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VITALITY AGE V.3

Technical Report

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Preface

This report defines and describes an updated Vitality Age model. Vitality Age is a risk-adjusted health assessment tool giving individuals a snapshot of their overall health based on lifestyle choices and clinical risk factors. Building on the original Vitality Age model developed by the University of Cape Town and the Sports Science Institute of South Africa, the new model maintains the core concept principles – it reflects an individual's overall health status through a single number, the Vitality Age – yet it expands the number of input factors used in the analysis and builds on more comprehensive and consistent data sources. This report summarises the updated model and methodology, data used for its calibration and calculation, and the calculation algorithm itself.

This research was funded by the Discovery group of companies, part of Discovery Limited. Discovery was also a collaborator in the work, including contributions by co-authors Francois Millard and Howard Bolnick.

Discovery Limited is a South African-founded financial services organisation that operates in the healthcare, life assurance, short-term insurance, savings and investment products and wellness markets. Discovery employs its Vitality Shared-Value Insurance model, which incentivises healthier behaviour for the benefit of clients, insurers and society.

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Summary

Vitality Age is a health indicator concept giving individuals a snapshot of their overall health based on lifestyle choices – including diet, alcohol consumption and exercise habits – and clinical factors such as blood pressure, cholesterol and body-mass index. Vitality Age was originally developed by the University of Cape Town and the Sports Science Institute of South Africa for Vitality globally. RAND Europe has been commissioned by the Discovery group of companies, part of Discovery Limited to update the existing algorithm and the underlying data in order to make it more up-to-date and accurate.

Vitality Age adjusts an individual's age to their life expectancy, by comparing their health to that of the average population. This is done by calculating a bespoke life expectancy estimate using a predefined set of the individual's risk factor measures and comparing that to the life expectancy of an average person with the same sex, age and country characteristics. The Vitality Age is thus the actual chronological age adjusted by the difference in life expectancy; it estimates the individual's remaining years of life and produces an adjusted age estimate so that their life expectancy remains unchanged. Vitality Age lower than actual age thus reflects additional estimated remaining years of life compared to an average individual of the same age and characteristics. Vitality Age higher than actual age, however, is a negative sign, as it signals a lower-than-average number of years of life remaining, with the difference between Vitality Age and actual age being equal to the estimated change in life expectancy.

In summary:

$$\text{Vitality Age} = \text{actual age} + \text{population life expectancy} - \text{individual life expectancy}.$$

This report presents an updated Vitality Age (VA.3) methodology, making it more detailed, more up-to-date and also better applicable to varying geographical contexts. Most importantly, the new model incorporates age-related mortality as compared to single parameters used for individuals of all ages in the previous version. It also considers the impacts of individual's health and lifestyle on each identified disease separately, providing more transparency and information on the estimated effects. At the same time, the underlying concept remains unchanged from the previous Vitality Age model – it still covers behavioural and metabolic risk factors and reflects an individual's overall health status through a single number, the Vitality Age – but it expands the number of input factors used in the analysis and builds on more a comprehensive and consistent data source.

VA.3 uses data from the Global Burden of Disease Study (GBD), a large database quantifying modifiable risks of death, disease and disability through systematic reviews of the existing literature. Led by the Institute for Health Metrics and Evaluation (IHME) at the University of Washington, the GBD study

involves over 1,000 researchers from more than 100 countries, including 26 low- and middle-income countries. To create the database, researchers collate findings from all appropriate published epidemiological studies and data sources such as hospital data, disease registry data or censuses, and combine the information using a Bayesian meta-regression framework. The GBD provides a consistent and comparative quantification of more than 300 diseases and injuries in 188 countries, by age and sex, from 1990 to the present day, and is updated regularly. GBD data are widely used in scientific literature and have the advantage of not being associated with a single cohort of individuals or methodology, but rather being a product of a multitude of studies from countries all over the world. VA.3 is thus based on a recognised third-party dataset and should remain up-to-date in the future. Moreover, its estimates are likely to gradually improve as the quality of the data provided by the GBD database does, and its potential will also improve as new variables are added.

In principle, the calculation of a bespoke life expectancy estimate is based on an adjustment of the 'baseline' mortality rates (i.e. age-sex-country-disease-specific mortality rates in the absence of all identified and quantifiable risk factors such as alcohol consumption, smoking, suboptimal diet or elevated blood pressure) according to the risk factor profile of a given individual. The VA.3 model uses relative risks associated with the particular risk factor values, looking separately at each individual risk factor-cause of death pair and comparing it to a counterfactual scenario in which the individual is not at risk, either through complete non-existence of the risk factor (e.g. no alcohol consumption) or being within the assumed healthy range (e.g. 110–115 mmHg for systolic blood pressure). The risk factor and relative risk classifications come from the GBD database and differ for each risk factor-cause of death pair, creating a matrix of links between risk factor determinants of an individuals' health and their health assessment.

Following the GBD methodology, the VA.3 model partially estimates joint risk factor burden for combinations of risks using a set of identified mediation factors. That is, a risk factor may affect another risk factor that lies in the physiological pathway to a disease outcome, such as the effect of obesity through an increase in fasting plasma glucose and later cardiovascular disease outcomes. The assessment of joint effects is used both in the determination of the baseline mortality rates and in the subsequent adjustment according to the individual's risk factor profile. However, the set of modelled interactions is limited to those identified in the epidemiological literature. The remaining risk factor interactions that are not captured within the estimated mediation factors, due to practical limitations, are adjusted for in the formulas used to compute the joint parameters.

VA.3 improves the way an individual's risk factor profile is translated into the Vitality Age model inputs by simulating changes in risk factor values over time rather than assuming constant inputs throughout one's life, as was the case in the original model. It also improves handling of missing data, estimating unknown values for biometric indicators from other risk factors values using predictive regression analysis and allowing the use of population average exposure in place of missing values for other risk factors. By considering age- and cause-specific mortality rates, VA.3 also improves the life expectancy calculation compared to the original model, which implicitly assumes that causes of death do not vary by age and thus misstates life expectancy for other than average age. Lastly, the model introduces various other minor computational improvements, such as more realistic mortality curve adjustment for higher ages.

Additional adjustments are made to introduce mental health to the model without affecting its internal coherence.

Aiming to deliver an optimal user experience, VA.3 substantially expands the possibilities for sensitivity analysis of results, allowing disaggregation of the effects, for example through assessment of the most important positive and negative contributors to the model outputs, as well as recalculation of the outputs based on changes to a subset of risk factors. This consequently allows the creation of interactive tools that may be used by individuals to see how potential changes to their lifestyle or medication may improve their Vitality Age.

Relying on sets of established questions from reviewed literature, VA.3 uses a bespoke survey to represent an individual's risk factor profile as a set of model input values. The survey has been developed with the aim of capturing sufficient variation in risk factor values, while being relatively short and understandable to the general public. To this end, the survey uses sets of images in place of text descriptions and categorical questions in place of open questions, and it opens the way to introducing various modern health and lifestyle trackers, such as Apple Watch or Fitbit devices, as sources of data inputs.

Finally, using the country-specific data on mortality rates and risk factors from the GBD database, VA.3 substantially improves adjustability to new geographical contexts, allowing selection from more than 70 risk factors to be used in the model, according to their relative importance in a given region and using country-specific mortality rates.

Acknowledgements

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Abbreviations

ACC	American College of Cardiology
AHA	American Heart Association
AUSDRISK	Australian type 2 diabetes risk assessment tool
BD	Baseline deaths
BP	Blood pressure
BMI	Body-mass index
CKD	Chronic kidney disease
CVD	Cardiovascular disease
DALY	Disability-adjusted life years
DBP	Diastolic blood pressure
FPG	Fasting plasma glucose
GBD	Global Burden of Disease Study
HDLC	High-density lipoprotein cholesterol
IHME	Institute for Health Metrics and Evaluation
LDLC	Low-density lipoprotein cholesterol
MF	Mediation factor
mmol/L	Millimoles per litre
NHANES	National Health and Nutrition Examination Survey
NICE	National Institute for Health and Care Excellence
MR	Mortality rate
PA	Physical activity
PAF	Population attributable fraction
RA	Rheumatoid arthritis
RF	Risk factor
RR	Relative risk
SBP	Systolic blood pressure

SEV	Summary Exposure Value
SIR	Smoking impact ratio
TC	Total cholesterol
TX	Treatment
TMREL	Theoretical minimum risk exposure level
T2D	Type 2 diabetes mellitus
VA.3	Vitality Age version 3
WCRF	World Cancer Research Fund
WEMWBS	Warwick-Edinburgh Mental Wellbeing Scale

1. Introduction

Many researchers have attempted to improve people's health by providing tailored and up-to-date information about it; however, the range of existing approaches to health assessment suggests that there is no universal ideal health risk score. The utility of any score depends on both the methodological robustness and statistical properties of the risk calculator, and also the context in which it is used. Importantly, there are different routes via which risk scores could be expected to improve health outcomes: these include through guiding clinical decision-making (for example around prescribing decisions), supporting planners and commissioners of health services to most appropriately direct healthcare resources, and through guiding areas for future research (Noble et al. 2011; Payne 2012). A further motivation for risk prediction is the development of actuarial models.

However, one of the most important impacts of risk scores is in their use by individuals in self-assessment (where people assess their own risks, for example using an online tool). This can directly lead to changes in lifestyle or may indirectly impact health outcomes, where individuals, having assessed their own risk, are prompted to consult with healthcare professionals for further investigation or advice on prevention (Noble et al. 2011).

Vitality Age is a health indicator concept giving individuals a snapshot of their overall health based on lifestyle choices and clinical factors such as blood pressure, cholesterol and body-mass index. Vitality Age was originally developed by the University of Cape Town and the Sports Science Institute of South Africa for Vitality globally. Vitality Age is embedded into Vitality wellness programmes, including the annual survey for the competition for Britain's Healthiest Workplace,[1] and as an online tool accessible by the public. It is designed to support individual risk assessment, to provide personalised feedback in a simple and relevant format, as a motivating tool to promote healthier lifestyles, and for population risk surveillance and reporting.

Vitality Age adjusts an individual's age to their life expectancy, by comparing their health to that of the average population. This is done by calculating a bespoke life expectancy estimate using a predefined set of the individual's risk factor measures and comparing that to the life expectancy of an average person with the same sex, age and country characteristics. The Vitality Age is thus the actual chronological age adjusted by the difference in life expectancy; it estimates the individual's remaining years of life and produces an adjusted age estimate so that their life expectancy remains unchanged. Vitality Age lower than actual age thus reflects additional estimated remaining years of life compared to an average

[1] https://www.rand.org/randeurope/research/projects/britains-healthiest-workplace.html#2016-

individual of the same age and characteristics. Vitality Age higher than actual age, however, is a negative sign, as it signals a lower-than-average number of years of life remaining, with the difference between Vitality Age and actual age being equal to the estimated change in life expectancy.

In summary:

$$\text{Vitality Age} = \text{actual age} + \text{population life expectancy} - \text{individual life expectancy}.$$

RAND Europe has been commissioned by the Discovery group of companies, part of Discovery Limited to update the existing Vitality Age algorithm and the underlying data it uses in order to make it more up-to-date and accurate. This report defines and describes the updated and improved Vitality Age model (VA.3), explaining in detail its individual elements, such as its theoretical framework, as well as the research steps taken throughout its creation, with the purpose of informing existing and future stakeholders and identifying areas that may need future improvement.

Building on the original Vitality Age model, the new version maintains the core concept principles, but it expands the number of input factors used in the analysis, builds on a more comprehensive and consistent data source, incorporates age-related mortality, improves handling of missing data, , and substantially expands the possibilities for sensitivity analysis of results.

Structure of this report

In Section 2, we outline existing mortality and general health risk calculators. In Section 3 we describe the methodological framework used in VA.3. In Sections 4, 5, and 6, we describe the detailed implementation of VA.3, with these chapters setting out the selection of risk factors, how data is collected and processed, and the specific survey questions used.

2. Review of existing mortality and disease risk calculators

In this section we present the methods used for our literature review of existing mortality and disease risk calculators, an overview of the relevant literature identified, and the findings with respect to the range of outcomes and time horizons considered in the models, their structure and the risk factors linked to the outcomes. The review was performed to garner information about the latest developments in the area of life expectancy assessment – and thus to inform what may be the best way of approaching the VA.3 theoretical model. Besides the literature relating to particular calculators presented below, the review also identified several methodological studies that are not described further in detail in this report, since they were not considered relevant to the approach taken. However, the model presented in one of the studies, Lim et al. (2015), has been used as a baseline for the VA.3 framework discussed in the next section. The main findings are summarised in Box 1 and are presented in detail in Section 2.2 below.

Box 1. Main literature review findings

In summary, we found that extracting coefficients from systematic reviews and meta-analyses on risk factors related to all-cause and disease-specific mortality appears to be an under-utilised approach in risk calculator development. Specifically, models calculating risk using existing empirical estimates extracted from systematic reviews and meta-analyses may lead to models calculating risk with higher sensitivity than scoring based on consensus opinion. Furthermore, whilst this approach would not have the accuracy and predictive performance achieved by algorithms derived from cohort studies, it has the advantage of being applicable to a broader range in populations. An additional advantage of deriving risk factors from pooled resources is the increased power in estimating risk factors relating to mortality – a limitation of cohort-based calculations, where often insufficient events occur within cohort follow-up timeframes. Lastly, pooling existing empirical evidence does not require researchers to follow a selected cohort for an extended period of time and may therefore be more practical for most applications.

At the same time, the method of using data from systematic reviews has several potential limitations, the greatest of which is difficulty in comparing risk factors. Indeed, in methods based on a single cohort, the relative impact of different risk factors can be directly compared and incorporated, whereas systematic reviews need to combine effects on different populations. The method is also fully reliant on the existence, coverage and quality of existing studies. This may lead to underrepresentation of certain populations or geographical locations, as well as questionable quality of the resulting data if selection of the studies is not done properly.

2.1. Literature review

We conducted a comprehensive literature review to identify online risk calculators currently in use and with their development (and validation) published in the scientific literature. This consisted of searches in major relevant databases, scanning reference lists of identified publications and examining webpages of relevant bodies (the National Institute for Health and Care Excellence (NICE), the American College of Cardiology/American Heart Association (ACC/AHA), the Heart Foundation of Australia, the New Zealand Heart Foundation and the European Society of Cardiology) to identify calculators recommended for clinical use in a number of countries. Calculators were excluded if they were designed for a specific population (e.g. diabetics, older people) or for a particular situation (e.g. chronically institutionalised patients, post-surgery, post-event). Upon inspection, many international risk calculators were found to be based on Framingham calculations; only a select few were included in the assessment as they essentially follow the same methodology and use the same data sources. In cases where multiple studies were found to relate to the same calculator, a single article – the most recent that provided comprehensive summary of the calculator – was included in the review. Table 1 identifies the databases searched and the specific set of search terms used. The results were initially screened in terms of title and/or abstract by two members of the research team; the inclusion criterion was 'description of a health risk calculator applicable to single individuals', while the exclusion criteria were 'aim at a specific population' (e.g. diabetics, post-surgery patients) and 'duplicity in relation to a single calculator'. The initial review was then followed by a more detailed full-text screening. No quality assessment of the reviewed studies was undertaken.

Table 1. List of search terms

Database	Search terms
Pubmed	"calculator" [all fields] AND "mortality" [all fields]
	"mortality risk calculator(s)" [all fields]; "cardiovascular risk calculator(s)" [all fields]; "heart disease risk calculator(s)" [all fields]; "mortality predictors and calculation" [all fields]; "predicting cardiovascular risk" [title only]; "cardiovascular risk assessment" [title only]
Embase	"calculator" [all fields] AND "mortality" [all fields]
Google Scholar	"CVD risk calculator validated", "mortality risk calculator validated"

The following information was extracted from publications related to risk calculators and tabulated: name; year; cohort (sex, age range, location/country, ethnicity); validation; mortality or event; mortality (specific or all cause); risk factors; risk factor coefficients; justification for inclusion of risk factor); model structure; model performance; (lifestyle) recommendations included (results from online tool); reference(s); comments; and calculations.

2.2. Results of the literature review

2.2.1. Overview of the literature on existing calculators

The database queries resulted in 5,823 identified articles in total. Out of these, 5,374 were excluded on title and/or abstract screening and 434 were excluded on full-text review, resulting in a selection of 15 articles relating to mortality and morbidity calculators, which covered:

- A range of outcomes (five-year cardiovascular disease risk to all-cause mortality).
- A range of risk factor types (biomarkers only, combined lifestyle and biomarker risk factors, and lifestyle-only risk factors).
- A range of underlying model structures (derived from single and pooled cohort evidence, consensus opinion based on systematic review and results of randomised controlled trials).

A summary of the features of these risk calculators is given in Table 2. The selected calculators covered the cardiovascular disease (CVD) risk calculators recommended for clinical CVD risk assessment in the UK (QRISK2), United States (Joint ACC/AHA CV Risk Score), Europe (SCORE), Australia (Australian Absolute Cardiovascular Disease Risk Calculator) and New Zealand (PREDICT/Your Heart Forecast).

Table 2. Summary of existing health risk calculators

Name	Outcome	Health risk factors	Structure	Data extraction	Reference and link to calculator
Healthy Heart Score	CVD event (20-year risk)	Lifestyle + smoking (diet score, age, smoking, BMI, alcohol, exercise)	Pooled prospective cohorts	Multivariable Cox proportional hazards model	Chiuve et al. (2014) healthyheartscore.sph.harvard.edu/
Life's Simple 7	CVD and stroke mortality	Lifestyle + biomarker (TC, BP, FPG, PA, diet score, smoking, BMI)	Consensus opinion	Additive points system	Lloyd-Jones et al. (2010) mylifecheck.heart.org/mobile/assessment.aspx
Your Disease Risk (your Heart Risk, Your Diabetes Risk)	CVD Event or T2D incidence (risk compared to average for age and sex)	Lifestyle + biomarker (sex, family history, BMI, waist, smoking, BP, ethnicity, (T2D), TC, HDLC, PA, diet score, alcohol, vitamin B supplements)	Consensus opinion	Additive points system	Colditz et al. (2000) (original methods) www.yourdiseaserisk.wustl.edu/
QRISK2*	CVD (major) event (10-year risk)	Lifestyle + biomarker + concurrent disease (ethnicity, age, sex, smoking, SBP, TC:HDLC, BMI, family history, Townsend deprivation score, hypertension TX, RA, CKD, T2D, atrial fibrillation)	Prospective open cohort	Multivariable Cox proportional hazards model (sex-specific)	Hippisley-Cox et al. (2008) www.qrisk.org/
Framingham Risk Score	CVD event (10-year risk)	Lifestyle + biomarker (Age, BMI, DBP, SBP, T2D TX / FPG, TC, LDLC,	Prospective cohort[a]	Multivariable Cox proportional	Wilson et al. (1998) cvdrisk.nhlbi.nih.gov/

		HDLC, smoking)		hazards model (sex-specific)	
Framingham Risk Score (for use in primary care)	CVD event (10-year risk)	Biomarker (+ smoking) (age, TC, HDLC, SBP, BP TX, smoking, T2D)	Prospective cohort[a]	Multivariable Cox proportional hazards model (sex-specific)	D'Agostino et al. (2008)
SCORE*	CVD mortality	Biomarker (+ smoking) (sex, age, smoking, SBP, TC, low-/high-risk region)	Pooled prospective cohorts	Weibull proportional hazards model (cohort and sex-specific)	Conroy et al. (2003) http://www.heartscore.org/en_GB/access
Ubble	All-cause and cause-specific mortality	Self-reported data only (sex, age, vehicles use (M), individuals in household (M), smoking, health rating, walking pace, T2D (M), cancer, CVD (M), recent life trauma, government allowances, # children (F), chronic disability, illness or infirmity (F), anxiety/depression (F))	Prospective cohort	Multivariable survival model	Ganna & Ingelsson (2015) www.ubble.co.uk
Lee Schonberg Index	All-cause mortality	Self-reported data only (age, sex, T2D, cancer, chronic lung disease, heart failure, smoking, BMI, difficulty bathing, walking, managing finances, pushing/pulling heavy objects)	Prospective cohort (>50 years)	Multivariable logistic regression model	Lee et al. (2006) eprognosis.ucsf.edu/leeschonberg.php
AUSDRISK*	Incident T2D (5-year risk)	Lifestyle + biomarker + concurrent disease (age, sex, ethnicity, family history, high BP, BP TX, smoking, PA, waist circumference)	Prospective cohort	Additive scoring system based on coefficients from multivariable logistic regression	Chen et al. (2010) www.health.gov.au/internet/main/publishing.nsf/Content/diabetesRiskAssessmentTool
ACC/AHA CV Risk Calculator*	CVD event (10-year risk)	Lifestyle + biomarker (age, TC, HDLC, TX SBP, SBP, smoking, T2D)	Pooled prospective cohorts	Multivariable Cox proportional hazards model (sex & ethnicity-specific)	Stone et al. (2014)
ACC/AHA CV Lifetime Risk Calculator	CVD mortality	Biomarker (TC, BP, T2D/FPG, smoking, BMI)	Prospective cohort[a]	Modified Kaplan-Meier survival analysis	Lloyd-Jones et al. (2006)
Single risk tool for CVD, CKD & T2D	Cardio-metabolic disease (7-year risk)	Lifestyle + self-reported (age, sex, BMI, smoking, family history, BP TX, waist circumference)	Pooled prospective cohorts	Multivariable logistic regression model (sex-	Alssema et al. (2012)

				specific)	
Your Heart Forecast*	CVD event (5-year and projected mortality risk)	Lifestyle + biomarker (age, sex, SBP, smoking, TC:HDLC, T2D, ethnicity, family history)	Prospective cohort[a]	Multivariable logistic regression model	Wells et al. (2010) www.knowyournumbers.co.nz/
Heart age (a global tool)	CVD mortality	Lifestyle + biomarker (age, sex, SBP, smoking, TC:HDLC, T2D, ethnicity, family history)	Prospective cohort[a]	Multivariable logistic regression model (adapted with local mortality data)	Lloyd-Jones et al. (2006)

Website URLs active as of 29 November 2017.
* Tools recommended for use in clinical practice by National guidelines, relevant charity organisations and health alliances.
[a] based on the Framingham prospective cohort.
Source: RAND Europe analysis.

Findings from the 15 included articles outlined above are summarised in the following sub-sections on outcomes, model structure and risk factors. These observations are then used to determine the ideal VA.3 model structure described in Section 3.

2.2.2. Outcomes considered in the selected calculators

The first area of interest related to the range of outcomes (i.e. mortality or morbidity, selection of diseases and conditions). Our review of the literature identified very few published/validated calculators designed for the general (healthy) population that estimate lifetime risk or adjusted age. An exception was the Ubble calculator, which calculated all-cause and disease-specific mortality. An additional unique feature of this calculator was that all survey data were included in order to mathematically derive the most relevant risk factors. This is in contrast to most existing risk calculators where a process of risk factor selection is based on prior knowledge and consensus opinion. However, the Ubble calculator is based on an unusual set of risk factors limited to the self-reported questionnaire and tested over a very short follow-up period, resulting in low incident rate and low accuracy.

Most calculators are based on the five- or ten-year risk of developing a disease, concentrating on cardiometabolic diseases (cardiovascular diseases, chronic kidney disease and type 2 diabetes mellitus). The advantage of these time-limited risk calculators is increased accuracy in predicting the relative contribution of risk factors derived from cohort study data (Lloyd-Jones 2010). It is possible to project lifetime risk from five- and ten-year risk models, a feature that is built into some calculators. However, a review of CVD risk calculators indicated that lifetime risk could not be accurately projected from five- and ten-year risk scores (NICE 2014). A noteworthy limitation of five- or ten-year risk calculators is that they will mostly classify young people as low risk even though their lifetime risk might be very high (Chiuve et al. 2014; Wells et al. 2010). Calculators that predict five- and ten-year risk are primarily aimed at people aged over 50 or 60 and are therefore not broadly applicable, particularly in a workplace setting.

Some tools combined five- or ten-year risk with lifetime risk (Your Heart Forecast, ACC/AHA CV risk) in order to achieve accuracy (time-limited prediction) with a metric that was deemed more

comprehensible to the patient or general population. A disadvantage of this approach was conflicting results due to the different algorithms used to calculate both metrics (Goff et al. 2013).

2.2.3. Model structure

Most of the identified risk calculators are based around algorithms derived from cohort studies. Importantly, the risk predictions are limited to the demographics of the cohort from which the algorithms are derived. This is demonstrated by the poor agreement in risk prediction between 25 risk calculators from different regions (one in three risk calculators will assign the same patient to a different risk category) (Allan et al. 2013). Analysis using non-recruited population cohorts (QRISK2 is based on data collated from GP practices) or pooled cohorts (such as those used to derive SCORE and ACC/AHA CV risk calculator) can address some of these issues.

An additional consideration of cohort-derived risk calculations is that a broad definition of outcomes has been included in order to increase the number of events and hence the power to detect potential risk factors. For example the Framingham-based calculations include angina as an event (and this constitutes around 50 per cent of events), although this is arguably not considered a major CVD event. Consequently, risk calculators based on Framingham calculations tend to overestimate risk in most populations (Beswick et al. 2008; Collins & Altman 2009). This reduced power in estimating contributions of risk factors related to low event numbers is a particular problem dealing with mortality as an outcome in cohort studies.

Almost all calculators from single or pooled cohort studies are built using coefficients from logistic regression or Cox proportional hazard models. In some calculators the coefficients are simplified into scores using the method of Sullivan et al. (2004), which then allows practitioners to assess an individual's health without a calculator or computer, although this is more commonly seen in chart-based rather than online risk calculators.

Some calculators have also been derived from scoring systems based on consensus opinion of evidence from systematic reviews and randomised controlled trials. These calculators have the advantage of being applicable to a broader population (in terms of age, ethnicity, geography, etc.) and appear to predict risk well. The Life's Simple 7 score (an example of a consensus-based score) was found to correlate well with the probability of having a CVD and all-cause mortality in ~45,000 participants of the National Health and Nutrition Examination Survey (NHANES) in the United States (Lloyd-Jones et al. 2010).

2.2.4. Risk factors considered in the selected calculators

There is consistency amongst risk factors included in the selected calculators, particularly in the case of CVD risk calculators (see Table 2). The greatest accuracy in risk prediction comes from using biomarker intermediaries (such as BMI or cholesterol blood glucose) as a measured impact between lifestyle exposures (such as diet or physical activity) and outcome (CVD, all-cause mortality) (Alessma et al. 2012). Whilst these intermediaries change in response to lifestyle factors, some calculators omitted lifestyle factors from their calculations as there was no improvement in risk prediction obtained from their inclusion. This may also be a result of the relatively low availability of reliable data (a situation that is

improving over time with technological advancement, as more individuals use wearable activity tracking devices or smart scales).

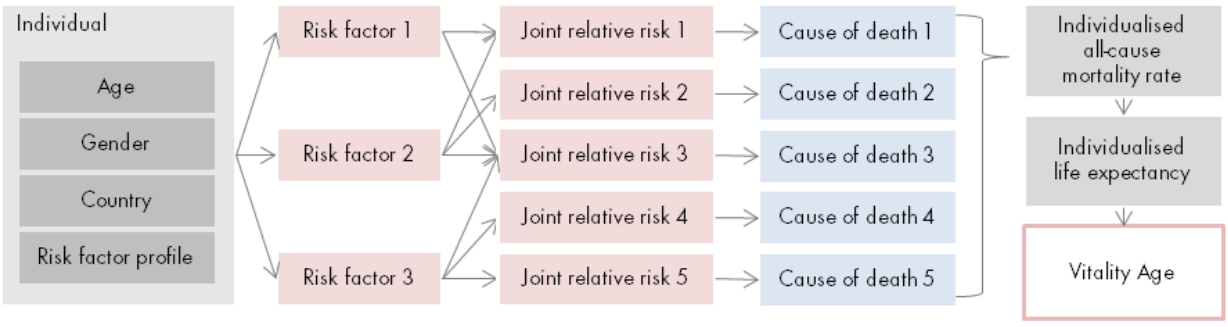
Most CVD-risk calculators have been designed as clinical tools to guide treatment options, and biomarker measures are readily available in this setting. However, in terms of using the calculators more generally (i.e. by individuals in non-clinical setting), the majority of the population do not know the values for many of the variables (for example periodic testing of cholesterol is not offered in the UK prior to age 40). Some calculators intentionally omitted risk factors that required medical measurements for this reason (Healthy Heart Score, Ubble, Lee Schonberg Index and the Single risk tool for CVD, CKD & T2D).

3. Methodological framework for VA.3

In this section we discuss the theoretical model behind the VA.3 calculator, which is then transformed into a computer script and combined with appropriate data to allow the health assessment of individuals.

Based on the original Vitality Age methodology and drawing on the recent work done by Lim et al. (2015), the proposed approach to an individual's health assessment uses elementary risk factor-cause of death pairs and the associated mortality rates and relative risks, combined into joint relative risks, to compute a series of bespoke annual individualised all-cause mortality rates. That is, the algorithm looks separately at each risk factor and each cause of death in turn, determines whether and how they are connected, and the extent to which the individual's risk factor profile affects the estimated mortality rates associated with the given cause of death, mediated through the given risk factor. This is a significant improvement compared to the previous Vitality Age algorithm, which multiplied the default all-cause mortality rates by the individual relative risks, as it provides substantially more insight into the particular drivers of lower- or higher-than-average life expectancy and allows detailed sensitivity analysis of the results. The VA.3 methodological framework is depicted in Figure 1.

Figure 1. VA.3 methodological framework flowchart



Note: Not all risk factors are associated with every cause of death; hence the joint relative risks 2, 4 and 5 are modelled using only a single risk factor while the joint relative risks 1 and 3 are associated with two and three risk factors, respectively. The terminology 'joint relative risk' is used for all relative risks for simplicity.
Source: RAND Europe, based on Lim et al. (2015).

The methodological framework is based on Lim et al. (2015) and follows the generally accepted concept of diseases and conditions being (partially) affected by risk factors. In this section we discuss the selection of data sources to be used for the estimation of the framework, risk profile data inputs and adjustments, and the particular implementation of each step in the diagram above based on the selected source of parameters. Finally, we present alternative scenarios in which the new Vitality Age may be calculated.

3.1. Selection of data sources for the VA.3 calculator

Given the focus on lifetime all-cause mortality risk in the Vitality Age concept (compared to the five- or ten-year focus of the majority of other calculators), its applicability to individuals of all ages and sexes, and the demand for a high degree of geographical adjustability, the same focus – using data collected from systematic reviews – was selected for the new calculator. This contrasts with the use of data from cohort studies, which offer limited applicability to other populations. However, it also differs from the original Vitality Age calculator, which uses relative risk estimates for all-cause mortality from systematic reviews, and applies this estimate of the relative risk to age-, sex- and country-specific life tables (i.e. the all-cause mortality, rather than to each single-cause mortality individually). That is, steps three and four in Figure 1 would consist of only a single element – the all-cause joint relative risk and all-cause mortality – rather than cause-specific parameters. What is more, the original Vitality Age model does not assume varying relative risk estimates for different ages, sexes or countries. For example, the adverse effect of high blood pressure is considered to be the same for young and old individuals, and for men and women. The Vitality Age results are thus misstated, particularly for individuals with substantially lower or higher age than the average age.

As we have seen, most of the calculators presented in Section 2 rely on prospective cohort studies or consensus opinions as opposed to the systematic-review approach selected for VA.3. Rather than conducting a meta-analysis of the relevant epidemiological literature, we followed the approach set out by Lim et al. (2015) and selected the Global Burden of Disease Study (GBD)[2] as the only data source for virtually all parameters used in the algorithm. GBD is an outcome of a large-scale initiative to identify and quantify modifiable risks of death, disease and disability through systematic reviews of the existing literature. It provides a consistent and comparative quantification of more than 300 diseases and injuries in 188 countries, by age and sex, from 1990 to 2016 and is annually updated. Most importantly, the GBD data are publicly available and widely used in the scientific literature and provide unmatched coverage and consistency of estimates across age, sex and country dimensions. Using GBD data thus ensures the utmost achievable consistency of parameters used in the model as well as good sustainability due to regular database updates.

In the GBD database, each risk factor is modelled in a separate relation to each relevant potential cause of death (rather than to overall mortality) in a complex system of Bayesian meta-regressions, pooling together all relevant epidemiological studies on the subject that pass the explicit quality checks (see below) and approximating data points where little or no evidence is found – e.g. for smaller countries – based on values for similar units. The method uses a theoretical minimum risk exposure level (TMREL) to quantify the extent to which a disease burden could be decreased by lowering exposure to the individual risk factors. Risk-outcome pairs are included based on availability of sufficient data to estimate risk factor

[2] http://www.healthdata.org/gbd

exposure, evidence to support a causal[3] relation, and evidence that these effects can be applied to a general population.

The GBD researchers use the World Cancer Research Fund (WCRF) grading system of convincing, probable, possible and insufficient evidence (Forouzanfar et al. 2015), and only risk-outcome pairs that are convincing or probable are included in the analysis. The study focuses on behavioural, environmental, occupational and metabolic risk factors, not including genes, health interventions and broader socio-economic and cultural factors.

The GBD study also considers the attribution of burden of disease to various combinations of risk factors or to all risk factors combined, computing the joint risk factor burden for metabolic risks and combination of metabolic risk factors with other behavioural or environmental risk factors. This is done through a literature review of risk factor mediation (i.e. the way one risk factor affects another in relation to a given cause of death). Note that the set of modelled mediation factors is limited to those estimated with a sufficient degree of certainty in the epidemiological literature. The remaining risk factor interactions that are not captured within the estimated mediation factors due to practical limitations are adjusted for in the formulas used compute the joint parameters. All variables are estimated for ages 0–95 in five-year age groups.

Overall, the GBD database provides unrivalled coverage across risk factors, causes of death, geographical locations, sexes and ages. The available data cover all parameters used in the model except for mortality rate estimates for extremely high ages (95+ years), which must be supplied from other sources. For UK localisation, the data come from the national life tables for Great Britain published by the Office for National Statistics.[4]

3.2. Mortality rate calculation

The principal purpose of the Vitality Age algorithm is to calculate the individualised all-cause lifetime risk of death, as depicted in Figure 1. This is done in four main steps. Firstly, the population cause-specific mortality rates for given sex, age and location are taken as a starting point – these are approximately applicable to an individual with the population average risk factor profile. Secondly, counterfactual baseline mortality rates for an individual with no history of heightened exposure to any risk factor are calculated from the population mortality rates using population attributable fractions. Thirdly, individualised probability of dying rates specific to the assessed individual are calculated from the baseline mortality rates (transformed into probability of dying within 12 months) using risk-cause-specific relative risks. Finally, the cause-specific probabilities of dying are combined in all-cause probabilities of dying. This is done for each age from an individual's actual age onwards, assuming that the underlying risk factor

[3] Causation indicates that one event is the result of another event (e.g. that excessive consumption of salt leads to increased blood pressure), as opposed to correlation, which describes relationship between two variables but does not need to imply that one event is a result of the other (e.g. individuals who smoke are more likely to consume alcohol as well, yet alcohol consumption is not caused by smoking).

[4] https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesgreatbritainreferencetables

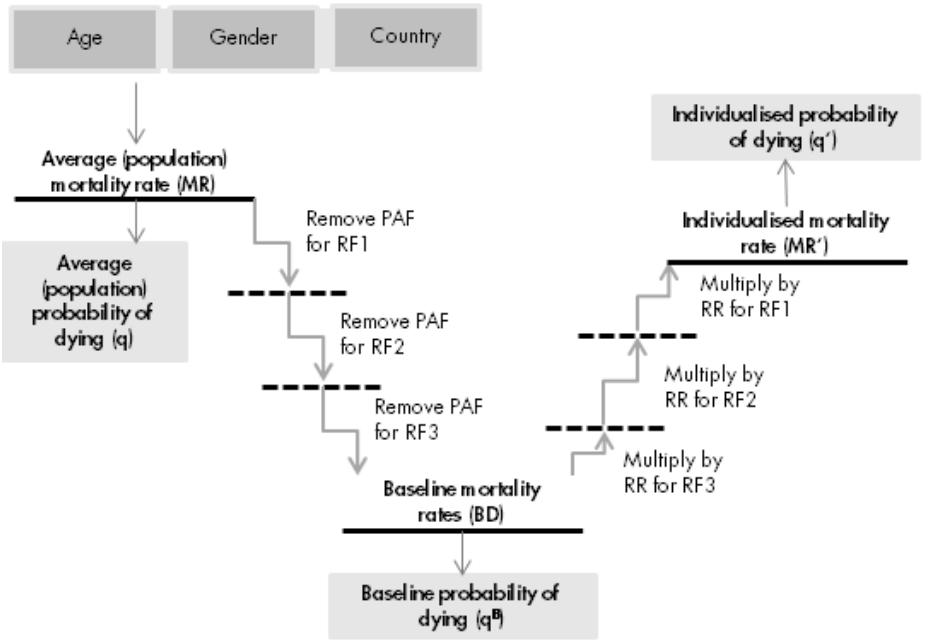
profile changes over time based on projections using empirical observations. The all-cause probabilities of dying are subsequently used to calculate the individualised life expectancy. The process is represented in Figure 2 below.

The model works with five main groups of variables obtained from the online GBD database[5] and Online Appendix to Abajobir et al. (2017a), which covers some of the GBD results not provided in the online database. Those are relative risks (RR), mediation factors (MF), mortality rates (MR) and population attributable fractions (PAF), which are then used in combination with the TMREL and related units of relative risk used in the GBD analysis. The TMREL defines the approximate level of risk factor exposure at which the associated relative risks are minimised. For instance, the TMREL for systolic blood pressure is estimated at 110–115 mmHg, meaning that any level of blood pressure above this threshold is assumed to increase probability of death due to related diseases. PAF is the proportional reduction in population disease or mortality for a specific cause that would occur if exposure to a risk factor were reduced to TMREL.

The variables can be combined in the methodological framework outlined above as follows. As a first step, population mortality rates (i.e. the average mortality rate across all individuals, MR) in combination with all relevant (average) PAFs are combined to give an estimate of risk-free probability of death (baseline deaths or BD). This rate is again the same for all individuals. Analogously to PAFs, given a risk factor exposure above TMREL, RR is the ratio of the probability of dying from cause X to the probability of a risk-free individual dying (i.e. one with risk factor exposure within the TMREL range). We can therefore use RR in combination with BD in an inverse process to the above to systematically estimate the individualised mortality rates for each cause of death, taking into account the individual's exposure to the relevant risk factors. However, in order to calculate an individual's life expectancy, the mortality rates need to be transformed into probabilities of dying (see below for details). Corresponding to the mortality rate variables above we can therefore identify individualised probabilities of dying (q') for an individual with known risk factor exposure, the baseline probabilities of dying (q^B) and the population-level probabilities of dying (q). Finally, the cause-specific probabilities of death are combined in an all-cause probability of death estimate used to calculate the Vitality Age, as depicted in Figure 1. This is visualised in Figure 2.

[5] ghdx.healthdata.org/gbd-results-tool

Figure 2. Determination of individualised mortality rates for a single cause of death



Source: RAND Europe, based on Lim et al. (2015).

Note that since all operations presented in Figure 2 are multiplications, we can collapse the whole process of decreasing and adding mortality rates using PAFs and RRs to a single step, where all PAFs are multiplied in a single joint PAF and all RRs are combined into a single joint RR. This simple calculation, however, does not work if the risk factors are not considered independent – i.e. they affect each other. For example, high BMI affects probability of death due to heart disease and, simultaneously, may lead to elevated blood pressure, which again increases the probability of death due to heart disease. Indeed, the simple framework described above would lead to double-counting some of the effects. Where possible, the risk factor mediation is estimated in the GBD data using a mediation factor (MF) describing to what extent, and in which direction, one risk factor is translated through another. For instance, according to the latest GBD 2016 data release, 31.2 per cent and 64.7 per cent of the effect of high BMI on ischaemic heart disease and ischaemic stroke MRs, respectively, are expressed through high blood pressure. Similar logic applies for the determination of PAFs; adding PAFs related to overlapping individual risk factors may produce combined PAFs higher than 100 per cent and the MFs thus need to be applied when estimating joint effects.

In addition, the set of mediation factors is available only for risk factor links with sufficient evidence of joint effects from the epidemiological literature. Other, weaker effects are lost in the risk factor estimation. This is because the single-cause mortality models in the GBD database have been re-scaled according to the uncertainty around the cause-specific mortality rate, so that the sum of all mortality models would be equal to the all-cause mortality envelope. Similarly, the GBD authors endeavoured to evaluate RRs that were controlled for confounders; however, given the full reliance on external literature, this could not be achieved at all times. The standard competing risk model (see below) is used to automatically compress the joint PAFs and MFs so that that they cannot exceed one.

The framework of joint effects used in the GBD study is replicated in the Vitality Age model and is generally based on Lim et al. (2015), with some GBD-specific formulas taken from Abajobir et al. (2017a). Firstly, it estimates the counterfactual baseline mortality rates (BD) for each cause of death if exposure to all selected risk factors is at the TMREL. This is done using the rate of cause-, age-, sex-, country- and year-specific deaths[6] in combination with PAFs for each risk factor-cause of death pair (again differentiated by age, sex and location) and MFs (data for which are not differentiated in any way).

Formally, the baseline mortality rate for outcome o, age a, sex s, country c and time t is given by:

$$BD_{oasct} = MR_{oasct} \times (1 - PAF_{Joasct}), \quad (1)$$

where

$$PAF_{Joasct} = 1 - \prod_{j=1}^{J}\left[1 - PAF_{joasct} \times \prod_{i=1}^{I}(1 - MF_{ijo})\right]. \quad (2)$$

where PAF_{joasct} is the PAF for risk factor j, outcome o, age a, sex s, country c and time t; MF_{ijo} is the modifying factor for risk factor j mediated through i for outcome o; MR_{oasct} is the population mortality rate for outcome o, age a, sex s, country c and time t; and J is the set of all risk factors relevant to outcome o.

As a second step, the algorithm determines the (joint) RR for any given set of risk factors applicable to a cause of death, determined as a combination of individual RRs and the respective MFs.

Formally, the joint RR for the set of risk factors J, outcome o, age a, sex s, country c and time t is given by:

$$RR_{Joasct} = \prod_{j=1}^{J}\left[\left(1 + \left(RR_{joasct} - 1\right)\prod_{i=1}^{I}(1 - MF_{ijo})\right)^{m_j}\right]. \quad (3)$$

where RR_{joasct} is the RR for risk factor j, outcome o, age a, sex s, country c and time t and $m_j \in [0; \infty)$ denotes multiplier – a variable reflecting an individual's exposure to risk factor j beyond the TMREL level. In short, m_j, in combination with a baseline RR (obtained from the GBD database), determines the individualised RR value conditional on an individual's risk factor profile. The formulas to calculate the value of m_j from an individual's risk factor exposure above TMREL are obtained from the GBD study, as described in detail in the following section.

As outlined in Figure 2

[6] Year-specific deaths refer to estimates for a given calendar year, capturing changes in relative importance of causes of death over time.

Figure 2, the joint RRs can be used in combination with q^B to calculate individualised probabilities of dying within 12 months, which can then be used (as opposed to mortality rates) for life expectancy calculation. Following Lim et al. (2015), this is done using a standard life table calculation:

$$q_{oasct} = \frac{n \times MR_{oasct}}{1+(n-{}_n a_x)\times MR_{oasct}} \quad (4)$$

where n is length of the assumed period in years (hence $n = 1$ as we are interested in probability of dying within 12 months) and ${}_n a_x$ is the proportional distribution of deaths in the interval, assumed to be 0.5 (a uniform distribution). The process is replicated for both the population mortality rates, resulting in population-level probability of dying q^p, and for the baseline mortality rates BD, resulting in the baseline probability of dying q^b:

$$q^b_{oasct} = \frac{n \times BD_{oasct}}{1+(n-{}_n a_x)\times BD_{oasct}} \quad (5)$$

The baseline, cause-specific probability of dying can then be transformed into individualised probability of dying q' by multiplying it by the cause-specific joint relative risk reflecting an individual's risk factor profile:

$$q'_{\mathcal{P}oasct} = RR_{\mathcal{R}oasct} \times q^b_{oasct}, \quad (6)$$

where $\mathcal{P} \in [0, \infty)^{\mathcal{R}}$ is the individual's risk factor profile.

Finally, the probabilities of dying are aggregated to all-cause probability of dying. Note that unlike mortality rates, probabilities of dying are not additive and need reflect the existence of competing risks in aggregation. Consequently, we use the standard competing risk model:

$$Q_{\mathcal{P}asct} = 1 - \prod_o^{\mathcal{M}} (1 - q'_{\mathcal{P}oasct}), \quad (7)$$

where $\mathcal{M}$ refers to the set of all causes of deaths in the GBD database. This again works as an implicit compression mechanism, preventing the probability of dying exceeding one for excessively unhealthy individuals.

This approach may be replicated for each relevant sex-country-risk factor combination. Note that the model allows the individualised probability of dying (and therefore Vitality Age) to be both higher and lower than the population average – the starting point. Considering a simple example with a single risk factor and cause of death in the world, individuals with risk factor exposure below the population average will then have higher life expectancy than the average population, while those with higher-than-average exposure will have lower-than-average life expectancy. Analogous reasoning applies to multiple risk factors and causes of death, with relative risks serving as weights for each risk factor.

Specifically, consider a world with one cause of death o with age-standardised mortality rate of 0.1 and two risk factors, j_1 and j_2, with $PAF_1 = 0.3$ and $PAF_2 = 0.4$, respectively. Consider that there are no joint effects between j_1 and j_2, i.e. the effect of each risk factor on o is independent of the other risk factor. Consider also that risk factor exposure is measured by multiplier m and that there are two

individuals, one with risk profile characterised by $m_1^1 = 0.3$ and $m_2^1 = 0.7$ and the other one with $m_1^2 = 1.2$ and $m_2^2 = 2.1$. Finally, consider that the impact on mortality rates can be characterised by sample relative risks $RR_1 = 2.22$ and $RR_2 = 1.5$. Then we can calculate the individualised mortality rates as follows:

- Generally: $MR' = (MR - MR \times PAF) \times RR = MR(1 - MR \times PAF_1 - MR \times PAF_2 + PAF_1 \times PAF_2) \times RR_1^m \times RR_2^m$
- Individual 1: $MR^{1\prime} = 0.1 \times (1 - 0.3 - 0.4 + 0.3 \times 0.4) \times 2.22^{0.3} \times 1.5^{0.7} = 0.071$
- Individual 2: $MR^{2\prime} = 0.1 \times (1 - 0.3 - 0.4 + 0.3 \times 0.4) \times 2.22^{1.2} \times 1.5^{2.1} = 0.256$

Note that the exponential interaction between multipliers m and relative risks RR come from the equation (3), with $MF = 0$ as there are no joint effects. The 'population' equation then demonstrates that individuals with a risk factor profile equivalent to the population average will have the population average mortality rate.

We can see that the first individual with risk factor exposure below the population average faces about 30 per cent lower estimated mortality rate than the population, and more than three times lower than the second individual. The same reasoning applies to probabilities of dying instead of mortality rates; q^B will always be lower than or equal to both q and q', which will differ based on an individual's health.

With the full set of sex-age-country all-cause probabilities of dying, we can calculate life expectancy and Vitality Age as follows:

1. Calculate the probability of surviving up to age i and dying exactly at that age by age i, resulting in factor $t_{i,oasct}$, using

$$t_{i,asct} = (1 - Q_a) \times (1 - Q_{a+1}) \times (1 - Q_{a+2}) \times \dots \times (1 - Q_{i-1}) \times Q_i \times i, \quad (8)$$

   where Q_a stands for Q_{asct} for simplicity, a denotes an individual's actual age (as of their last birthday), and $i \in \{a, \dots, 120\}$ denotes an age between an individual's actual age a and an arbitrary maximum age, set to 120 in the model as it is nearly impossible to live to that age (only one person has ever managed it). This particular choice of maximum age has no practical impact on the results as virtually no one is projected to survive until the age of 120, based on mortality rates obtained from the GBD database.

2. Calculate standard life expectancy (SE) using

$$SE_{asct} = t_a + t_{a+1} + t_{a+2} + \dots + t_{120} \quad (9)$$

   supressing subscripts a, s, c and t in $t_{i,asct}$.

3. Replicate steps 1–2 using the adjusted probabilities of dying Q' to get the adjusted terms t' (all subscripts suppressed) and adjusted life expectancy, $AE_{\mathcal{P}asct}$.

4. Determine Vitality Age VA as

$$VA_{\mathcal{P}asct} = a + (SE_{asct} - AE_{\mathcal{P}asct}) + f \quad (10)$$

where f is the time from the last birthday to the date of the calculation as a fraction of a year.

Given that the MR data in the GBD database are reported in five-year age groups, MRs for individual years of age are calculated using linear interpolation between the two neighbouring estimates, with the MRs considered to be exact at the midpoint of the interval. Additional adjustments are then made for ages of 95 years and above to reflect increased chance of dying. These are not discussed in detail in this report. The particular form of interpolation within the age groups is not particularly critical since both the population and individualised MRs are adjusted in the same way and the resulting Vitality Age is virtually independent of the function used for interpolation. The linear function was tested against an exponential function without a visible impact on the results.

As we discuss in Section 4, only a subset of risk factors included in the GBD database is actively used in the VA.3 model, so that it remains accessible to the general population. This is possible because the proposed approach works with any subset of risk factors while using the entire GBD mortality rate dataset for the life expectancy calculation, considering the remaining risk factor exposure (and the associated mortality rates) to be at the population average. This property also implies that any missing data (due to, for example, individuals not remembering their risk factor readings) may be completely left out of the model, implicitly assuming that they are at the population average. This is in contrast with the original Vitality Age algorithm, where unknown values needed to be explicitly replaced by sample values.

3.3. Relative risk multipliers

Going back to equation (3) from the previous section, the individual's risk factor profile – specifically exposure beyond the TMREL level – is introduced into the model through the interaction of the RR for risk factor j with a multiplier m_j to allow the calculation of mortality rates representing an individual's health. In essence, the RR denotes the extent to which each unit change of a risk factor affects the probability of dying of a disease and m_j denotes the number of such units. For continuous risk factors (e.g. consumption of fruit), m_j is calculated as the number of GBD units for a given risk factor above the TMREL threshold. For binary or categorical risk factors, m_j is set to equal one and the detrimental effect is wholly expressed through the RR. Note that since the interaction in (3) is exponential, the marginal effect for continuous risk factors increases with exposure. In addition, since joint RR is calculated as a product of individual RRs, the relative effect of a unit increase in m_j has a higher impact for causes of death associated with multiple risk factors, at least two of which have RRs greater than one.

The particular formula to calculate m_j depends on the nature of the risk factor. For continuous risk factors with RR increasing with intake, such as diet high in processed meat, m_j is the difference between risk factor exposure (in terms of GBD units) and TMREL. Moreover, there is no theoretical upper bound on m_j, meaning that the more processed meat a person eats, the higher the risk of developing an associated disease. Such risk factors have RRs implicitly bounded from below at 1 (when $m_j = 0$) in case the individual is at or below the TMREL level (which is possible since in reality TMRELs for different people form a non-constant distribution).

Analogously, m_j for continuous risk factors with relative risk decreasing with intake, such as diet low in fruit, is calculated as the amount that risk factor exposure is *below* the TMREL. It is bounded from above by $m_j =$ TMREL and from below by $m_j = 0$. Hence, eating more than the TMREL amount of fruit does not lead to further decrease in the probability of dying (according to the GBD data) and not eating any fruit at all exposes an individual to the maximum risk.

These differences can be summarised as follows:

- Continuous risk factor, risk increases with intake: $m_j = \max(0, \frac{i_j}{x_j} - TMREL_j)$
- Continous risk factor, risk decreases with intake: $m_j = \max(0, TMREL_j - \frac{i_j}{x_j})$
- Categorical risk factor: $RR = RR_a$ if $j = a$

where $x_j \in [0; \infty)$ is continuous risk factor exposure (intake), j is categorical risk factor exposure, k_j is GBD unit conversion factor and a denotes categories of relative risks. The GBD units for each risk factor are described in Online Appendix 1 to the Abajobir et al. (2017a) study; selected risk factors are presented in Table 3 below. The full list of formulas is presented in Table 11.

Table 3. Risk factor multiplier formulas

Risk factor	Input units (portions)	GBD units (intake measure)	TMREL	Formula (x = intake)
Alcohol	grams per day	grams per day	Zero alcohol intake	Categorical (0g / 12g / 24g / 36g / 48g / 60g / 72g)
Diet low in fruits	80 grams per day	100 grams per day	2–3	$m_j = \max(0;\ 3 - x \times 0.8)$
Diet high in processed meat	50 grams per day	50 grams per day	0–0.08	$m_j = \max(0; \frac{x}{50})$
High body-mass index	kg/m^2	5 kg/m^2	20–25	$m_j = \max(0; \frac{x}{5} - 20)$
Low physical activity	Metabolic equivalents (METs) per week	METs per week	3000–4500	Categorical (<600, 600–3,999, 4,000–7,999, and >=8,000 METs);
Smoking	-	-	Not smoking	Categorical (smoker/non-smoker)

Note: Zero alcohol consumption is the TMREL when considering only the harmful effects of alcohol use; see Section 6.1.1 for details.

Source: RAND Europe, based on Abajobir et al. (2017a).

3.4. Adjustments for wholly attributable causes of death

The mortality rate calculation described above does not work for causes of death wholly attributable to a single risk factor (i.e. those with PAF of 1) because the baseline deaths calculated using equation (1) from Section 3.2 would be zero and thus would not change when multiplied by the appropriate relative risk using equation (6). In addition, the model would implicitly overestimate probability of dying for

individuals not at risk with respect to a given risk factor (e.g. non-drinkers cannot die due to alcohol use disorders) and at the same time underestimate probability of dying for those who are at risk because the mortality rates reported in the GBD database use the entire appropriate age-sex-location population in their denominator, not just those at risk. The risk-cause pairs relevant to VA.3 (i.e. related to risk factors selected for the model as described in Section 4) are:

- Alcohol use disorders – Alcohol use
- Chronic kidney disease due to diabetes mellitus – High fasting plasma glucose
- Chronic kidney disease due to hypertension – High systolic blood pressure
- Cirrhosis and other chronic liver diseases due to alcohol use – Alcohol use
- Diabetes mellitus – High fasting plasma glucose
- Hypertensive heart disease – High systolic blood pressure
- Liver cancer due to alcohol use – Alcohol use.

To resolve the issue, the model adjusts the baseline mortality rates BD so that only causes of death applicable to an individual (i.e. those that they may die from) are considered in the model. Mortality rates for the remaining causes of death wholly attributable to a single risk factor are then proportionally increased to reflect that only a subset of the population is at risk. Specifically, we can calculate the individualised mortality rates with PAF of 1 using:

$$MR^{w}_{oasct} = MR^{POP}_{oasct} / SEV_{asctr} \tag{11}$$

where MR^{w}_{oasct} is the adjusted individualised mortality rate for given age a, sex s, country c, outcome o and time t; MR^{POP}_{oasct} is the population mortality rate; and SEV_{sctr} is the summary exposure value for risk factor r to which cause o is fully attributable. SEV is a risk-weighted measure of prevalence of a risk factor in a given population, with relative risk serving as the weight:

$$SEV_{asctr} = \frac{\sum_{i=1}^{n} Pr_i RR_{iasctr} - 1}{RR^{max}_{asctr} - 1} \tag{12}$$

Here, Pr_i is prevalence of category i exposure; RR_{iasctr} is relative risk of category i, for given age a, sex s, country c and time t; and RR^{max}_{asctr} is the maximum relative risk observed (between categories). SEV values are estimated for each age, sex, location and year, and reported in the GBD database.

Lastly, given the way SEV is calculated, the formula for the assessment of joint RR must be adjusted so as not to overestimate the burden of the disease. Specifically, RRs for individuals at risk need to be scaled down relatively to RR^{max}, with RR for those in the maximum risk category equal to one:

$$RR' = \begin{cases} \frac{RR-1}{RR^{max}-1} & \text{if } RR < RR_{max} \\ 1 & \text{if } RR = RR_{max} \end{cases} \tag{13}$$

Consider the example of alcohol use disorder, which is wholly attributable to alcohol use. A person who never drinks alcohol cannot develop alcohol use disorder and subsequently die from it. For simplicity, consider population MR of 0.5 and that there are just three types of alcohol drinkers: non-drinkers, moderate drinkers and heavy drinkers. In addition, consider that the RR associated with moderate and heavy drinking is 1.8 and 2.1, respectively, and that there are 30 per cent of moderate drinkers and 20 per

cent of heavy drinkers in the population. Clearly, the baseline mortality rate BD is zero, because if no one consumed alcohol in the whole population, alcohol use disorders would eventually completely disappear. We can calculate the adjusted mortality rate as follows:

- $SEV_{asctr} = \frac{\sum_{i=1}^{n} Pr_i RR_{iasctr} - 1}{RR_{asctr}^{max} - 1} = \frac{0.5*1+0.3*1.8+0.2*2.1-1}{2.1-1} = 0.418$
- $MR_{caso}^{w} = \frac{MR^{POP}}{SEV} = \frac{0.5}{0.418} = 1.195$
- Number of deaths: $\left(\frac{(1.8-1)}{(2.1-1)} \times 0.3 + \frac{2.1}{2.1} \times 0.2\right) \times 1.195 = 0.5$

Using this method, the mortality rates correctly reflect that only the subgroup of the population at risk may die due to a given cause of death and that the observed mortality rates are a function of both prevalence and exposure levels in the population at risk. Note that the process of individualised probability of dying calculation remains the same as for other causes of death, but it uses the updated population mortality rates. Specifically, being exposed to a risk factor with PAF of 1 is a necessary condition for potentially dying from a related cause, yet other factors, as well as the extent of exposure to the given risk factor, may determine the probability of death. For instance, one cannot die due to liver cancer caused by alcohol use without drinking alcohol, yet the amount of alcohol as well as smoking and high BMI determine the actual probability of dying for drinkers.

For dichotomous risk factors, such as diabetes, the process above remains unchanged but it is simplified to only two cases: those who are not diabetic are considered not at risk at all, whereas for diabetics the mortality rates are simply divided by the share of population that is diabetic. Note that relative risks associated with causes of death fully attributable to dichotomous risk factors are simply equal to one as all of the excess risk is captured through the mortality rate adjustment.

3.5. Counterfactuals

The calculation of individualised mortality rates for each cause-risk pair allows explicit comparison of counterfactual scenarios, including comparison of an individual's risk factor profile to alternative population averages. This property has two practical impacts for the model:

1. It is possible to determine the relative importance of each assessed risk factor for any of the considered causes of death and the overall life expectancy/Vitality Age *and* determine what would be the outcomes in the case that the risk factor exposure changed – at the present or at any time in the future – without re-estimating the entire model. Consequently, one can not only receive an exceptionally detailed feedback from the model but there is also an option to create a standalone interactive feedback tool allowing users to change the projected future risk factor profile and immediately see the resulting changes in Vitality Age.
2. Rather than calculating Vitality Age as a difference between individual and population life expectancy, the concept can be altered to compare an individual's health to an alternative population – e.g. non-smokers, diabetics or highly physically active individuals. This may be particularly useful as a motivational tool for healthy individuals whose standard Vitality Age results suggest that they are doing very well compared to the general population. Briefly, the calculation would follow the same

principles as above, but rather than only adjusting the individual's mortality rates, the population averages would be adjusted as well using the same set of formulas and given risk factor values. For instance, using non-smokers as comparison group, the population mortality rates would then be adjusted so that no one in the population would be considered a smoker (i.e. subtracting PAFs for smoking for all smoking-related causes of death), keeping all other parameters unchanged.

4. Selection of risk factors

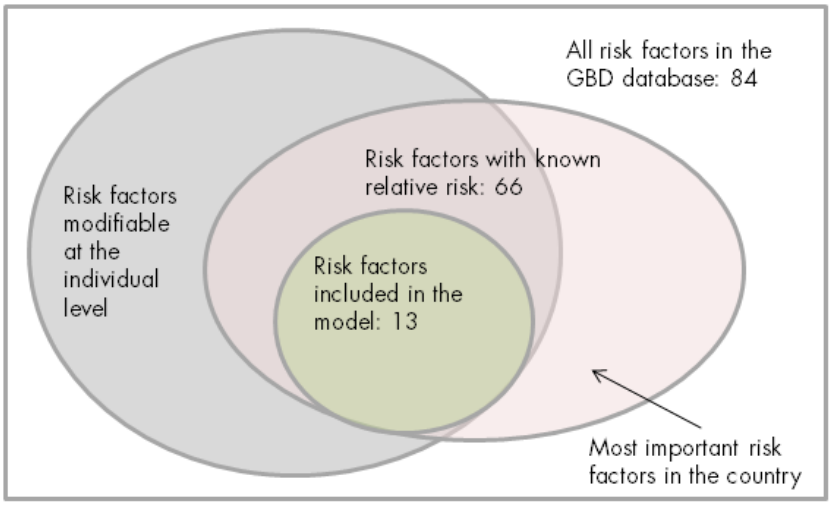
4.1. Rationale and selection criteria

In this section we look at the set of risk factors included in VA.3 and how they were selected. On the one hand, a long list of risk factors provides a more comprehensive picture of individual's health and may therefore lead to more accurate Vitality Age results. But on the other hand, the selection of risk factors is limited by data availability – both in terms of the existence of relevant parameters in the literature and the ability of individuals to assess their exposure – and affects user experience, as each risk factor takes certain amount of time to be determined.

A particular advantage of using the GBD database, particularly compared to tailored cohort studies, is its extremely wide coverage in terms of geography, age, causes of death and risk factors. Overall, the database covers 84 distinct behavioural, environmental, occupational and metabolic risk factors, 66 of which have estimated RR available and may thus be used in the model. What follows in this section is related specifically to the UK context, although equivalent analysis could be done for any other country in the GBD dataset.

Given the focus of Vitality Age on modifiable risk factors affecting all-cause mortality, only risk factors modifiable at the individual level can be included in the model (primarily leaving out various risk factors related to pollution). Out of the remaining set of risk factors, we selected a limited number of the most important (assessed using the all-cause mortality associated with them), exposure to which is likely to be known about by the general population, in order to keep the model questionnaire accessible and relatively short. This process is depicted in Figure 3.

Figure 3. Risk factors in the GBD 2016 database



Source: RAND Europe analysis.

4.2. Selection process

Analogously to PAF, the GBD database contains information on the number of deaths due to a specific risk factor (for each cause of death separately and as an aggregate measure). Looking at the case of the UK, which was selected as a representative developed country, we iteratively analysed the list of risk factors associated with the highest number of deaths for all age groups and sexes by downloading the full list of causes of death and relevant risk factors for each sex-age pair. We identified that the 15 top risk factors (which accounted for ~89 per cent of total deaths attributable to risk factors) remain broadly consistent across both sexes and all age groups for the UK adult population (although their particular order may change). In fact, these risk factors, shown in Table 4, are consistently the most important across all developed countries, with the occasional inclusion of particularly unsafe sex, which is a risk factor for HIV/AIDS.

Table 4. The 15 most important risks in terms of all-cause mortality in individuals in the UK

Rank	Risk factor	Attributable deaths	Confidence intervals	Share of total attributable deaths	Cumulative share of attributable deaths
1	Smoking (excluding smokeless tobacco)	111,254.49	[118,011, 105,823]	18.17	18.17%
2	High systolic blood pressure	94,543.64	[107,335, 82,180]	15.44	33.61%
3	High body-mass index	57,201.32	[82,178, 34,400]	9.34	42.95%
4	High total cholesterol	48,587.63	[63,925, 34,943]	7.94	50.89%
5	High fasting plasma glucose	36,199.16	[50,897, 24,215]	5.91	56.80%
6	Alcohol use	32,517.81	[54,564, 14,812]	5.31	62.11%
7	Ambient particulate matter pollution	24,231.48	[30,602, 18,848]	3.96	66.07%
8	Diet low in whole grains	23,459.56	[32,787, 15,641]	3.83	69.90%
9	Diet low in fruits	19,734.80	[28,780, 11,334]	3.22	73.12%
10	Diet low in nuts and seeds	18,632.15	[26,214, 11,285]	3.04	76.16%
11	Occupational exposure to asbestos	18,035.63	[20,819, 15,152]	2.95	79.11%
12	Impaired kidney function	17,055.73	[19,107, 15,151]	2.79	81.90%
13	Low physical activity	16,502.65	[24,616, 8,827]	2.69	84.59%
14	Diet low in vegetables	13,346.04	[22,439, 6,055]	2.18	86.77%
15	Diet low in seafood omega-3 fatty acids	11,129.43	[18,970, 4,438]	1.82	88.59%

Source: GBD 2016 database, selection across all ages and both sexes. Red highlighting represents risk factors not modifiable at the individual level.

We can see that the 15 risk factors included a number of lifestyle factors (such as dietary variables, physical activity, smoking, alcohol, etc.) in addition to biological markers (such as fasting plasma glucose), for which data is less likely to be known by respondents. With the exception of ambient particulate matter and occupational exposure to asbestos, all of these risk factors are modifiable at the individual level. Many of them are largely consistent with those used in the original Vitality Age calculator and with many of the risk factors included in other existing and validated CVD and mortality risk calculators (see Table 2).

Biological markers appear to be generally more important than lifestyle factors. However, since they are also partially determined by lifestyle factors, such as physical activity and dietary variables, lifestyle risk factors are arguably at least as important as the biological markers themselves. Moreover, tailored feedback on behaviour may be more comprehensible and useful for the individual, again increasing the importance of lifestyle risk factors for the model. Indeed, offering specific feedback on lowering processed meat intake appears to be more tangible to the user than advising them to lower their blood cholesterol (Lloyd-Jones et al. 2010; Chiuve et al. 2014; Lim et al. 2015).

To reflect the potential multiplicative long-term effect of the lifestyle risk factors in particular on other variables (which cannot be explicitly modelled within the context of the methodology presented in Section 3), one may assume that the affected risk factors change over time as a function of the lifestyle risks (e.g. that an individual who does high amount of physical activity regularly will have lower blood pressure than an otherwise equal individual who does not do much physical activity). This would in turn affect the Vitality Age results. Such risk factor interactions are not assumed in the VA.3 model, constituting a limitation since the projected risk factor profile does not implicitly take into account the secondary (indirect) effects of one's lifestyle. See below for additional discussion.

Note that data on clinical/biological markers (blood pressure, cholesterol and fasting plasma glucose) are likely to be unknown by many respondents. Data from the Britain's Healthiest Workplace survey conducted by RAND Europe in the UK indicate that 47 per cent of the 32,000 respondents had never had their total cholesterol measured, or could not indicate whether it was low-normal; borderline high or high. Similarly, 57 per cent of respondents had never had their blood glucose measured or could not indicate whether it was normal or high.

Given these considerations, we selected the most important risk factors modifiable at the individual level that are too important to be left out (e.g. blood pressure, total cholesterol) or likely to be known (or reasonably estimated) by a majority of respondents (smoking, diet low in fruits). On this basis, we excluded low glomerular filtration rate (impaired kidney function) and diet low in seafood omega-3 fatty acids because individuals are less likely to be able to provide reliable information about their exposure to these risk factors. We also added diet high in processed meat (number 17 on the list, not shown in Table 4) and use of smokeless tobacco, as these are important from the behavioural perspective – individuals may not be aware of their adverse effects – and complement the other risk factors.

Risk factors selected for the UK version of the model thus include: alcohol use; diet low in fruits, nuts and seeds, vegetables, and whole grains; diet high in processed meat; physical activity; high body-mass index; high fasting plasma glucose; high systolic blood pressure; high total cholesterol; smoking; and use of smokeless tobacco.

4.3. Physical activity in VA.3

As we can see from Table 4, physical activity is not considered a particularly important risk factor in the GBD database, which may be surprising given the emphasis of official recommendations on doing at least moderate amounts of physical activity per week.[7] The reasons for this are threefold. Firstly, the GBD database considers only the direct effect of physical activity on outcomes and does not explicitly recognise any indirect effects through a set of mediation factors or through long-term causal impacts. For instance, there is no formal link identified in the GBD database between physical activity and blood pressure, yet physical activity has been shown to lower blood pressure over time (see, for example, Arroll & Beaglehole 1992). In fact, the long-term effects of physical activity are likely to be visible in other risk factors, such as

[7] See, for example the UK and US government physical activity guidelines (https://www.gov.uk/government/publications/uk-physical-activity-guidelines and https://health.gov/paguidelines/).

blood glucose or body-mass index, as well. Since this temporal sequence is not yet fully modelled in the GBD database, the fact that individuals doing high amounts of physical activity may be more likely to have a better risk factor profile overall than otherwise similar individuals doing little or no physical activity cannot be modelled in VA.3 by default and needs to be addressed through other means.

One such adjustment would be a series of assumptions on future risk factor profile given the current/future amount of physical activity in combination with other lifestyle characteristics. Specifically, it could be assumed that by doing a good amount of physical activity while maintaining a healthy lifestyle, one can either keep a current risk factor profile (if healthy) or substantially improve it (if unhealthy) in the long term. The projected future risk factor values can then serve as inputs to the Vitality Age calculator and produce improved results.[8]

The second reason for the low importance of physical activity is the focus on activity vs sedentary behaviour, rather than on physical exercise. Specifically, the GBD database is based on studies considering physical activity in all domains of life, including leisure/recreation, work/household and transport. However, as discussed in Ross et al. (2016), for example, there is mounting evidence that other activity-related measures, such as cardiorespiratory fitness, are not only directly linked to numerous causes of death but also that they may be potentially stronger predictors of mortality than established risk factors such as smoking, hypertension, high cholesterol or type 2 diabetes mellitus. Looking only at non-sedentary behaviour thus may not provide a full picture of physical activity as a risk factor. Future versions of the GBD study may substitute 'fitness' for 'activity'; although measuring cardiorespiratory fitness is generally difficult, there are ways of doing so (e.g. the VO2 max measurement).

Lastly, related to the two previous points, the relative risks associated with low physical activity are low – mostly below 1.5 even for individuals with highly sedentary behaviour – with only five causes of death being affected by physical activity. This further adds to the low importance of physical activity in terms of preventable deaths in the population average, suggesting that the difference in mortality rates between individuals doing low and high levels of physical activity is not substantial.

Given the links between the these key points, using other activity-related measures and/or considering the indirect effects of physical activity through other risk factors would both likely lead to a significant gain in importance of physical activity as a risk factor. The changes may be introduced in the future revisions of the GBD database if there is enough empirical evidence in epidemiological studies. Until then, the only way of reflecting the unaccounted effects of physical activity in the Vitality Age model is through explicit assumptions regarding future changes in the risk factor profile.

Having outlined the theoretical framework for the VA.3 model, the source of parameters and the set of risk factors to be included, in the next section we discuss the exact specification of the available data, how to obtain and process it, and how the newly created dataset can be used in the designed model framework.

[8] Note that the risk factor profile is considered constant throughout one's life by default in the original Vitality Age model. The new model introduces additional dynamics over time. This is not discussed in this report in detail.

5. Data collection and processing

5.1. Data collection

As described earlier, the theoretical framework for the VA.3 model is based on five groups of GBD data downloaded from the GBD Data Results Tool[9] and the Online Appendix 1 to Abajobir et al. (2017a): relative risks (RR), mediation factors (MF), mortality rates (MR), population attributable fractions (PAF) and theoretical minimum risk exposure levels (TMREL). In this section we describe each data category in detail, including its format and where data can be downloaded from, and explain how all data were merged together, creating a consistent dataset used in the calculation.

5.1.1. Mortality rates

Mortality rates for all individual causes of death were downloaded from the GBD Data Results Tool in form of deaths per 100,000 person-years for a given country and each five-year age group and sex separately.[10,11] The data thus represent the central death rate MR, as discussed earlier. The GBD cause list is a set of mutually exclusive and collectively exhaustive hierarchical categories (i.e. the list covers all causes of death identified in the world) and the sum of cause-specific mortality, defined according to the International Classification of Diseases (ICD)[12] underlying cause rules, equals all-cause mortality. That is, each death is attributed to one, and only one, cause of death and the sum of deaths across all causes is equal to the total number of deaths in a given area and timeframe. In particular, the number of total deaths is controlled for in assessing mortality rates attributable to individual causes of death. Only data for elementary causes of death (i.e. not for categories covering multiple elementary causes, such as communicable diseases) were downloaded, which are hereafter referred to also as level 4 causes of death.[13]

[9] ghdx.healthdata.org/gbd-results-tool

[10] The full list of age categories is: 0–6 days, 7–27 days, 28–364 days, 1–4 years, 5–9 years, 10–14 years, 15–19 years, 20–24 years, 25–29 years, 30–34 years, 35–39 years, 40–44 years, 45–49 years, 50–54 years, 55–59 years, 60–64 years, 65–69 years, 70–74 years, 75–79 years, 80–84 years, 85–89 years, 90–94 years, and 95+ years.

[11] The 2016 data for the UK in a given specification can be downloaded using the following permalink:
http://ghdx.healthdata.org/gbd-results-tool?params=gbd-api-2016-permalink/5a11a38262dbe7d6becc2d4676f83a62

[12] http://www.who.int/classifications/icd/en/

[13] The GBD classification recognises five distinct levels in which causes of death are structured, with 'all causes' being level 0 and each subsequent level containing subcategories or causes of death included in the preceding one. For instance, typhoid fever is classified as a level 4 cause, with the full hierarchy being all causes –> communicable, maternal, neonatal and nutritional diseases –> diarrhoea, lower respiratory and other common infectious diseases –> intestinal infectious diseases –> typhoid fever.

The raw mortality rates do not need to be processed in any way, except by being divided by 100,000 (as they are reported in number of deaths per 100,000 person-years rather than actual rates). Three data points are available from the GBD database for all variables: the lower bound, mean estimate and the upper bound. Only the mean estimates were used throughout this section. Table 5 shows a snapshot of the data.

Table 5. Snapshot of mortality rates data

Location	Cause of death	Sex	Age	Year	Metric	Mean
United Kingdom	Pancreatic cancer	Male	50 to 54	2016	Deaths per 100,000	9.0374968
United Kingdom	Pancreatic cancer	Female	50 to 54	2016	Deaths per 100,000	6.5670779

Source: GBD 2016 database.

5.1.2. Population attributable fractions

PAFs were also downloaded from the GBD Data Result Tool for each five-year age group and sex,[14] reported in the form of share of deaths that are directly attributable to a selected (group of) risk factor(s). Analogously to causes of death, individual (elementary) risk factors are subsets of broader risk factor groups (e.g. smoking is a subset of tobacco smoke which is a subset of behavioural risks), where all the broader risk factor groups are a subset of the 'All risk factors' category, an overarching category covering every identified risk factor. However, since not all causes of death in the GBD database have been identified to have a link to one or more of the risk factors, the complement of the 'All risk factors' category is a 'No risk factor' category. We can thus distinguish between total mortality rate (as a result of both 'All risk factors' and 'No risk factor') and mortality rate due to a selected (group of) risk factor(s).

The data thus show deaths that can be directly attributed to any/all risk factors analysed in the GBD study, as well as those that cannot be directly attributed to any of them. Unlike mortality rates, PAF corresponding to a group of risk factors is not equivalent to a sum of individual PAFs corresponding to each risk factor due to the existence of joint effects (as discussed in Section 3). Specifically, some risk factors may contribute to increased mortality rates in a similar way or even be mediated one through another; improving multiple such risk factors at the same time will thus decrease marginal effects per risk factor.

Note that PAFs cannot be directly paired with mortality rate data as there are more PAFs than causes of death. Indeed, while for some causes of death, such as epilepsy, there is only one relevant risk factor (alcohol use), other causes, such as ischaemic stroke, are associated with numerous risk factors at the same time. In addition, other causes, such as encephalitis, have no risk factor associated with them because

Elementary causes of death are thus defined as those that contain no other causes at lower levels. Note that not all elementary causes of death are at level 4.

[14] The 2016 data for the UK in a given specification can be downloaded using the following permalink:
http://ghdx.healthdata.org/gbd-results-tool?params=gbd-api-2016-permalink/742aaa67f6e03bb3271d011f26499cd3

there is insufficient evidence in the epidemiological literature of any causal relationship between risk and cause.

The raw data do not need to be processed in any way as they come in a format usable in the model. Table 6 shows a snapshot of the data. Only the mean estimate was used.

Table 6. Snapshot of population attributable fraction data

Location	Cause	Risk	Sex	Age	Year	Metric	Mean
United Kingdom	Ovarian cancer	High fasting p. glucose	Female	55 to 59	2016	Per cent	2.32%
United Kingdom	Ovarian cancer	High body-mass index	Female	55 to 59	2016	Per cent	4.10%

Source: GBD 2016 database.

5.1.3. Relative risks and TMREL

The relative risks in the GBD database are based on a Comparative Risk Assessment (CRA) method (Boutin et al. 1998) that evaluates how much of the excess mortality associated with a risk factor can be attributed to past exposure to a risk. They are reported in the form of a ratio, representing the probability of dying from a given cause if exposed to exactly one GBD unit of the specific related risk factor, compared to a counterfactual null risk factor exposure. Relative risks are computed for both individual risk factors and for clusters of risk factors, for example the joint risk associated with high BMI, high cholesterol and high systolic blood pressure.

Relative risk data are not reported in the online database but come from tables 1a–1c in the Online Appendix 1 to Abajobir et al. (2017a), which is the official publication accompanying the GBD database. That appendix also determines the form of GBD unit and TMREL level for each risk factor (e.g. 'diet low in fruit' is reported in 80 grams per day portions with TMREL between 200 and 300 grams per day). For continuous risk factors, relative risks are reported as a single number to be adjusted using a multiplier (see Section 3 for details). For categorical risk factors, relative risk factors for each category are reported separately. Unlike MRs and PAFs, relative risks and TMRELs are not country-specific, with TMREL being equivalent also across sex and age groups. The same appendix reports relative risks for both morbidity and mortality calculations, with most risk factors having a single identified relative risk for both.

Since TMREL values are mostly given in the form of an interval, a single data point needs to be chosen arbitrarily within the interval. We have selected the least forgiving value for each risk factor (i.e. the upper bound for risk factors with relative risk decreasing in exposure – e.g. low physical activity – and the lower bound for risk factors with relative risk increasing in exposure – e.g. high systolic blood pressure). This will result in comparatively higher Vitality Age than if a mid-point or the most forgiving value were selected.

A snapshot of the relative risk dataset is shown in Table 7. The full list of TMREL values and the formulas to calculate relative risk multipliers for the selected risk factors are shown in Table 11. Only mean estimates and relative risks associated with mortality or both morbidity and mortality were used.

Table 7. Snapshot of relative risks (confidence intervals in parentheses)

Risk	Cause	Category	Sex	Mortality/ Morbidity	Age category		
					35–39	40–44	45–49
Smoking	Bladder cancer	SIR	Male	Both	3.332 (2.367 to 4.556)	3.332 (2.367 to 4.556)	3.332 (2.367 to 4.556)
Smoking	Bladder cancer	SIR	Female	Both	2.582 (1.926 to 3.42)	2.582 (1.926 to 3.42)	2.582 (1.926 to 3.42)

Source: Abajobir et al. (2017a).

5.1.4. Mediation factors

The data on mediation factors were obtained from table 7 in the Online Appendix 1 to Abajobir et al. (2017a), and a snapshot of these is shown in Table 8. The data consist of three variables: the (distal) risk factor, the proximal risk factor (path) and the cause, where the distal risk factor affects the cause partially/fully through the proximal risk factor. Each risk factor may be mediated through multiple paths and each path may be associated with multiple risk factors. Only the mean values were used.

Table 8. Mediation factors data download

Risk	Path	Cause	Mean
High body-mass index	High fasting plasma glucose	Ischaemic heart disease	15%
Diet low in whole grains	High fasting plasma glucose	Diabetes mellitus	100%

Source: Abajobir et al. (2017a).

5.2. Data processing

As a first step in data processing, a common terminology across causes of deaths, risk factors, mediation factors, ages and sexes was established due to slightly different nomenclature across the selected datasets. For instance, only a single smoking-related risk factor was recognised in the PAF dataset, whereas in the relative risk dataset a distinction was made between parameters estimated using the smoking impact ratio (SIR) and using a prevalence approach, each of which is applicable for different causes of death. Subsequently, names and categories in all four datasets were replaced to match the common terminology and assigned a unique ID obtained from the GBD database.

For the next step, all non-elementary (non-level 4) causes of death and risk factors were excluded from the dataset. These were groups of causes and risk factors, such as behavioural risk factors, that are represented in the model through inclusion of all of their individual elements. We also excluded all relative risks equal to one (i.e. having no impact on the mortality rates) associated with 'not at risk' categories (e.g. non-smoker, non-exposed, etc.) as these are essentially redundant in the model.

As a third step, records with a single data point in one dataset and multiple data points in others were duplicated in order to be matched properly. For instance, relative risk values sometimes referred to 'both' sexes; the value was thus duplicated and renamed so that the relative risk would appear twice, once for males and once for females, as in the other datasets. Similarly, smoking, high fasting plasma glucose and

lead exposure in blood were duplicated and renamed to smoking/smoking (prevalence approach); high fasting plasma glucose/high fasting plasma glucose (continuous); and lead exposure in blood/lead exposure in bone, in order to match with the relative risk factor categories. All MR records with 'smoking' as a risk factor were duplicated and renamed so that they could be automatically merged with the RR dataset, which distinguished between smoking (measured using SIR) and smoking (prevalence approach). In order to prevent double counting, only the relevant category was then kept for each risk-cause pair.

The individual datasets were then merged into a single dataset with the following variables:

- Cause of death
- Risk factor
- Distal risk factor
- Risk factor category
- Age
- Sex
- Mortality rate
- PAF
- Relative risk
- Mediation factor.

Here, distal risk factor corresponds to 'risk' in Table 8, i.e. the original risk factor that is mediated through the proximal risk factor (appearing as 'risk factor' in the combined dataset and 'path' in Table 8), and risk factor category corresponds to 'category' in Table 7.

The data were collated according to the following rules. The mortality rates dataset with a single entry for each cause-age-sex record was used as a baseline and combined with the PAF dataset using cause, age and sex as the key for matching. For causes of death with no identified risk factors, this had no effect on the baseline dataset and the risk factor and PAF records were left empty. For causes of death with exactly one relevant risk factor, the risk factor and PAF data were recorded within the particular cause-age-sex record. Finally, for causes of death with multiple identified risk factors, each cause-age-sex record from the baseline dataset was duplicated so that each risk factor and PAF value could be stored as a separate record. Missing values, representing causes of death without any matching identified risk factor in the epidemiological literature, were subsequently replaced by zeros, which are implicitly equivalent to no effect identified as the PAF value is subtracted from MR.

Subsequently, the same approach was used in combining the new cause-PAF dataset and the relative risk dataset, using cause of death, risk factor, age and sex as the matching key. For cause-risk pairs with no recorded relative risk, the category and relative risk records were left empty; for risk factors with one risk factor category (i.e. all the continuous and binary risk factors), the data was entered in the matching record in the baseline dataset;[15] and for risk factors with multiple categories the whole cause-risk-age-sex record was duplicated so that each category can be recorded separately. Missing values, representing cause-

[15] For binary risk factors, only the 'at risk' category is included as not being at risk is associated with relative risk of one. The algorithm automatically assigns relative risk of one to anyone not at risk.

risk pairs with no available relative risk (and also, therefore, category), were replaced with ones, which is implicitly equivalent to a no-effect situation as the RR value is multiplied by BD.[16]

Finally, the mediation factor and distal risk factor were entered in the newly created joint dataset in all matching records (and hence duplicated as necessary) using cause of death and risk factor (matching on proximal risk factor) as the matching key. A snapshot of the combined dataset is shown in Table 9.

Table 9. Combined dataset

Cause	Risk factor	Distal RF	Category	Sex	Age	MR	PAF	RR	MF
Malignant skin melanoma	-	-	-	Male	50–54	0.000%	0.0%	1.00	0.0%
Bladder cancer	High fasting plasma glucose	-	Diabetic	Male	50–54	0.003%	2.7%	1.51	0.0%
Bladder cancer	Smoking	-	SIR	Male	50–54	0.003%	30.2%	3.33	0.0%
Brain and nervous system cancer	-	-	-	Male	50–54	0.009%	0.0%	1.00	0.0%
Ischaemic heart disease	Smoking (prevalence approach)	-	Smoker (five-year lag)	Male	50–54	0.073%	30.7%	2.95	0.0%
Ischaemic heart disease	High fasting plasma glucose (continuous)	High total cholesterol	mmol/L	Male	50–54	0.073%	9.7%	1.20	3.0%

Source: RAND Europe analysis based on Abajobir et al. (2017a).

With the GBD parameters ready, the last element missing in the model is representation of the individual's risk factor profile, which is used, in combination with the predefined parameters, to calculate the individualised life expectancy. In the next section, we describe the development of a survey created for this purpose – to transform details of an individual's health and lifestyle into a set of input variables for the model.

[16] This has no effect on the calculation and any arbitrary value would work as well; the algorithm skips all cause-risk pairs with missing risk factor category and considers the individual's associated probability of death to be at the population average.

6. Survey questions

In this section we present a set of survey questions that aim to elicit details of an individual's health and lifestyle, which are essential to calculate their Vitality Age. Specifically, we structured the overall risk factor profile – smoking behaviour, diet, physical activity, etc. – according to the GBD database and designed a (set of) question(s) for each individual risk factor discussed in Section 4, so that the information on an individual's health and behaviour can be transformed into a set of input variables for the model. The input variables are in form of risk factor multipliers m_j and interact with the other parameters in the model by adjusting the RR values as described in equation (3) in Section 3. This in turn determines the individualised MRs and a bespoke life expectancy estimate.

The survey questions are broadly based on existing studies and questionnaires such as USDA & USDHHS (2015) or NHMRC (2013), and are asked as a first step in the Vitality Age assessment. As set out in Section 4, the selected risk factors for the mortality risk calculation are:

1. Alcohol use
2. Diet low in fruits
3. Diet low in nuts and seeds
4. Diet low in vegetables
5. Diet low in whole grains
6. Diet high in processed meat
7. Low physical activity
8. High body-mass index
9. High fasting plasma glucose
10. High systolic blood pressure
11. High total cholesterol
12. Smoking
13. Use of smokeless tobacco.

6.1. Risk factor assessment questions

A brief, non-systematic literature review was done for each risk factor to provide information on questions used in the existing studies. In some cases, e.g. for blood pressure, there is very little variability in the way the questions may be asked, whereas in other cases, e.g. for physical activity, the set of questions to be used may depend on the particular definition of physical activity or a limit on the number of questions

that can be asked. In the following sub-sections we discuss the basis for the specific design of the questions used (as opposed to the reason for the selection of risk factors for inclusion).

6.1.1. Alcohol use

According to the GBD database, alcohol use has been shown to have both detrimental and positive effects on health, depending on the frequency and amount of alcohol consumption. Specifically, low alcohol consumption is estimated to reduce mortality rates associated with diabetes mellitus, ischaemic heart disease and ischaemic stroke (Bagnardi et al. 2008; Ronksley et al. 2011). Consequently, TMREL for alcohol is not zero but rather chosen as exposure that minimises risk of suffering burden from any given cause related to alcohol, weighting the risk for a particular cause in the aggregation by the proportion of DALYs due to that cause.[17]

Alcohol is additionally unique in being fully associated with a number of outcomes (i.e. having PAF of 100 per cent), meaning that nearly all of the risk, regardless of age or background, can be attributed to alcohol consumption. This applies to alcohol use disorders, cirrhosis and other chronic liver diseases due to alcohol use, and liver cancer due to alcohol use.

The GBD exposure definition is average daily alcohol consumption of ethanol (measured in grams/day) in current drinkers who have consumed alcohol during the past 12 months. However, the protective effects of alcohol consumption are only applicable if the low average alcohol consumption is a result of low, regular consumption rather than occasional excessive drinking. Two sets of survey questions were designed to capture both of these dimensions:

1. On average, how many times per week would you have the following?

   1.1. Beer, cider or alcopops (0.5 l bottle or pint) [integer]
   1.2. Beer, cider or alcopops (0.3 l bottle or half pint) [integer]
   1.3. Wine or champagne (glass) [integer]
   1.4. Wine or champagne (bottle) [integer]
   1.5. Spirits (40%, 25 ml) [integer]

2. How often do you have [if male: '4 glasses of wine, 8 shots or 5 large bottles of beer'; if female (1.1.b): '3 glasses of wine, 6 shots or 4 large bottles of beer'] or more on one occasion?

   2.1. Never [checkbox]
   2.2. Less than monthly [checkbox]
   2.3. Monthly [checkbox]
   2.4. Weekly [checkbox]
   2.5. Daily [checkbox]

We chose a one-week reference period for the first question as a compromise between ability to capture long-term drinking patterns and reliability of answers. The original set of 16 common alcoholic beverages

[17] Note that in Section 3 we set the TMREL value of alcohol at zero for simplicity, as there we referred specifically to the harmful effects of alcohol.

was reduced to five items with similar strength and size (and therefore alcohol content). Each category was then transformed into amount of pure alcohol per week using the number of standard UK alcohol units contained in a typical beverage (Goddard 2007) and the fact that one standard unit contains 8 grams of pure alcohol. The approximate average number of UK alcohol units per category was identified as follows:

- Beer, cider or alcopops (0.5 l bottle or pint) 2.5 units
- Beer, cider or alcopops (0.3 l bottle or half pint) 1.5 units
- Wine or champagne (glass) 2 units
- Wine or champagne (bottle) 9 units
- Spirits (40%, 25 ml) 1 unit

Heavy episode (binge) drinking is defined as consumption of at least 60 grams of pure alcohol (7.5 units) for males and 48 grams (6 units) for females on a single occasion at least once per month (Rehm et al. 2003).

6.1.2. Dietary risk factors

The development of survey questions to assess dietary patterns was done in two ways. Firstly, a literature review was performed to identify relevant sets of questions that would fulfil the requirements set by Discovery Limited of being relatively short (no more than six questions per category) but also able to capture most of the variance in the more extensive questionnaires. Secondly, we conducted a series of pilot surveys with Vitality South African, UK and US employees, asking slight modifications of the question sets – using only a subset of the questions, replacing text descriptions with images, or using multiple choice answers instead of open-ended questions asking individuals to give a number. Based on the analysed correlations between answers to different modifications of the same question set (e.g. asking one or two questions on intake of nuts and seeds), a final set of questions was determined and is presented below. The previous versions of the GBD database included 'diet high in sodium' and 'diet high in sugar-sweetened beverages', which were excluded from the 2016 iteration as they have been shown to be wholly mediated through other risk factors (high systolic blood pressure and high body-mass index, respectively).

Diet low in fruits and vegetables

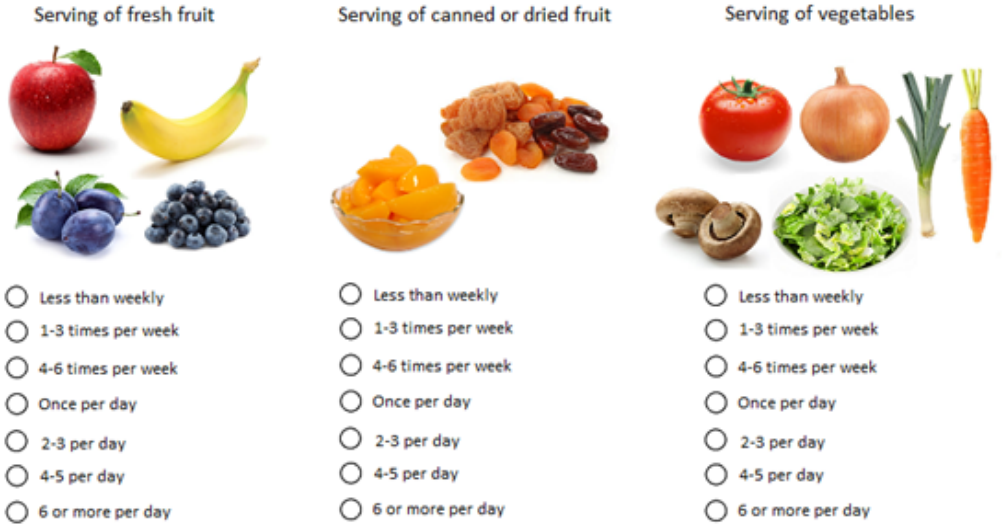
Intake for fruit and vegetables in the original Vitality Age model was built around questions from a standard validated food frequency questionnaire, the EPIC-Norfolk Food Frequency Questionnaire (EPIC-Norfolk Study team 2014), which asks about average intake over the past year for a given portion size. However, the recall period was again changed to one week in order to increase reliability of answers and the form of input was changed to a selection from predefined options rather than asking respondents to enter a number of portions. Fruit and vegetables portion sizes are converted to the GBD unit of 100 grams/day by using the UK Food Standards Agency portion size guide (UKFSA, 2016), which defines number of 80g portions of fruit in each selected item. For instance, 1 slice of pineapple will be recorded as 0.5 portion, i.e. 0.5*80/100 = 0.4 GBD units.

In the GBD study fruits were defined as fresh, frozen, cooked, canned, or dried fruit, excluding fruit juices and salted or pickled fruits, with a minimum intake (TMREL) of 200-300 grams a day, or 2-3 servings of 100 grams. Vegetables are defined as fresh, frozen, cooked, canned, or dried vegetables,

excluding salted or pickled vegetables, juices, nuts and seeds, legumes, and starchy vegetables such as potatoes or corn, with a TMREL of 290-430 grams per day, or 2.9-4.3 servings of 100 grams.

To reduce the number of categories, the individual categories from the EPIC-Norfolk Food Frequency Questionnaire were adjusted so that each represents a single 80-gram portion and subsequently all grouped together, forming a single question on fresh fruit, canned or dried fruit, and vegetables. The model input for fruit then consists of a sum of the two individual fruit questions. Moreover, in order to further simplify the questionnaire, all textual descriptions were replaced by images in which all pictures in a given category (e.g. an apple, three plums, handful of blueberries) represent a portion. The resulting set of questions is presented below.

3. On average, how many times per week would you have the following?



For the purposes of the VA.3 model, the answer options for fruit as well as all other dietary questions were transformed into the number of servings per day using the following key (based on the GBD methodology):

- Less than weekly = 0 servings per day
- 1–3 times per week = 0.3 servings per day
- 4–6 times per week = 0.8 servings per day
- Once per day = 1 unit
- 2–3 times per day = 2.5 servings per day
- 4–5 times per day = 4.5 servings per day
- 6 or more per day = 7 servings per day

Diet low in nuts and seeds

Nuts contain many healthy components including unsaturated fatty acids, vegetable proteins, fibre, folate, minerals, antioxidants and phytochemicals, which improve cardiometabolic risk factors (Carughi et al. 2015). In addition, nut consumption is linked to improved antioxidant capacity, reduced systemic inflammation and reduced glucose and insulin responses (Afshin et al. 2014).

The minimum required intake of nuts and seeds to reduce risk (TMREL) is between 12 and 20 grams per day, which constitutes approximately 3 to 5 GBD units of 4.05 grams per day. Following the same approach as for fruits and vegetables, an approximately 25-gram serving of nuts and seeds, based on the average UK portion size (Lewis, Ahern & Jebb 2012), was presented in the form of a picture with the same set of answer options:

On average, how many times per week would you have the following?

Diet low in whole grains

Whole grain content of foods differs substantially between countries and types of food. We have based the portion size definitions for the UK population on those reported in the UK national Diet and Nutrition survey (Ruston et al. 2004), the McCance and Widdowson's 'composition of foods integrated dataset on the nutrient content of the UK food supply' (Public Health England 2015), the WHOLEheart study (Brownlee et al. 2010) and cohort studies from the UK (Thane et al. 2007), using a middle value where portion sizes diverged. The TMREL is between 100 and 150 grams per day of whole grains, and intake is measured in GBD units of 50 grams per day.

To remain consistent, we again followed the approach to survey questions used for fruits, vegetables and nuts and seeds. However, given that wholegrain content varies strongly between types of food, we distinguish between three EPIC-Norfolk FFQ questions to assess wholegrain intake:

- A bowl of wholegrain-rich cereals (e.g. wheat biscuit such as Weetabix/Weet-Bix, wholegrain muesli, bran flakes, puffed wholegrain or porridge).
- A slice of wholemeal or rye bread, a wholemeal roll, wholemeal flatbread, cereal bar or two crispbread or two oatcakes.
- A cup of wholegrain pasta or 1/2 cup of brown rice.

These represent standard servings equating to 30, 20 and 60 grams of whole grains, respectively. The three questions and options for answers were presented as follows:

On average, how many times per week would you have the following?

A bowl of wholegrain-rich cereal

- Less than weekly
- 1-3 times per week
- 4-6 times per week
- Once per day
- 2-3 per day
- 4-5 per day
- 6 or more per day

Serving of wholegrain pasta or brown rice

- Less than weekly
- 1-3 times per week
- 4-6 times per week
- Once per day
- 2-3 per day
- 4-5 per day
- 6 or more per day

Serving of other wholegrains

- Less than weekly
- 1-3 times per week
- 4-6 times per week
- Once per day
- 2-3 per day
- 4-5 per day
- 6 or more per day

Diet high in processed meat

Processed meat increases the risk of colorectal cancer, ischaemic heart disease and diabetes (see, for example, Micha et al. 2010). The latter two outcomes are speculated to be the consequence of the high sodium and nitrate content observed in processed meats, however the complete pathway between high processed meat consumption and ischaemic heart disease and diabetes remains unclear.

We determined portion sizes for processed meat using guidelines from the British Heart Foundation, as well as reports on UK portion sizes (Church 2008; Lewis, Ahern & Jebb 2012), and we assess intake with the EPIC-Norfolk FFQ question: *'How often would you eat a serving of processed meat (e.g. 1 sausage, 2–3 slices of bacon, 2 snacking meats e.g. pepperoni, 2 slices of ham or similar deli meat, 4 thin slices of salami or similar)?'.* The TMREL is 0–4 grams a day, which is the equivalent to 0–0.08 GBD units of 50 grams. The question and options for answers were presented as follows:

Serving of processed meat

- Less than weekly
- 1-3 times per week
- 4-6 times per week
- Once per day
- 2-3 per day
- 4-5 per day
- 6 or more per day

6.1.3. Low physical activity

Despite the large number of studies that support the importance of physical activity (more than 100 studies informed the RR of low physical activity in the GBD), only five outcomes (breast cancer, colorectal cancer, diabetes, ischaemic heart disease and ischaemic stroke) are directly related to low levels of physical activity. As discussed in Section 4.3, there are other indirect effects of physical activity – and other lifestyle factors – on the risk factors included in the Vitality Age model, particularly body-mass index and blood pressure. The GBD estimation methodology accounts for the joint effects of multiple risk factors on a single cause of death but the causative and/or correlative temporal effects among risk factors are not fully modelled, meaning that the effects of physical activity on other risk factors over time are not explicitly recognised. The PAF and RR estimates thus represent the estimated direct effect of low physical activity on the relevant causes of death and are rather low. Unfortunately, this cannot be changed within the context of the GBD parameters, yet it can be addressed through a series of assumptions on the long-term impacts of one risk factor on another. For instance, there is no formal link in the GBD database between physical activity and blood pressure, yet physical activity has been shown to lower blood pressure over time (see, for example, Arroll & Beaglehole, 1992). One can thus project future changes in blood pressure based on parameters identified in the literature.

Physical activity in the GBD database is measured in metabolic equivalents (METs), a ratio of metabolic rate during a specific physical activity to a resting metabolic rate. One MET is defined as 1 kcal/kg/hour and is roughly equivalent to the energy cost of sitting quietly. The GBD database uses METs/week as the unit to assess the risk related to low levels of physical activity. Importantly, the GBD risk factor classification refers to *all* types of physical activity, including walking and other non-sedentary activities in addition to physical exercise.

Physical activity in the GBD database is a categorical risk factor, with categories being <600 METs/week, 600–3,999 METs/week, 4,000–7,999 METs/week, and ≥8000 METs/week. The TMREL is estimated at 3,000-4,000 METs/week; being in the latter two categories is thus equivalent of not being at risk.

Physical activity in the newly developed questionnaire is assessed in two ways: with the help of physical activity trackers counting steps throughout the day (if available) and/or using a set of standard questions based on the International Physical Activity Questionnaire (IPAQ) (IPAQ Group 2010), which ask about time spent on different types of activities. Specifically, individuals who own activity trackers and are able to provide information on the number of steps they take per day on average are only asked about time spent doing vigorous physical activity, whereas those who do not own activity trackers are also asked about moderate physical activity. The reasoning is provided below.

Average MET scores for each type of activity were derived from Jette et al. (1990) and include the following values: casual walking = 3.3 METs/minute, moderate-intensity physical exercise = 4.0 METs/minute, and vigorous-intensity physical exercise = 10.0 METs/minute. Assuming an average step length of 2.5 feet (0.762 metres) and excluding slow walking pace (3 km/h) from moderate physical exercise, we can use the above values to determine the average MET equivalent of a single step, approximated as 0.0379 METs. Hence, the recommended daily amount of 10,000 steps is roughly equal to 379 METs.

The two questions asked in addition to the number of steps are as follows:

4. How many times per week and for how long do you do:

	Times per week	Minutes per occasion (average)
Moderate leisure-time physical activities for at least 10 minutes that cause light sweating or moderate increases in breathing or heart rate (e.g. carrying light loads, cycling at a normal pace or doubles tennis)?	[ ]	[ ]
Vigorous leisure-time physical activities for at least 10 minutes that cause heavy sweating or large increases in breathing or heart rate (e.g. lifting heavy things, digging, aerobics or fast cycling)?	[ ]	[ ]

One problem with these questions is that the activity trackers will also count steps during moderate and vigorous physical activity. In order to reduce the double-counting of METs, the question on moderate physical activity is asked only if a person does not know their average daily step count. The reasoning behind this and also the exclusion of other potential physical activity questions (e.g. questions on other non-sedentary activities such as gardening or housework) is that knowing the precise amount of physical activity is not necessary from the calculation perspective. Only classification into one of the four broad physical activity categories is required for the analysis.

Indeed, one can reach the second lowest category (600–3,999 METs/week) by doing just 2,300 steps per day, or 150 minutes of moderate physical activity per week, or 100 minutes of vigorous physical activity per week. The two questions presented above should thus be sufficient to determine whether a person is at least somewhat physically active. At the same time, reaching the TMREL threshold, equivalent to being in the top two categories, would require doing more than 15,000 steps per day or 150/100 minutes of moderate/vigorous physical activity per week. Since other non-sedentary physical activities are associated with fairly low MET equivalents and one would still need to do a substantial amount of exercise/walking in addition to them, the non-sedentary physical activity questions were not included in the survey. This approach potentially results in slightly worse model results for individuals who would otherwise be included in one of the higher categories. The same applies to the approach taken to counter steps/moderate physical activity double-counting. However, given the relatively low relative risk values for physical activity, the potential distortion is minimal.

Table 10 below presents the weekly MET-equivalent of various combinations of the average number of steps made per day within a single week (excluding double-counted steps) and minutes of vigorous physical activity done per week, i.e. the two questions asked in the survey. The colour-coding represents the four physical activity categories defined in the GBD database.

Table 10. Correspondence between amount of physical activity, METs and GBD categories

Number of steps per day \ Minutes of vigorous physical activity per week	0	50	100	150	200	300	500
0	0	500	1,000	1,500	2,000	3,000	5,000
2,000	531	1,031	1,531	2,031	2,531	3,531	5,531
4,000	1,061	1,561	2,061	2,561	3,061	4,061	6,061
6,000	1,592	2,092	2,592	3,092	3,592	4,592	6,592
8,000	2,122	2,622	3,122	3,622	4,122	5,122	7,122
10,000	2,653	3,153	3,653	4,153	4,653	5,653	7,653
12,000	3,184	3,684	4,184	4,684	5,184	6,184	8,184

Note: Red background represents the <600 METs/week category, yellow background represent the 600–3,999 METs/week category, light green the 4,000–7,999 METs/week category, and the intense green the ≥8000 METs/week category.
Source: RAND Europe analysis.

6.1.4. High body-mass index

The metric for body weight is body-mass index (BMI), computed as body mass (in kg) divided by the square of body height (m^2). The relative risk associated with excess body weight is defined within the GBD as the number of GBD units (expressed in 5 kg/m^2) above the TMREL of 20–25 kg/m^2. Excess body weight is a direct risk for 33 different outcomes, ranging from diabetes to cardiovascular diseases to various cancers. In addition, BMI has a wide range of indirect effects when combined with high blood pressure, high fasting plasma glucose and high total cholesterol.

BMI is obtained by asking participants for their height and weight, with a choice to answer in imperial or metric units:

5. What is your height? Please provide your answer in only one format (either in centimetres or in feet and inches).

   5.1. Feet [ ]
   5.2. Inches [ ]
   5.3. Centimetres [ ]

6. What is your weight? Please provide answer in only one format (in kilograms or in pounds or in stones and pounds).

   6.1. Weight in stones [ ]
   6.2. Weights in pounds [ ]
   6.3. Weight in kilograms [ ]

The previous Vitality Age algorithm further distinguished between individuals with unhealthy high BMI and healthy high BMI, represented by muscular physique, through a separate question on waist circumference. Since the GBD data do not make such a distinction, high BMI is always considered an adverse risk factor in the VA.3 model. However, it is possible to explicitly assume individuals with certain BMI/waist circumference ratio are not at risk in the model.

6.1.5. High systolic blood pressure, high total cholesterol and high fasting plasma glucose

Systolic blood pressure, total cholesterol and fasting plasma glucose have in common that their associated relative risk is directly linked to a single measurement, and therefore can be obtained with a single question. However, some/all of the readings might be unknown to participants. For this reason the questionnaire allows individuals to enter the exact reading as well as to choose from one of the predefined options:

1. What is your systolic/diastolic blood pressure reading?

   1.1. Systolic blood pressure (mmHg) [ ]

   1.2. Low (110/60 mmHg systolic/diastolic) [checkbox]
   1.3. Normal (115/75 mmHg systolic/diastolic) [checkbox]
   1.4. High (140/85 mmHg systolic/diastolic) [checkbox]
   1.5. Don't know [checkbox]

2. What is your total cholesterol reading?

   2.1. Total cholesterol (mmol/l) [ ]

   2.2. Low (4.7 mmol/l) [checkbox]
   2.3. Normal (5.2 mmol/l) [checkbox]
   2.4. Borderline high (5.7 mmol/l) [checkbox]
   2.5. High (6.2 mmol/l) [checkbox]
   2.6. Don't know [checkbox]

3. What is your fasting glucose reading?

   3.1. Fasting glucose (mmol/l) [ ]

   3.2. Low (4.0 mmol/l) [checkbox]
   3.3. Normal (5.6 mmol/l) [checkbox]
   3.4. Borderline high (6.5 mmol/l) [checkbox]
   3.5. High (7.0 mmol/l) [checkbox]
   3.6. Don't know [checkbox]

As discussed in Section 3, if the respondent does not know their exact or approximate readings, missing data can be entered into the model resulting in given risk factor exposure being considered at the population level.

The TMREL for systolic blood pressure is 110–115 mmHg, or 11–11.5 times the GBD unit of 10 mmHg. The predefined options are taken from the UK's National Health Service guidelines (NHS 2017). Total cholesterol is measured as millimoles per litre (mmol/l) and individuals are at risk when their cholesterol exceeds the TMREL of 2.8–3.4 mmol/L. The GBD measures total cholesterol in units of 1

mmol/l. The predefined options are based on the Framingham Heart Study (Mahmood et al. 2014). Fasting plasma glucose is also measured in millimoles per litre, with TMREL estimated between 4.5 and 5.4 mmol/l. The categories were selected so that:

- The 'low' category is below the TMREL threshold.
- The 'normal' category is the midpoint of the interval between the TMREL and the lower bound of the pre-diabetic level.
- The 'borderline high' category is the midpoint of the pre-diabetic interval.
- The 'high' category represents diabetic levels.

Since fasting plasma glucose as a risk factor is included twice in the GBD dataset – once as a continuous variable as described here and once in a binary form (diabetic/non-diabetic) – entering a value at or higher than 7 mmol/l also results in the binary variable to be stored as diabetic.

Note that other relevant measures such as diastolic blood pressure, LDL/HDL cholesterol or glycated haemoglobin (HbA1c) are not included in the current release of the GBD database. Since this may be problematic in certain countries, the alternative readings can be used as primary input data and subsequently transformed into VA.3 model inputs using predefined cross-walks.

6.1.6. Smoking and smokeless tobacco

In the GBD, the RR for smoking is based on two different measures – the smoking impact ratio (SIR) and the five-year lagged smoking prevalence – because there are different risks associated with each. The SIR, developed by Peto, Lopez and colleagues, is used for cancers and chronic respiratory disease such as chronic obstructive pulmonary disease, and interstitial lung disease attributable to tobacco exposure (Peto et al. 1992). The five-year lagged prevalence of tobacco exposure, on the other hand, is used for outcomes that have a more short-term effect, such as cardiovascular outcomes, tuberculosis, diabetes and asthma. Risk factor exposure is assessed using the following two questions:

1. Do you currently smoke cigarettes/cigars/pipes?
    1.1. No, I have never smoked cigarettes [checkbox]
    1.2. No, but I used to smoke cigarettes [checkbox]
    1.3. Yes, I currently smoke cigarettes [checkbox]
2. How many years ago did you stop smoking cigarettes/cigars/pipes? (if less than 1 year enter 0)
    2.1. [float] years

Consequently, an individual can be classified as a current smoker; a past smoker, who stopped smoking within the last five years; a past smoker who stopped smoking more than five years ago; or a never-smoker.

Current use of smokeless tobacco was assessed using the following question:

1. Do you currently use smokeless tobacco products, such as chewing tobacco?
    1.1. Yes [checkbox]
    1.2. No [checkbox]

6.2. Model inputs

Using information on servings, GBD units, TMREL thresholds, and the formulas described in Section 3, we can combine the inputs from the questionnaire into risk factor multipliers m, as used in the model. The full set of risk factors included in the model and the respective input units, GBD units, TMREL thresholds and formulae for calculating m are presented in Table 11.

Table 11. Summary of the selected risk factors and their characteristics

Risk factor	Input units (portions)	GBD units (intake measure)	TMREL	Formula (x = intake)
Alcohol	g/day	g/day	Zero alcohol intake	Categorical (0g/12g/24g/36g/48g/60g/72g)
Diet low in fruits	80 g/day	100 g/day	2–3	$m_j = \max(0,3 - x \times 0.8)$
Diet low in vegetables (excluding legumes)	80 g/day	100 g/day	2.9–4.3	$m_j = \max(0,4.3 - x \times 0.8)$
Diet low in nuts and seeds	25 g/day	4.05 g/day	3–5	$m_j = \max(0,5 - \frac{x \times 25}{4.05})$
Diet low in whole grains	20 g/day	50 g/day	2–3	$m_j = \max(0,2 - \frac{x \times 2}{5})$
Diet high in processed meat	50 g/day	50 g/day	0–0.08	$m_j = \max(0, \frac{x}{50} - 0)$
Low physical activity	METs/week	METs/week	3,000–4,500	Categorical (<600, 600–3,999, 4,000–7,999, and >=8,000)
High body-mass index	kg/m^2	5 kg/m^2	20–25	$m_j = \max(0, \frac{x}{5} - 20)$
High blood pressure	mmHg	10 mmHg	11.0–11.5	$m_j = \max(0, \frac{x}{10} - 11)$
High total cholesterol	mmol/L	mmol/L	2.8–3.4	$m_j = \max(0, x - 2.8)$
High fasting plasma glucose (dichotomous)	-	-	Non-diabetic	Categorical (Diabetic/Non-diabetic)
High fasting plasma glucose (continuous)	mmol/L	mmol/L	4.5–5.4	$m_j = \max(0, x - 4.5)$
Smoking	-	-	Not smoking	Categorical (smoker/non-smoker)
Smoking (prevalence approach)	-	-	Not smoking	Categorical (smoker/non-smoker – five year lag)
Smokeless tobacco	-	-	Not exposed	Categorical (exposed/not exposed)

Note: See Section 3.3 for the reasoning behind the formulas. Zero alcohol consumption is the TMREL when considering only the harmful effects of alcohol use; see Section 6.1.1 for details.
Source: RAND Europe analysis.

With the input variables and their method of collection defined, the VA.3 concept is complete – combining the input variables and the predefined parameters obtained from the GBD database in the framework outlined in Section 3, we can calculate the adjusted life expectancy of any selected individual and determine their Vitality Age by comparing it with that of the general population.

References

Abajobir, A.A. et al. 2017a. 'Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016.' *Lancet* 390(10100):1345–422.

Abajobir, A.A. et al. 2017b. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 390(10100):1151–1210.

Afshin, A., Micha, R., Khatibzadeh, S., & Mozaffarian, D. 2014. 'Consumption of nuts and legumes and risk of incident ischemic heart disease, stroke, and diabetes: a systematic review and meta-analysis.' *The American journal of clinical nutrition*, 100(1), 278-288.

Aitken, G.R., P.J. Roderick, S. Fraser, J.S. Mindell, D. O'Donoghue, J. Day & G. Moon. 2014. 'Change in prevalence of chronic kidney disease in England over time: comparison of nationally representative cross-sectional surveys from 2003 to 2010.' *BMJ Open* 4(9).

Allan, G.M., F. Nouri, C. Korownyk, M.R. Kolber, B. Vandermeer & J. McCormack. 2013. 'Agreement Among Cardiovascular Disease Risk Calculators.' *Circulation* 127(19):1948–56.

Alssema, M., Newson, R. S., Bakker, S. J., Stehouwer, C. D., Heymans, M. W., Nijpels, G., ... & Dekker, J. M. 2012. 'One risk assessment tool for cardiovascular disease, type 2 diabetes, and chronic kidney disease.' *Diabetes Care*, 35(4), 741-748.

Arroll, B., & R. Beaglehole. 1992. 'Does physical activity lower blood pressure: a critical review of the clinical trials.' *Journal of Clinical Epidemiology* 45(5):439–47.

Bagnardi, V., Zatonski, W., Scotti, L., La Vecchia, C., & Corrao, G. 2008. 'Does drinking pattern modify the effect of alcohol on the risk of coronary heart disease? Evidence from a meta-analysis.' *Journal of Epidemiology & Community Health*, 62(7), 615-619.

Ben, Q., M. Xu, X. Ning, J. Liu, S. Hong, W. Huang & Z. Li. 2011. 'Diabetes mellitus and risk of pancreatic cancer: a meta-analysis of cohort studies.' *European Journal of Cancer* 47(13):1928–37.

Beswick, A.D., P. Brindle, T. Fahey & S. Ebrahim. 2008. *A Systematic Review of Risk Scoring Methods and Clinical Decision Aids Used in the Primary Prevention of Coronary Heart Disease*. National Institute for Health and Clinical Excellence: Guidance. London: Royal College of General Practitioners (UK).

Boutin, B., M.B. Brown, R. Clark, J.C. Lipscomb, R. Miltner, P. Murphy, L.R. Papa, D. Reasoner & R. Rheingans. 1998. *Comparative Risk Framework Methodology and Case Study*. US Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Washington, DC.

Brownlee, I. A., Moore, C., Chatfield, M., Richardson, D. P., Ashby, P., Kuznesof, S. A., ... & Seal, C. J. 2010. 'Markers of cardiovascular risk are not changed by increased whole-grain intake: the WHOLEheart study, a randomised, controlled dietary intervention.' *British Journal of Nutrition*, 104(1), 125-134.

Carughi, A., M.J. Feeney, P. Kris-Etherton, V. Fulgoni, C.W. Kendall, M. Bulló & D. Webb. 2015. 'Pairing nuts and dried fruit for cardiometabolic health.' *Nutrition Journal* 15(1):23.

Chiuve, S.E., N.R. Cook, C.M. Shay, K.M. Rexrode, C.M. Albert, J.E. Manson, W.C. Willett & E.B. Rimm. 2014. 'Lifestyle-based prediction model for the prevention of CVD: the Healthy Heart Score.' *Journal of the American Heart Association* 3(6):e000954.

Church S. 2008 'Trends in portion sizes in the UK – A preliminary review of published information.' Available at: http://www.food.gov.uk/multimedia/pdfs/reviewportions.pdf.

Colditz, G. A., Atwood, K. A., Emmons, K., Monson, R. R., Willett, W. C., Trichopoulos, D., & Hunter, D. J. 2000. 'Harvard report on cancer prevention volume 4: Harvard Cancer Risk Index.' *Cancer causes & control*, 11(6), 477-488.

Collins, G.S., & D.G. Altman. 2009. 'An independent external validation and evaluation of QRISK cardiovascular risk prediction: a prospective open cohort study.' *BMJ* 339:b2584.

Conroy, R. M., Pyörälä, K., Fitzgerald, A. E., Sans, S., Menotti, A., De Backer, G., ... & Njølstad, I. 2003. 'Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project.' *European Heart Journal* 24(11): 987-1003.

Cosco, T.D., M. Stafford, D. Kuh & R. Cooper. 2016. 'Socioeconomic indicators and sociobehavioural mediators of high mental wellbeing despite low physical capability: the MRC National Survey of Health and Development.' *Lancet* 388(S39).

D'Agostino, R.B., & W.B. Kannel. 1989. 'Epidemiological background and design: The Framingham Study.' *Proceedings of the American Statistical Association Sesquicentennial Invited Paper Sessions*: 707–18.

D'Agostino, R. B., Vasan, R. S., Pencina, M. J., Wolf, P. A., Cobain, M., Massaro, J. M., & Kannel, W. B. 2008. 'General Cardiovascular Risk Profile for Use in Primary Care: The Framingham Heart Study.' *Circulation* 117(6): 743-753.

Danaei, G., E.L. Ding, D. Mozaffarian, B. Taylor, J. Rehm, C.J.L. Murray & M. Ezzati. 2009. 'The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors.' *PLoS Med* 6(4):e1000058.

Emerging Risk Factors Collaboration et al. 2010. 'Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies.' *Lancet* 375(9733):2215–22.

EPIC-Norfolk Study Tteam. 2014. 'EPIC-Norfolk Food Frequency Questionnaire (FFQ)' Available from http://www.srl.cam.ac.uk/epic/nutmethod/FFQ.shtml

Forouzanfar, M.H. et al. 2015. 'Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013.' *Lancet* 386(10010):2287–323.

Ganna, A., & Ingelsson, E. 2015. '5 year mortality predictors in 498 103 UK Biobank participants: a prospective population-based study.' *The Lancet* 386: 533-540.

Gavrilov, L.A., & N.S. Gavrilova. 2011. 'Mortality measurement at advanced ages: a study of the Social Security Administration Death Master File.' *North American Actuarial Journal* 15(3):432–47.

Gavrilova, N.S., & L.A. Gavrilov. 2014. 'Mortality trajectories at extreme old ages: a comparative study of different data sources on US old-age mortality.' *Living to 100 Monograph*.

GBD. 2015. 'Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1.8 million participants.' *Lancet* 383(9921):970–83.

Chen, L., Magliano, D. J., Balkau, B., Colagiuri, S., Zimmet, P. Z., Tonkin, A. M., ... & Shaw, J. E. 2010. 'AUSDRISK: an Australian Type 2 Diabetes Risk Assessment Tool based on demographic, lifestyle and simple anthropometric measures.' *Medical Journal of Australia*, 192(4), 197.

Goddard, E. 2007. 'Estimating alcohol consumption from survey data: updated method of converting volumes to units (No. 37).' *Cardiff: Office for National Statistics*.

Goff, D.C., D.M. Lloyd-Jones, R.B. D'Agostino, R. Gibbons, P. Greenland, D.T. Lackland, J. Robinson, J.S. Schwartz, S.C. Smith, N.J. Stone & P.W.F. Wilson. 2013. *2013 Report on the Assessment of Cardiovascular Risk: Full Work Group Report Supplement*. National Heart, Lung, and Blood Institute.

Hippisley-Cox, J., Coupland, C., Vinogradova, Y., Robson, J., Minhas, R., Sheikh, A., & Brindle, P. 2008. 'Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2.' *BMJ*, 336(7659), 1475-1482.

IPAQ Group. 2010. 'Validation of the New Zealand physical activity questionnaire (NZPAQ-LF) and the international physical activity questionnaire (IPAQ-LF) with accelerometry.' *British journal of sports medicine*.

Jette, M., Sidney, K., & Blümchen, G. 1990. 'Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity.' *Clinical cardiology*, 13(8), 555-565.

Kessler, R.C., G. Andrews, LJ. Colpe, E. Hiripi, D.K. Mroczek, S.L. Normand, E.E. Walters & A.M. Zaslavsky. 2002. 'Short screening scales to monitor population prevalences and trends in non-specific psychological distress.' *Psychological Medicine* 32(6):959–76.

Lee, S. J., Lindquist, K., Segal, M. R., & Covinsky, K. E. 2006. 'Development and validation of a prognostic index for 4-year mortality in older adults.' *JAMA*, 295(7), 801-808.

Lee, J.Y., I. Jeon, J.W. Kim, Y.S. Song, J.M. Yoon & S.M. Park. 2013. 'Diabetes mellitus and ovarian cancer risk: a systematic review and meta-analysis of observational studies.' *International Journal of Gynecological Cancer* 23(3):402–12.

Lewis HB, Ahern AL, Jebb SA. (2012) 'How much should I eat? A comparison of suggested portion sizes in the UK.' *Public Health Nutrition*. 2012 November; 15(11):210-2117. Available at: http://europepmc.org/articles/PMC3477828

Lim, S., E. Carnahan, E. Nelson, C. Gillespie, A. Mokdad, C. Murray & E. Fisher. 2015. 'Validation of a new predictive risk model: measuring the impact of the major modifiable risks of death for patients and populations.' *Population Health Metrics* 13(1):27.

Liu, J., Y. Hong, R.B. D'Agostino Sr et al. 2004. 'Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese Multi-Provincial Cohort Study.' *JAMA* 291(21):2591–99.

Lloyd-Jones, D. M., Leip, E. P., Larson, M. G., d'Agostino, R. B., Beiser, A., Wilson, P. W., ... & Levy, D. 2006. 'Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age.' *Circulation*, 113(6), 791-798.

Lloyd-Jones, D.M. 2010. 'Cardiovascular Risk Prediction: Basic Concepts, Current Status, and Future Directions.' *Circulation* 121(15):1768–77.

Lloyd-Jones, D.M. et al. 2010. 'Defining and setting national goals for cardiovascular health promotion and disease reduction: The American Heart Association's Strategic Impact Goal through 2020 and beyond.' *Circulation* 121(4):586–613.

Mahmood, S. S., Levy, D., Vasan, R. S., & Wang, T. J. 2014. 'The Framingham Heart Study and the epidemiology of cardiovascular disease: a historical perspective.' *The Lancet*, 383(9921), 999-1008.

Micha, R., S.K. Wallace & D. Mozaffarian. 2010. 'Red and processed meat consumption and risk of incident coronary heart disease, stroke, and diabetes mellitus: a systematic review and meta-analysis.' *Circulation* 121(21):2271–83.

NHMRC. 2013. *Eat for Health: Australian Dietary Guidelines*. National Health and Medical Research Council of the Australian Government.

NHS (UK National Health Service). 2017. Available from: https://www.nhs.uk/conditions/high-blood-pressure-hypertension/

NICE. 2014. *Lipid modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease*. NICE clinical guideline CG181. London.

Noble, D., R. Mathur, T. Dent, C. Meads & T. Greenhalgh. 2011. 'Risk models and scores for type 2 diabetes: systematic review.' *BMJ* 343:d7163.

Payne, R.A. 2012. 'Cardiovascular risk.' *Br J Clin Pharmacol* 74(3):396–410.

Peto, R., Boreham, J., Lopez, A. D., Thun, M., & Heath, C. 1992. Mortality from tobacco in developed countries: indirect estimation from national vital statistics. *The Lancet*, 339(8804), 1268-1278.

Prince, M., V. Patel, S. Saxena, M. Maj, J. Maselko, M.R. Phillips & A. Rahman. 2007. 'No health without mental health.' *Lancet* 370(9590):859–77.

Pitchforth, J.M., R.M. Viner & D.S. Hargreaves. 2016. 'Trends in mental health and wellbeing among children and young people in the UK: a repeated cross-sectional study, 2000–14.' *Lancet* 388(S93).

Public Health England. 2015. 'Composition of foods integrated dataset (CoFID).' Available from https://www.gov.uk/government/publications/composition-of-foods-integrated-dataset-cofid

Rehm, J., G. Gmel, C.T. Sempos & M. Trevisan. 2003. 'Alcohol-related morbidity and mortality.' *Alcohol Research & Health* 27(1):39–51.

Ronksley, P. E., Brien, S. E., Turner, B. J., Mukamal, K. J., & Ghali, W. A. 2011. 'Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis.' *BMJ*, 342, d671.

Ross, R., S.N. Blair, R. Arena, T.S. Church, J.P. Després, B.A. Franklin et al. 2016. 'Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a scientific statement from the American Heart Association.' *Circulation* 1349(24):e653–e699.

Ruston D., Hoare J., Henderson L., Gregory J., Bates C.J., Prentice A., Birch M., Swan G . and Farron M. 2004. 'National Diet and Nutrition Survey: adults aged 19-64 years. Volume 4: Nutritional Status (anthropometry and blood analytes), blood pressure and physical activity.' *London: TSO*.

Schubert, C.M., N.L. Rogers, K.E. Remsberg, S.S. Sun, W.C. Chumlea, E.W. Demerath, S.A. Czerwinski, B. Towne & R.M. Siervogel. 2005. 'Lipids, lipoproteins, lifestyle, adiposity and fat-free mass during middle age: the Fels Longitudinal Study.' *Int J Obes Relat Metab Disord* 30(2):251–60.

Stewart-Brown, S., A. Tennant, R. Tennant, S. Platt, J. Parkinson & S. Weich. 2009. 'Internal construct validity of the Warwick-Edinburgh mental well-being scale (WEMWBS): a Rasch analysis using data from the Scottish health education population survey.' *Health and Quality of Life Outcomes* 7(1):15.

Stone, N. J., Robinson, J. G., Lichtenstein, A. H., Merz, C. N. B., Blum, C. B., Eckel, R. H., ... & McBride, P. 2014. '2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.' *Journal of the American College of Cardiology*, 63(25 Part B), 2889-2934.

Stranges, S., P.C. Samaraweera, F. Taggart, N.B. Kandala & S. Stewart-Brown. 2014. 'Major health-related behaviours and mental well-being in the general population: the Health Survey for England.' *BMJ Open* 4(9):e005878.

Sullivan, L.M., J.M. Massaro & R.B. D'Agostino Sr. 2004. 'Presentation of multivariate data for clinical use: The Framingham Study risk score functions.' *Statistics in Medicine* 23(10):1631–60.

Thane, C. W., Jones, A. R., Stephen, A. M., Seal, C. J., & Jebb, S. A. 2007. 'Comparative whole-grain intake of British adults in 1986–7 and 2000–1.' *British Journal of Nutrition*, 97(5), 987-992.

UKFSA. 2016. *The Eatwell Guide: Helping you eat a healthy, balanced diet*. UK Food Standards Agency. As of January 2018:
https://www.food.gov.uk/sites/default/files/finaleatwellguide23mar2016nothernireland23rd.pdf

USDA & USDHHS. 2015. *Scientific Report of the 2015 Dietary Guidelines Advisory Committee*. Advisory Report to the Secretary of Health and Human Services and the Secretary of Agriculture. US Departments of Agriculture and Health and Human Services. Washington DC.

Wells, S., A. Kerr, S. Eadie, C. Wiltshire & R. Jackson. 2010. '"Your Heart Forecast": a new approach for describing and communicating cardiovascular risk?' *Heart* 96(9):708–13.

Wilson, P. W., D'Agostino, R. B., Levy, D., Belanger, A. M., Silbershatz, H., & Kannel, W. B. 1998. 'Prediction of coronary heart disease using risk factor categories.' *Circulation*, 97(18), 1837-1847.