLD based on median at level 3 of burden of disease causes (total, both sexes).

Burden of disease cause (level 3)	YLD_{mean}	YLD_{median}	Percentage change (in %)
ischemic heart disease	202.781,5	203.772,3	0,5%
lower back pain	1.434.132,0	950.290,0	-33,7%
tracheal, bronchus, and lung cancer	33.464,0	33.632,0	0,5%
stroke	102.268,8	102.826,5	0,5%
chronic obstructive pulmonary disease	301.819,1	303.154,3	0,4%
Alzheimer's disease and other dementias	235.566,2	237.238,6	0,7%
diabetes mellitus	526.822,9	528.728,1	0,4%
headache disorders	853.028,3	415.294,2	-51,3%
neck pain	473.412,9	218.443,5	-53,9%
depressive disorders	469.767,3	197.901,0	-57,9%
colon and rectum cancer	59.502,2	59.826,7	0,5%
anxiety disorders	500.130,3	501.167,0	0,2%
breast cancer	101.444,9	101.844,0	0,4%
alcohol use disorders	208.714,8	210.594,9	0,9%
road injuries	64.581,3	64.403,4	-0,3%
lower respiratory infections	13.041,5	13.050,5	0,1%
prostate cancer	69.976,4	70.628,7	0,9%
hypertensive heart disease	74.197,5	74.293,1	0,1%

Quelle: BURDEN 2020, own compilation

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