COHORT PROFILE

Cohort Profile: The Berlin Aging Study II (BASE-II)[†]

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Similar to other industrialized countries, Germany's population is ageing. Whereas some people enjoy good physical and cognitive health into old age, others suffer from a multitude of age-related disorders and impairments which reduce life expectancy and affect quality of life. To identify and characterize the factors associated with 'healthy' *vs.* 'unhealthy' ageing, we have launched the Berlin Aging Study II (BASE-II), a multidisciplinary and multi-institutional project that ascertains a large number of ageing-related variables from a wide range of different functional domains. Phenotypic assessments include factors related to geriatrics and internal medicine, immunology, genetics, psychology, sociology and economics. Baseline recruitment of the BASE-II cohort was recently completed and has led to the sampling of 1600 older adults (age range 60–80 years), as well as 600 younger adults (20–35 years) serving as the basic population for in-depth analyses. BASE-II data are linked to the German Socio-Economic Panel Study (SOEP), a long-running panel survey representative of the German population, to estimate sample selectivity. A major goal of BASE-II is to facilitate collaboration with other research groups by freely sharing relevant phenotypic and genotypic data with qualified outside investigators.

Why was the cohort set up?

Similar to other industrialized countries, Germany's population is ageing. In 2009, nearly 26% of Germans were aged over 60 years and approximately 19% were aged 18 years or younger.[1] Recent projections suggest that this imbalance will increase by 2050 when nearly 15% of Germans will be 80 years of age or older.[1] Whereas some individuals enjoy good physical and cognitive health into old age, others suffer from a multitude of age-related disorders and impairments which not only significantly reduce life expectancy but also severely reduce quality of life and

[†] A full list of BASE-II collaborators and their affiliations can be found at the end of the manuscript.

Table 1 Selection of sociodemographic characteristics of the BASE-II cohort and comparison with representative samples from Berlin and Germany

Characteristics	Young (Age 20-35 years)			Old (Age 60+ years)		
	BASE-II	Berlin	Germany	BASE-II	Berlin	Germany
Number of observations[a]	600	173	3802	1600	234	6487
Age[b]	27.32	27.83	27.64	66.76	69.62**	70.51**
Female	0.50	0.55	0.53	0.50	0.50*	0.52
German nationality	0.99	0.96*	0.93**	0.99	0.96**	0.96*
Family status[1]						
Married or living together	0.16	0.19	0.27**	0.57	0.65*	0.69**
Single	0.84	0.80	0.67**	0.09	0.06	0.03**
Divorced/separated	0	0.01	0.03**	0.29	0.14**	0.08**
Widowed	0	0	0	0.05	0.16**	0.19**
Highest school degree[2]						
Elementary school	0.01	0.08**	0.17**	0.16	0.31**	0.54**
Intermediate school	0.12	0.21**	0.33**	0.27	0.36**	0.20**
High school	0.86	0.62**	0.42**	0.51	0.29**	0.18**
No school or other school	0.01	0.09**	0.08**	0.06	0.05	0.08**
Employment status						
Employed	0.44	0.71**	0.72**	0.14	0.20**	0.16**
Self-rated health[3]						
Very good	0.17	0.12	0.19	0.08	0.03**	0.03**
Good	0.29	0.49**	0.53**	0.32	0.26	0.25**
Fair	0.18	0.28**	0.21*	0.33	0.47**	0.43**
Poor or very poor	0.36	0.12**	0.07	0.28	0.24	0.29
Satisfaction with life in general[4,c]	7.01	7.06	7.12	7.49	6.83**	7.00**

Data sources: BASE-II, SOEP (V28), and unpublished data. All variables for BASE-II are derived from the full baseline cohort ($n = 2200$), except where labelled with [1]($n = 2155$), [2]($n = 2172$), [3]($n = 2188$), [4]($n = 2079$).
[a]Values are presented as means for continuous variables and proportions for dichotomous variables.
[b]Age is calculated using 2009 as reference.
[c]As measured on a Likert scale[19] ranging from 0 ('completely dissatisfied') to 10 ('completely satisfied').
P-values are based on two-sample t-tests of proportions (for binary outcome variables) and two-sample mean comparison t-tests (for continuous outcome variables) comparing BASE-II with SOEP data for Berlin and Germany (not overlapping with BASE-II): *P-value $\leqslant$ 0.05; **P-value $\leqslant$ 0.01.

increase health care costs. For more than 20 years, our research group has been interested in identifying factors which distinguish 'healthy' from 'unhealthy' ageing. To this end, members of the group initiated the Berlin Aging Study (BASE) in 1988, a multidisciplinary investigation of residents of former West Berlin aged 70 to 100+ years. Between 1990 and 1993, 516 individuals were recruited into the core sample of BASE and broadly examined regarding their mental and physical health, psychological functioning and social as well as economic status. Since then, the study has been continued longitudinally, and surviving participants have been reexamined up to eight times.[2,3] References 4 and 5 highlight some of the scientific contributions of BASE to ageing research. Despite its accomplishments, BASE suffered

from several shortcomings such as small sample size, minimal collection of biological specimens from study participants and a comparatively limited array of health-relevant phenotypic assessments.

To overcome these limitations, we have launched and recently completed baseline recruitment of a second cohort, the Berlin Aging Study II (BASE-II), which comprises 2200 adult volunteers from the Berlin metropolitan area (Table 1). Even more so than its predecessor, BASE-II is a multidisciplinary project aimed at the identification and characterization of factors associated with 'healthy' vs 'unhealthy' ageing. BASE-II includes a multidisciplinary and multi-institutional ascertainment protocol that records a large number of variables from a wide range of different domains for each participant (Figure 1).
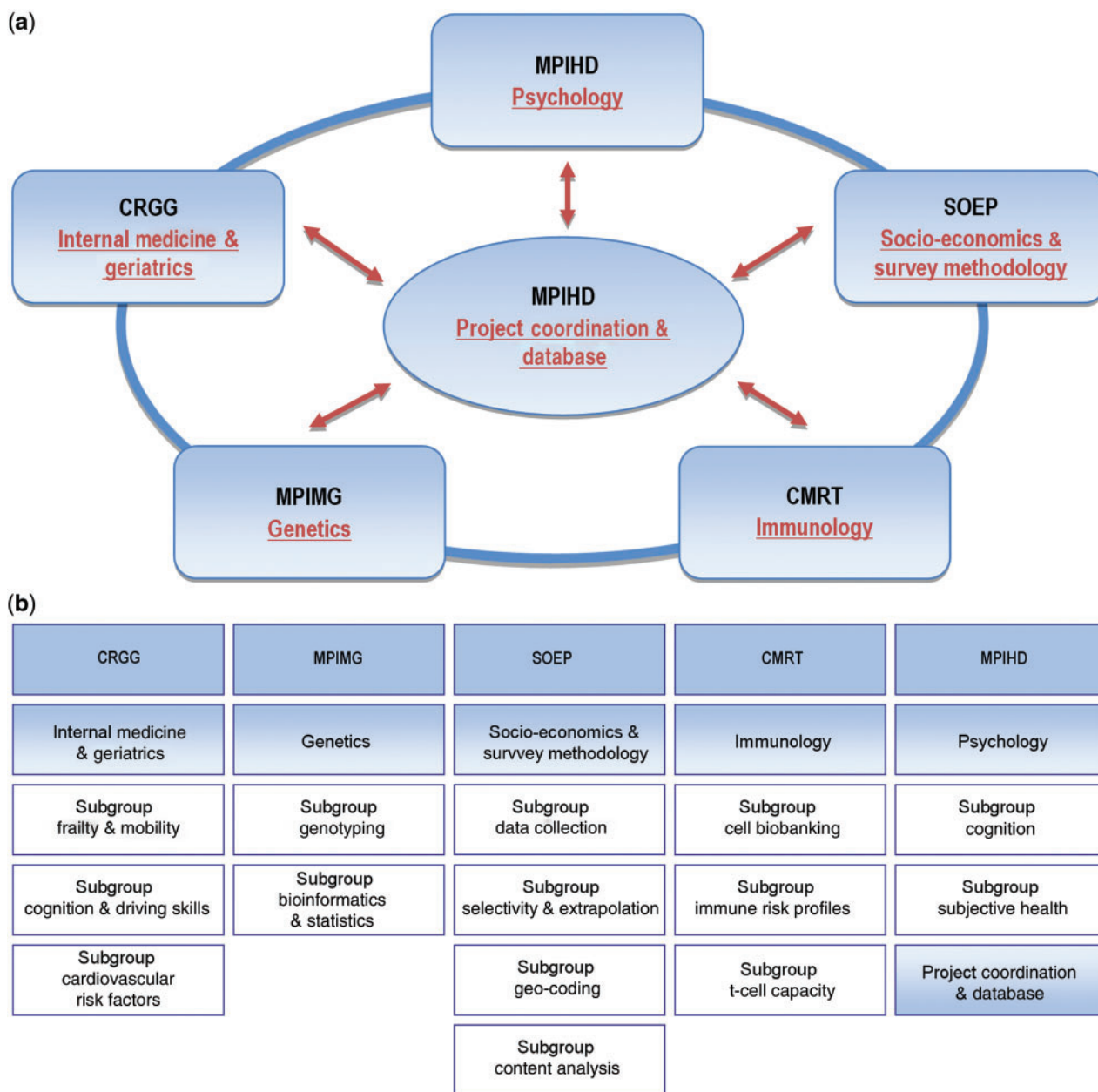
Figure 1 (a) Overall organizational structure of BASE-II and associated research teams. (b) Project subgroups of BASE-II research teams. CRGG, Charité Geriatric Research Group; MPIMG, Max Planck Institute for Molecular Genetics; SOEP, German Socio-Economic Panel Study; CMRT, Center for Medical Research Tübingen; MPIHD, Max Planck Institute for Human Development

The assessments include factors related to geriatrics and internal medicine, immunology, genetics, psychology, sociology and economics (see legend of Table 2 for details).

Who is in the cohort?

Only residents of the greater metropolitan area of Berlin, Germany, were eligible for participation in BASE-II. Potential participants were drawn from a pool of individuals originally recruited at the Max-Planck-Institute for Human Development as part of a number of earlier projects with a focus on neurocognition (a detailed description of these projects can be found at: http://www.mpib-berlin.mpg. de/sites/default/files/media/pdf/25/lip_report_11.pdf).

Briefly, participant recruitment for these and other studies was based on advertisements in local newspapers and the public commuter transport system. This led to approximately 10 000 responders of whom 2875 were invited for an additional screening

Table 2 Selection of topics covered in each of the five BASE-II research teams[a]

Team	Domain/research field	Example assessments/tests
CRGG	Anamnesis	Medical and family history, lifestyle, medication
	Questionnaires	Physical activity, social aspects (Nikolaus), sexuality, nutrition, hearing
	Laboratory values	>100 laboratory values incl. oral glucose tolerance test and leucocyte telomere length
	Physical status and functional tests	Tinetti Mobility Test, Timed 'Up & Go', Barthel Index, test of fine motor skills, grip strength, anthropometric parameters
	Psychological tests	MMSE, Clock Completion Test, DemTect, GDS, CERAD plus
	Other diagnostic tests	BIA, DEXA, ECG, long-term ECG, audiometry, spirometry; motion monitoring (belt)
CMRT	Immunology	PBMC surface marker determination by 14-colour flow cytometry; *in vitro* assays for immune cell integrity; plasma cytokine and chemokine quantification; presence and impact of common herpesviruses
MPIHD	Cognition	Executive control; episodic memory; processing speed and variability; risk and decision-making; fluid intelligence, reading abilities
	Subjective health	Questionnaires of subjective well-being and health
SOEP	Economics	Income; employment status
	Sociology	Social stratum
	Political science	Values; political preferences
	Psychology	Personality traits
	Survey methodology	Interviewer characteristics; geo-coding
MPIMG	GWAS	Microarray-based SNP genotyping; genome-wide association analyses; imputation
	Validation	Targeted follow-up genotyping in independent cohorts; meta-analysis
	Fine-mapping	Identification of biochemically functional DNA variants, e.g. by direct resequencing

Examples of the phenotypic and genotypic assessments performed in each BASE-II participant by the various research teams. For many of the domains listed, more assessments will actually be performed; please contact the study coordinator for more details. MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; BIA, Bioelectrical Impedance Analysis; DEXA, dual energy X-ray absorptiometry; ECG, electrocardiogram.
[a]BASE-II research teams (see also Figure 1) and status of completion of full baseline assessments: CRGG (full assessments completed in $n = 1502$ participants): Charité Geriatric Research Group (Main research topic: Internal medicine/geriatrics); CMRT ($n = 250$ completed from a total of 1350 biobanked samples): Center for Medical Research Tübingen (Immunology); MPIHD ($n = 2134$ completed): Max Planck Institute for Human Development (Psychology & Project Coordination); SOEP (n = 1447 completed): German Socio-Economic Panel Study (Socio-economics and survey methodology); MPIMG ($n = 1976$ completed): Max Planck Institute for Molecular Genetics (Genetics); GWAS: Genome-Wide Association Study.

(either in-house or by telephone), leading to 2262 individuals eligible for inclusion in BASE-II, i.e. 79% of those who were initially invited. From these, we selected 2200 individuals to represent the BASE-II baseline cohort (Table 1) based on their age and sex as follows. A total of 1600 participants were assigned to an older subgroup aged between 60 and 80 years, whereas the remaining 600 individuals were assigned to a younger subgroup (serving as a reference population) aged between 20 and 35 years. By design, each age subgroup contains equal numbers of males and females. See Table 1 for other socio-demographic details of the BASE-II baseline cohort.

Some ageing-related changes, such as decline in perceptual speed, begin in early adulthood. At the same time, recent longitudinal studies indicate that average performance on other cognitive abilities, such as episodic memory, is relatively stable until about 60 years of age, and starts declining thereafter.[6] Hence, we decided to start observing older adults at an age where most would show subsequent decline on most variables of interest.

Comparisons with representative survey data from Berlin and Germany, ascertained via the SOEP questionnaire (see below), reveal that BASE-II participants are characterized by higher education and better self-reported health status than the general population of Berlin and Germany (Table 1). In addition, BASE-II participants in the older subgroup report a significantly higher divorce/separation rate than

participants in the age-matched reference populations. For convenience samples such as BASE-II this is a commonly observed phenomenon.[7]

What has been measured?

Human ageing is a complex process affecting a large number of correlated domains. Consequently, ageing research requires multi-dimensional data collection as well as extensive multi-disciplinary collaborations. Both aspects are strongly emphasized in BASE-II where we have assembled a multi-disciplinary research team consisting of specialists in geriatrics, internal medicine, immunology, psychology, genetics, sociology, and economics (Figure 1). A major challenge for studies dealing with ascertained research cohorts is to systematically determine the degree of sampling bias and to judge the extent to which results can be generalized to the population as a whole. To this end, selectivity and representativeness of our sample is evaluated [via the German Socio-Economic Panel Study (SOEP)] and—whenever necessary—accounted for by a team specialized in survey methodology in the context of cohort studies. The scope and breadth of our assessments makes BASE-II unique in the field of human ageing research. Below we provide brief overviews of the various phenotypic domains examined in each participant by the respective research teams (see also Table 2).

(i) Internal medicine/geriatrics (Charité Research Group on Geriatrics; CRGG): In addition to providing an in-depth history of current and previous medical conditions, this branch of BASE-II is performing an exhaustive medical examination guided by an extensive array of laboratory and functional tests. All tests and examinations are part of a 2-day study protocol designed to assess each individual's objective and subjective health status. In addition to recording disease states, we also monitor domains which are known to deteriorate with normal ageing (e.g. grip strength, hearing, vision, mobility, bone density), and determine each participant's activities of daily living, nutritional habits, current and past use of medication, as well as self-rated health. Alongside the medical assessments, each person undergoes a neuropsychological screening for the detection of dementia or mild cognitive impairment [e.g. via the Mini-Mental State Examination (MMSE), clock drawing test and the early dementia screening test (DemTect)]. Overall, we assess more than 4000 individual phenotypic variables in this branch of BASE-II.

(ii) Immunology (Center for Medical Research, University of Tübingen; CMRT): The immunological assessments of BASE-II aim to determine specific 'immune risk profiles' (IRPs) of each participant. The IRP concept is tightly linked to the occurrence of immunosenescence, i.e. dysregulated or compromised immunity in the elderly, possibly modifying susceptibility to a number of age-related diseases.[8] Determining an individual's IRP entails measuring—at each visit—a number of immune parameters ex vivo, using peripheral blood mononuclear cells (PBMC) derived from whole-blood samples of each BASE-II participant. In addition we systematically determine antibody titres for common viral antigens [e.g. originating from infections with cytomegalovirus (CMV), herpes simplex virus (HSV) and other herpes viruses] and measure plasma levels of multiple cytokines and chemokines.

(iii) Psychology (Max Planck Institute for Human Development; MPIHD): Adequate cognitive functioning is a major prerequisite for many aspects of 'successful' ageing and for preserving a self-determined lifestyle. Hence, the psychology branch of BASE-II performs a large number of cognitive tests covering a comprehensive array of cognitive abilities. The 6-h assessment protocol is divided into two sessions of 3 h each and applies test batteries to evaluate working memory, attention control, word and object recall, fluid intelligence, verbal skills and decision making, as well as risk-taking behaviour. Another focus is to explore subjective parameters via the use of questionnaires. These cover areas such as self-rated health and well-being, coping and general attitudes towards the ageing process.

(iv) Socio-economics and survey methodology (German Socio-Economic Panel Study; SOEP): All BASE-II participants are asked to complete the SOEP questionnaire, which is applied to a representative longitudinal survey of ~20 000 adults in Germany.[9] The questionnaire assesses over 120 socio-economic and behavioural variables (such as marital status, income, self-rated health, personal traits etc.), which have been exhaustively tested for their validity and reliability in the context of panel studies.[10] In addition, all BASE-II survey data are 'geo-coded', i.e. each participant is assigned an almost exact geographical coordinate according to the street block of his/her residential address (Figure 2).[11] In the context of BASE-II these data are used to achieve two goals: First, SOEP data allow the identification of and adjustment for potential confounders in the phenotype/genotype assessments of the other branches. Owing to the availability of SOEP data for representative collections of ~1000 participants from Berlin (randomly drawn and not included in BASE-II) and ~20 000 individuals representative for all other
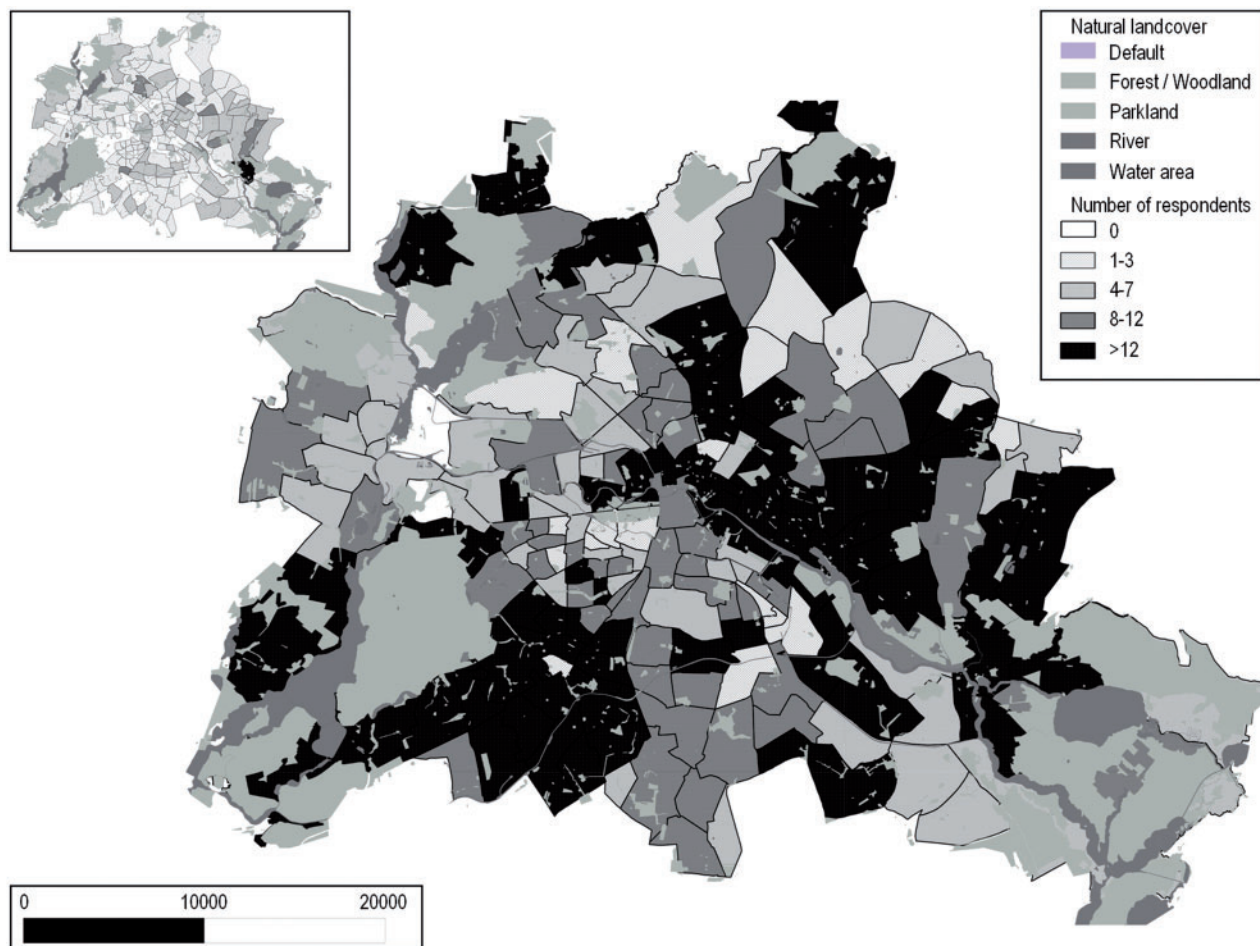
Figure 2 Example of geo-coding in the BASE-II cohort. Each BASE-II participant's address is first recoded to the coordinates of the centre of the home address street block and then mapped onto a local street map [provided by OpenStreetMap (http://www.openstreetmap.org)]. For each coordinate, a wealth of auxiliary environmental information is available (such as nearest distance to certain points of interest, climate, precipitation etc.) which can be incorporated in BASE-II specific analyses. The large map in the centre of the figure indicates geo-coded BASE-II participants with SOEP data currently available ($n = 1447$); the smaller map at the top left indicates the number of SOEP respondents living in Berlin not included in BASE-II ($n = 407$; see also Table 1)

regions across Germany, we are also able to systematically assess and adjust for ascertainment bias in the BASE-II cohort. Secondly, many SOEP items (e.g. subjective well-being, risk aversion) are interesting phenotypic outcome variables themselves and can be analysed with data from the other domains (e.g. genetics).

(v) Genetics (Max Planck Institute for Molecular Genetics; MPIMG): Many of the phenotypes measured in BASE-II are under 'complex genetic' control. That is, a substantial fraction of their phenotypic variance can be explained by the effects of common DNA sequence variants ('polymorphisms'). To elucidate the impact of genetics on the phenotypes assessed by the other subprojects, each BASE-II participant is subjected to microarray-based genome-wide genotyping of single nucleotide polymorphisms (SNPs) using the Genome-Wide Human SNP Array 6.0 from Affymetrix Inc. (already completed in ~90% of all participants).[12] This array directly measures approximately 900 000 SNP markers. Based on these data, we will be able to infer genotypes at several million untyped SNPs using recently developed imputation strategies. Using currently available genetic reference populations, we can impute genotypes of up to 10 million additional SNP markers for the actual association analyses.[13] The most compelling signals will be validated in data sets of up to 2000 independent individuals followed by systematic fine-mapping to identify the underlying functional DNA variants.[14] Ultimately, this subproject will lead to a comprehensive genome-wide 'map' of

validated genetic loci with significant effects on ageing-related phenotypes of relevance in BASE-II and other cohorts.

What has it found to date? Key findings and publications

At the time of writing (October 2012), in-depth examinations have been completed in approximately two-thirds or more (depending on the phenotypic domain) of the 2200 baseline BASE-II participants (see Table 2). This includes the microarray-based genotyping allowing preliminary genome-wide association analyses to be performed in this data set. In the following paragraph, we will highlight the results derived from BASE-II baseline data assessing the potential impact of genetic polymorphisms in brain-derived neurotrophic factor (*BDNF*) on cognitive performance.

BDNF is a neurotrophin that plays an important role in regulating activity-dependent synaptic plasticity, which is essential in human memory functions. The results summarized below and in Figure 3 are based on investigations of the effect of a well-established genetic polymorphism in the BDNF gene on episodic memory performance. This polymorphism (rs6265) leads to a substitution of one amino acid in the BDNF protein (i.e. changing a valine [Val] to methionine [Met] at codon 66; a.k.a. Val66Met) and appears to control the neuronal secretion of BDNF in humans in the sense that carriers of the Met allele show lower levels of BDNF as compared with the Val allele.[15] In one of our analyses, we compared older and younger BASE-II participants on backwards serial recall performance. Serial recall memory typically yields a U-shaped function, with better recall performance for items at the beginning and at the end of a list. We found a significant difference between Met- and Val/Val-carriers in the sample of older adults, but not in the sample of younger adults. These results, originally published in a subset of 948 BASE-II participants,[16] have been followed up in the full BASE-II cohort in individuals with genotype and phenotype data available ($n = 1570$). The updated results continue to show an overall correlation between memory performance and rs6265 Met-allele carrier status (F = 4.56; $P < 0.05$). However, the age x BDNF interaction was attenuated, now only showing a statistical trend for the effect to be more pronounced in older adults (P-value for age x BDNF interaction = 0.1; Figure 3). These findings hint at the possibility that some genetic effects may be 'magnified' with increasing age when brain and cognitive resources become more limited,[17] and emphasize the need to assess both young and old adults in projects aimed at elucidating ageing-related biological effects.
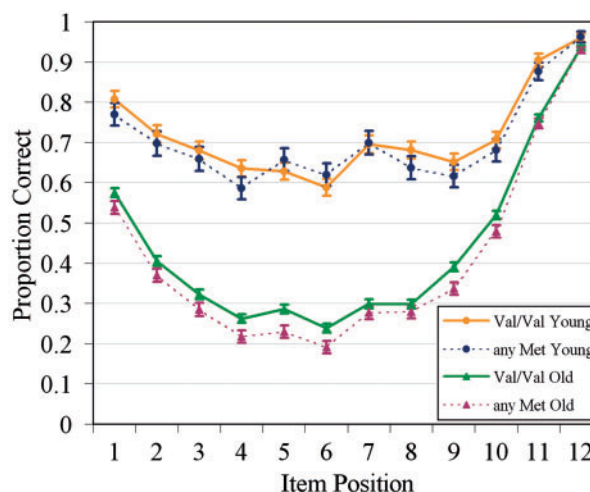
Figure 3 The impact of brain-derived neurotrophic factor (BDNF) on cognitive performance. Average proportion of items correctly recalled in a backward serial recall test separated by age and BDNF polymorphism. A difference in memory performance is observed between Met-carriers vs Val/Val-carriers, with the latter showing better memory performance. This effect appears to be slightly more pronounced in the older subsample, although the age x interaction only showed a marginal effect ($P = 0.1$; $n = 1570$ participants, see text for more details)

What are the main strengths and weaknesses?

As outlined above, we consider as major strengths of BASE-II the following: (i) The study's in-depth and multi-disciplinary examination and analysis protocol assessing a very large number of ageing-related phenotypes from very diverse domains. These include fields as diverse as psychology, molecular genetics, immunology, economics, sociology and survey methodology (Figure 1). Especially the survey data together with the detailed geo-coding (Figure 2) will allow us to detect and account for selectivity and other sources of bias with respect to the representativeness of our cohort. For instance, first comparisons between BASE-II participants and representative groups of older and younger adults in Berlin and Germany show that people with a higher educational background and those with a more positive outlook on life are more willing to participate (see Table 1). These findings suggest that weighting for these indicators in the context of medical and psychological surveys might be as important as in social scientific research. (ii) In addition to providing a broad assessment of phenotypic and genotypic variability associated with human ageing, another strength of BASE-II is the depth of its ascertainment with 2200 participants recruited at baseline. This sample size provides excellent power to detect even small effect sizes across a wide range of scenarios. For instance, in the older subgroup alone ($n = 1600$) we are able to detect genetic factors that explain down to 3% of

the phenotypic variance of quantitative traits with >90% power at an alpha-level of 5×10^{-8}, which represents a common threshold to declare the genome-wide significance of association findings.[12] (iii) Additionally, all of the principal research teams involved have a long-standing history of working together on related research projects. Furthermore, three teams (geriatrics, psychology and social sciences) were already involved in leading and completing BASE-II's predecessor study (BASE, see above). Collaboration across research groups will be greatly facilitated by the fact that all but one of the participating centres are located in the city of Berlin.

Potential weaknesses of BASE-II include the following. Owing to our heterogeneous ascertainment scheme, some of the hypothesis-generating results may be biased. Although this limitation can be addressed to a certain extent by adjustments (weighting) based on representative SOEP survey and geo-coded neighbourhood data, the possibility of selection bias always remains. Of course, this is not only true for every cohort study with non-random recruitment schemes (like BASE-II), but also for all studies based on voluntary participation. The latter is the case for all surveys and creates selective non-response. In addition, although the overall sample size of BASE-II is sufficiently large to address many research questions (see above), it is too small for other areas. For instance, many age-related disorders have prevalence rates <10% (e.g. Parkinson's disease, many age-related cancers), and can therefore not be sufficiently studied in BASE-II. At the same time, the scope of our multi-dimensional assessment and analysis protocol vastly increases the chances to identify many of the major factors underlying age-associated disorders and impairments. Hopefully in the not too distant future the results of our project—in concert with other related projects in Germany and elsewhere—will help to develop efficient measures to decelerate or even prevent some of the most pressing age-associated functional and social impairments.

Can I get hold of the data? Where can I find out more?

More details about BASE-II can be found at a dedicated website: http://www.base2.mpg.de. One of the declared goals of BASE-II is to enable and facilitate collaboration with other research laboratories. Interested groups should contact our study coordinator (Dr Katrin Schaar; contact details are available from the above website), for the data-sharing application form. Each application will be reviewed by the BASE-II Steering Committee (currently: L.B., U.L., G.P., E.St-T and G.G.W.) and the decision communicated to the applicants usually within 4 weeks of submission. Currently, BASE-II data are already being used in a number of collaborative research projects, including but not limited to studies on the genetics

of multiple sclerosis (University of Mainz, Germany)[18] and coronary heart disease (University of Schleswig Holstein, Lübeck, Germany), self-rated health (as part of the GENEQOL consortium led by the University of Amsterdam, the Netherlands) and the genetics of cognitive phenotypes (University of Southern California, USA).

Additional BASE-II investigators

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Funding

Acknowledgements

KEY MESSAGES

- BASE-II is a multi-disciplinary project aimed at identifying and characterizing factors associated with 'healthy' and 'unhealthy' ageing in 2200 adults from Berlin, Germany.

- Comparing BASE-II data with those from participants of the representative German Socio-Economic Panel Study (SOEP) showed a significant overrepresentation of persons with higher education and those with a higher life satisfaction.

- Overrepresentation of certain groups is relatively common in self-recruiting studies (convenience samples) and emphasizes the need to adjust for such non-demographic indicators, which is made possible for each BASE-II participant owing to the availability of representative SOEP data.

- Correlating memory performance with a common non-synonymous polymorphism (rs6265) in the gene encoding brain-derived neurotrophic factor (BDNF) revealed significantly better memory performance in carriers who were homozygous for the valine allele as compared with the remainder of the sample.

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