ERA AGE

European Research Area in Ageing

Report of the Research Priorities for Demography, Longevity and Genetics

ERA-AGE Scientific Workshop

1st December 2006

Organised in partnership with
The Institute for Biomedical Aging Research
of the Austrian Academy of Sciences

Held at the Hilton Hotel, Innsbruck, Austria

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* Due to document upload limitations these presentations are available as separate documents at the following website address:
http://www.era-age.group.shef.ac.uk/documents.php#document_type_3

SECTION 1

EXECUTIVE SUMMARY OF RECOMMENDATIONS

1.1 Demography

The demography working group focused on potential new ways of communication between demographers and biogerontologists while contemplating the question of 'how can demography profit from biogerontology and vice versa? Participants identified the following recommendations**:**

- Demographers need input from other disciplines and a good data base on the elderly population including:

  a) socioeconomic problems
  b) environment (nutrition, pollution)
  c) physicians (health, disability) <-> biogerontologists

- To achieve the above goal, the following will be required:

  d) training of young people (new European curriculum)
  e) training for established scientists (multidisciplinary meetings and working groups)
  f) joint project: longitudinal study

1.2 Longevity

Present longevity demographic development studies on how to reach healthy longevity are regarded by some experts as very important. The working group therefore focused on can how parameters which affect longevity be defined. The following recommendations were identified by participants:

- Coping, networks, lifestyle, income, education and gender issues may have a huge impact on healthy longevity, along with biological factors. An interdisciplinary longevity study is needed to enable comparisons and to identify important factors

- Longitudinal studies are needed though they require extensive resources and effort. Preparatory work is required to encourage different disciplines to talk to each other, to determine parameters before undertaking a large study. A platform for data collection is an essential tool but its design requires additional thought

- A pilot study on multidisciplinary interactions should be carried out which aims to define the terms of interaction between disciplines and to assess the quality of potential outcomes

- Bio markers need to be developed. Approach the 'marker', ask what would be your favourite parameter? and develop it further.

- The age range of studies depends on the design and goal of the research itself

1.3 Genetics

The working group focused on the question of whether genes or environment represent the determining factor to achieve healthy longevity. The following recommendations were identified:

- Longevity genes likely to be important but the phenotype and interactions are complex
- Large scale studies should be done, to minimise cohort effect
- Local effects might be identified in different human populations
- Animal models may identify key pathways
- Animal models are conceived in relation to specific conditions which do not mimic the human condition
- Gene effects in humans may alter depending on the age-related changes of the microenvironment of the individual
- Environment change in the last 100 years has altered gene exposure ie public health measures, electricity, harsh conditions, nutrition, pandemics, modern medicine; and this is different from current animal models and likely to be different for future studies on longevity
- Effect of environment is important
- Simple factors such as control of blood pressure, lipids/nutrition and smoking are making an impact
- Drugs/mimetics are of interest to drug companies in longevity studies but are longer term strategies
- Databases and longevity studies already in place should be a resource to inform on what biomarkers are important for quality longevity
- Management of a common biobank should be considered

SECTION 2

PROGRAMME

- Welcome by Beatrix Grubeck-Loebenstein (Director, Institute for Biomedical Aging Research of the Austrian Academy of Sciences, Innsbruck, Austria, and member of the ERA-AGE Steering Committee)

- **Session 1 presentations**
  (Chair: Beatrix Grubeck-Loebenstein)

  Key note: "The aging population, a European Problem" (Wolfgang Lutz, Vienna Institute of Demography, Austria)

  "LifeSpan: A project integrating research into development and ageing" (Rudi Westendorp, Leiden, The Netherlands, Coordinator of EU-Network of Excellence LifeSpan)

  "Combining biological and social data in population studies of aging – developing European biodemography of ageing" (Claudio Franceschi, Bologna, Italy, Coordinator of EU-integrated project GEHA)

  "The ageing cellular power plant, how can it influence longevity?" (Heinz Osiewacz, Frankfurt, Germany, Coordinator of EU-integrated project MiMAGE)

  "Changes in the structure and function of cells, how do they affect lifespan?" (Brian Clark, Aarhus, Denmark, Coordinator of EU-integrated project PROTEOMAGE)

- **Session 2 presentations**
  (Chair: Emanuele Scafato, Istituto Superiore di Sanita, Rome, Italy)

  "European coordination of funding for ageing research" (Alan Walker, Director of the European Research Area in Ageing, University of Sheffield, UK)

  "Developing effective multidisciplinarity in ageing research" (Tom Kirkwood, Institute for Ageing and Health, University of Newcastle, UK)

  "Choosing biogerontological research topics of industrial relevance" (Daniel Asselineau, Head, Skin and Ageing Life Science Research, L'Oréal, Clichy, France)

  "How can present research initiatives in biogerontology bring maximal added value for Europe?" (Stathis Gonos, Director of Research National Hellenic Research Foundation Dept. of Molecular & Cellular Ageing, Athens, Greece)

- **Working Groups on Developing Research Priorities**

  Demography: How can demography profit from biogerontology and vice versa? (Chair: Beatrix Grubeck-Loebenstein)

  Longevity: How can parameters which affect longevity be defined? (Chair: Pidder Jansen-Dürr, Head of the Molecular and Cell Biology Department, Institute for Biomedical Aging Research of the Austrian Academy of Sciences, Innsbruck, Austria)

  Genetics: Genes or environment: which is the determining factor to achieve healthy longevity? (Chair: Claudio Franceschi, Department of Experimental Pathology, University of Bologna, Director of the Inderdepartmental Centre “L. Galvani”, University of Bologna, Italy)

- **Final Plenary (Chair: Stathis Gonos)**
  Presentation of the results of the working groups (working group chairs)

- **Conclusion (Alan Walker)**

SECTION 3

AIMS OF THE SCIENTIFIC WORKSHOP

The aims of the Demography, Longevity and Genetics scientific Workshop were to:

- Bring together a range of research institute and stakeholder representatives from the field of ageing research
- Reflect on and discuss appropriate scientific recommendations taken from the Forum on Ageing report
- Futher discuss how healthy longevity can be achieved in our society with a particular emphasis on:
  - how genetics, biogerontology, social factors and environment may contibute to achieve this goal
  - what impact bio- and social sciences have on demography
- To utilise outcomes to:
  - develop potential transnational collaboration in the field of ageing research and
  - inform the European Forum of research funders.

SECTION 4

SUMMARY OF PRESENTATIONS

4.1 Key note: The aging population, a European problem

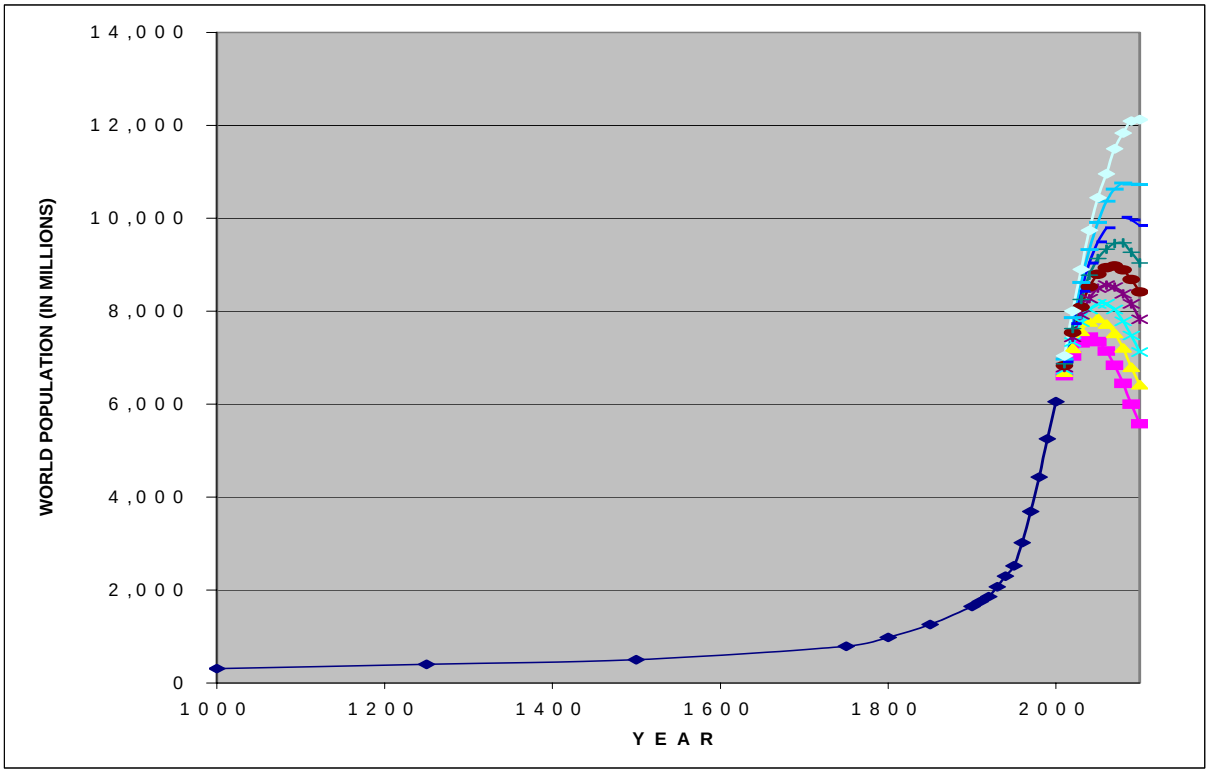
Professor Wolfgang Lutz
Vienna Institute of Demography, Austria

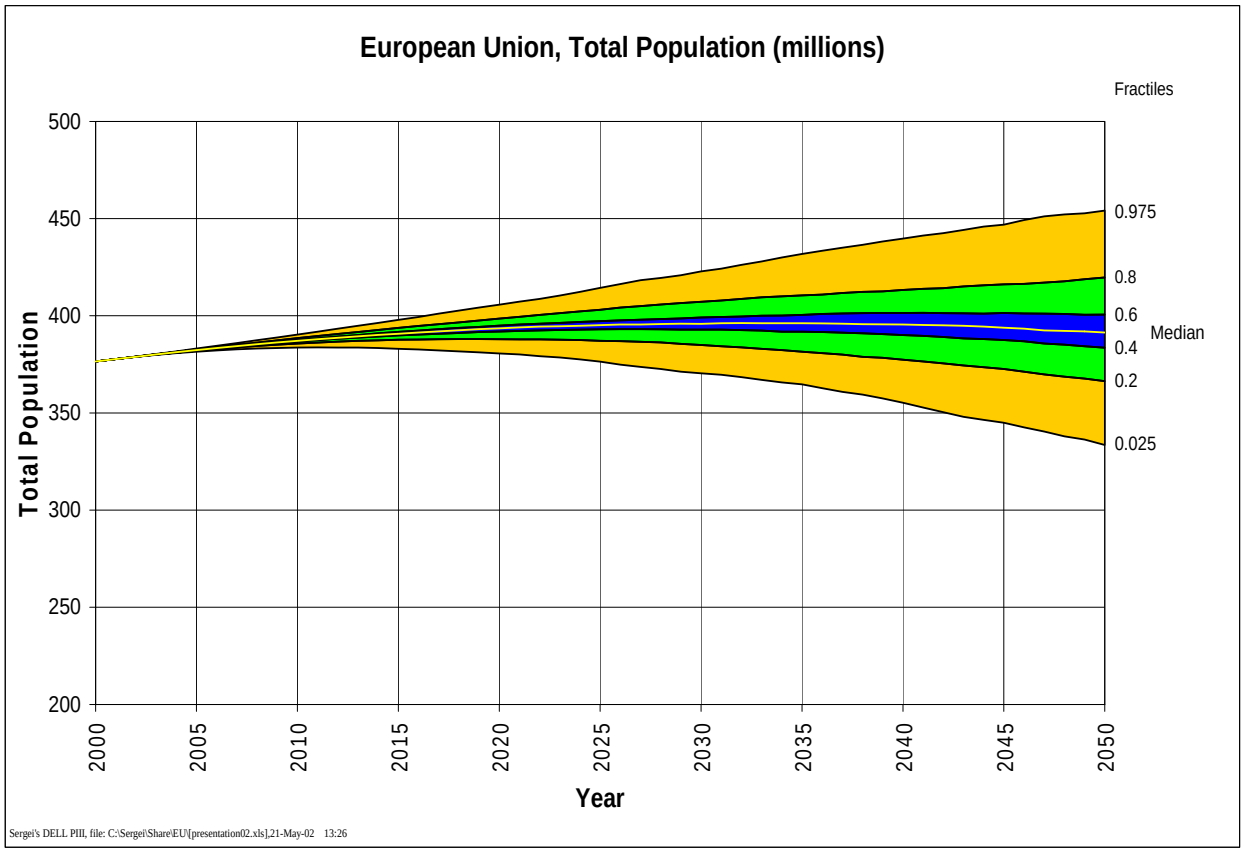
Global Population Context

- While the 20th century was the century of population growth (with the world population increasing from 1.6 to 6.1 billion).
- The 21st century will be that of population ageing (with the proportion above age 60 increasing from currently 0.10 to 0.25-0.45 by 2100).
- The world as a whole is likely to see the end of population growth during this century.
- But we will see a demographically divided world with excessive population growth still being an issue in Africa and Western Asia while Europe and East Asia will be concerned with rapid ageing.

World Population from the Year 1000 to 2100

(historical data from 1000 to 2000; deciles of IIASA's probabilistic forecasts to 2100)




European Union, Total Population (millions)
Fractiles
0.975
0.8
0.6
Median
0.4
0.2
0.025
Total Population
500
450
400
350
300
250
200
2000
2005
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2015
2020
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Year
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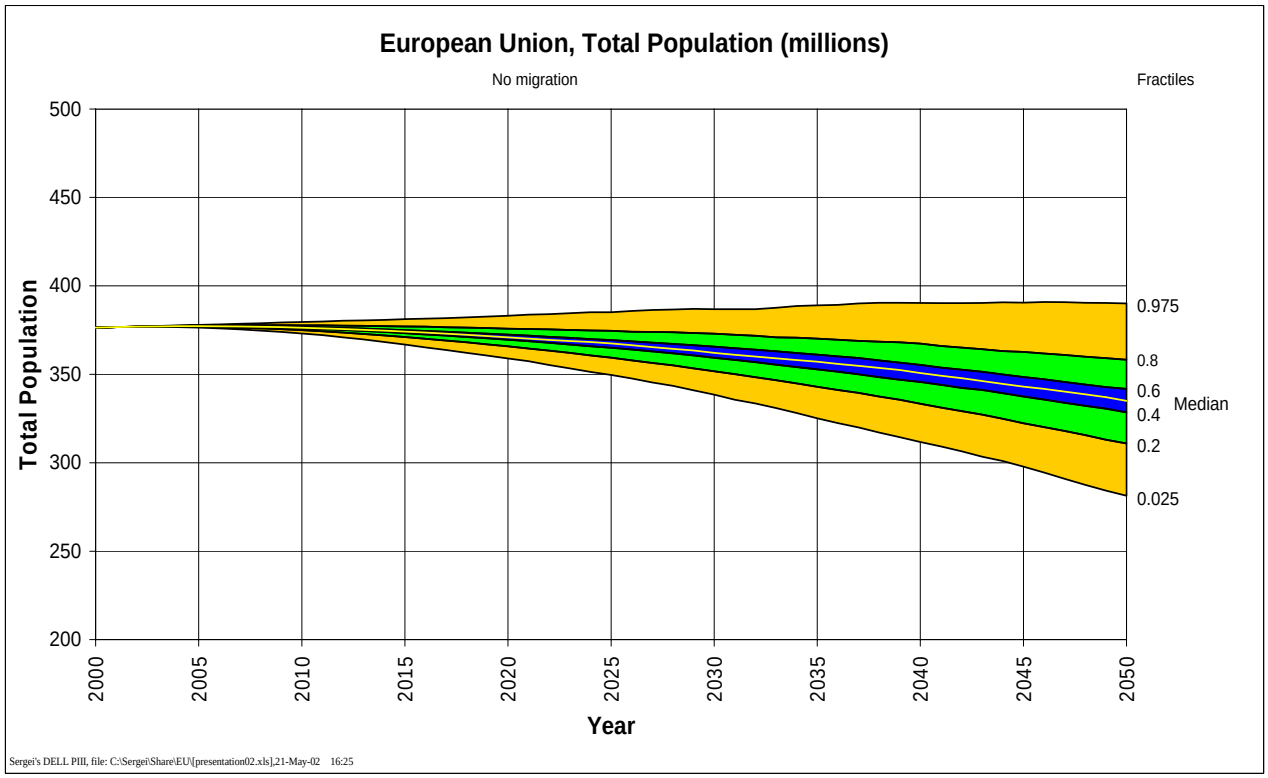
European Union, Total Population (millions)
No migration
Fractiles
0.975
0.8
0.6
Median
0.4
0.2
0.025
Total Population
500
450
400
350
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2000
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Year
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Forecasting the Population

- For forecasting the population we need the current population by age and sex for each region.
- We need to make assumptions on the three components of change:
- Fertility (birth rates)
- Mortality (death rates, life expectancy)
- Migration
- The future paths of all three factors are uncertain.
- Therefore we produce probabilistic population projections.

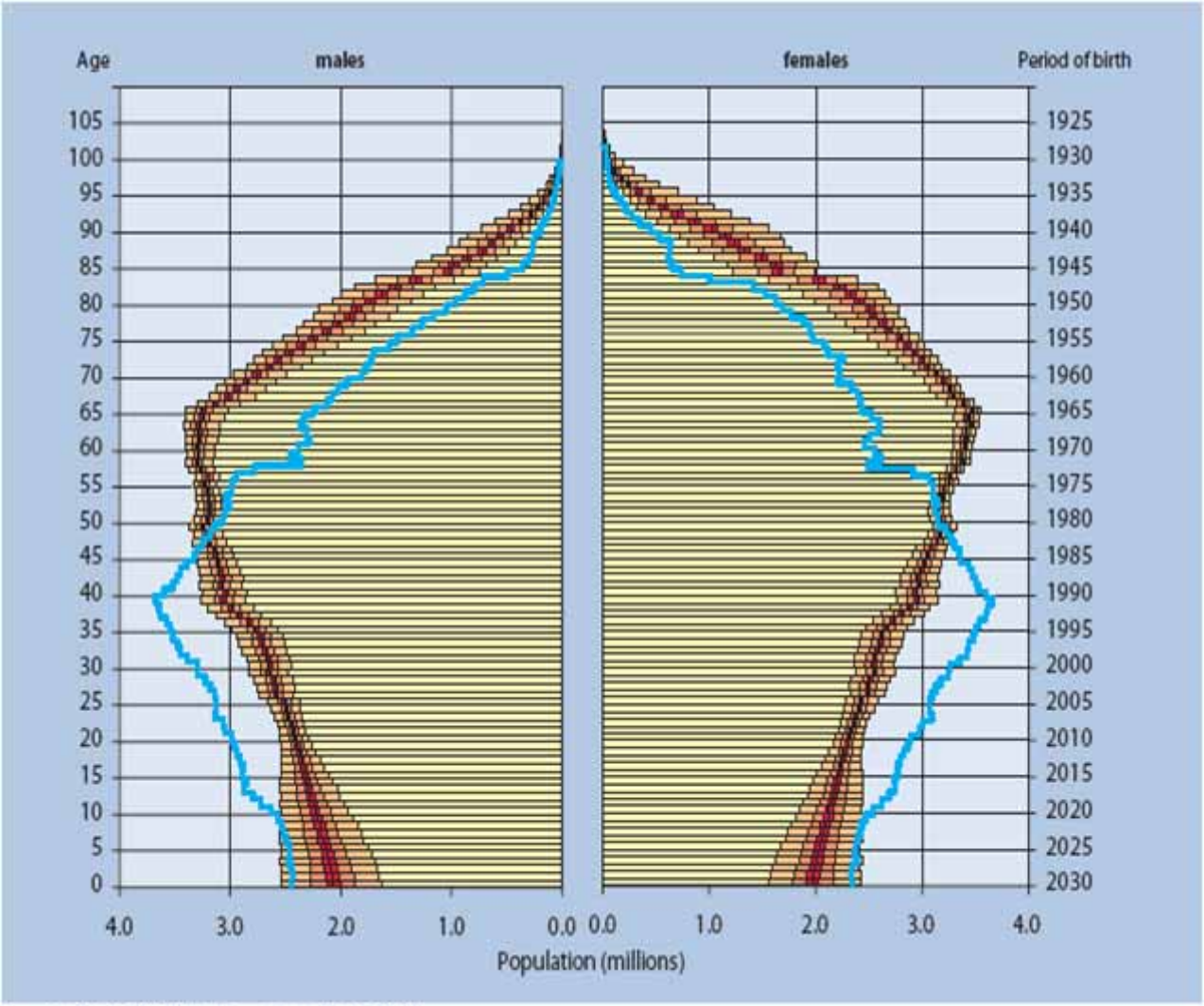
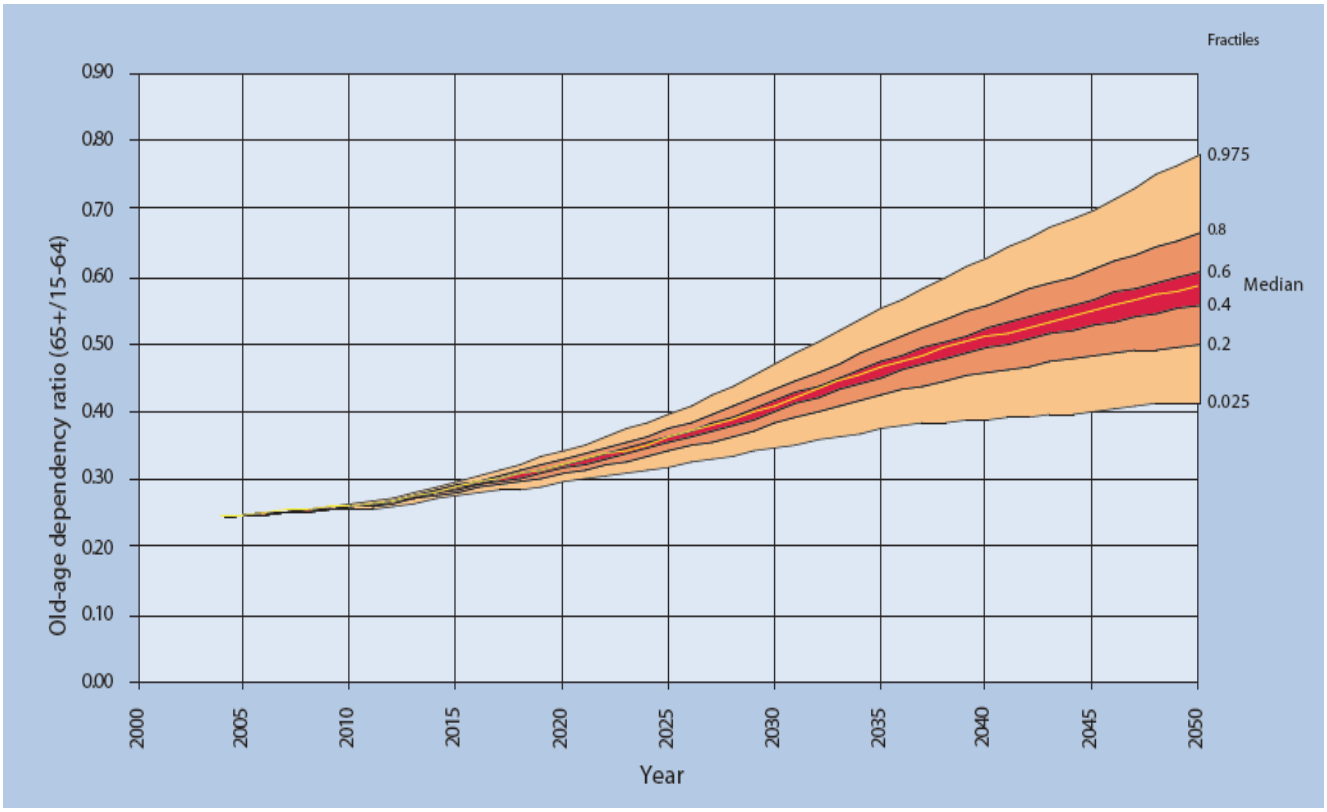
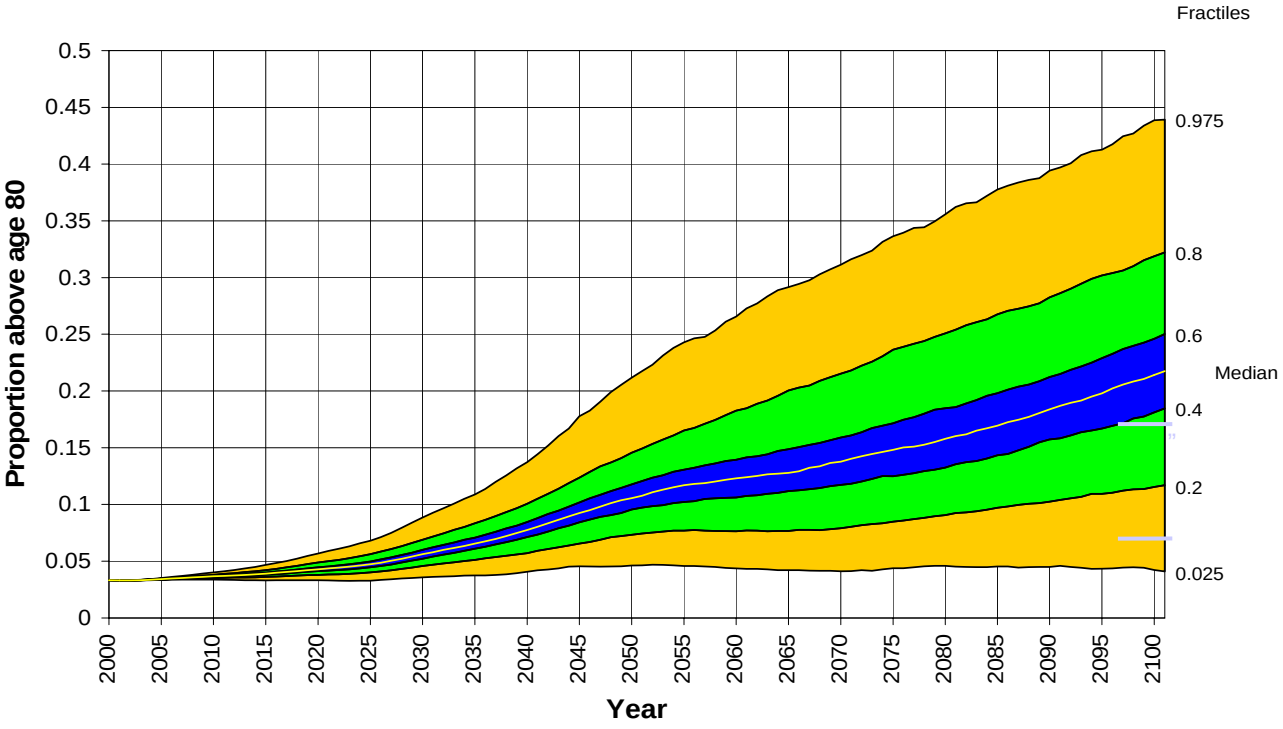


Figure 3: EU-25, 2030; blue line refers to EU-25, 2004

EU-25: Old-Age Dependency Ratio (65+/15-64)



Western Europe, Uncertainty Distribution of Proportion above Age 80 (2000-2100)



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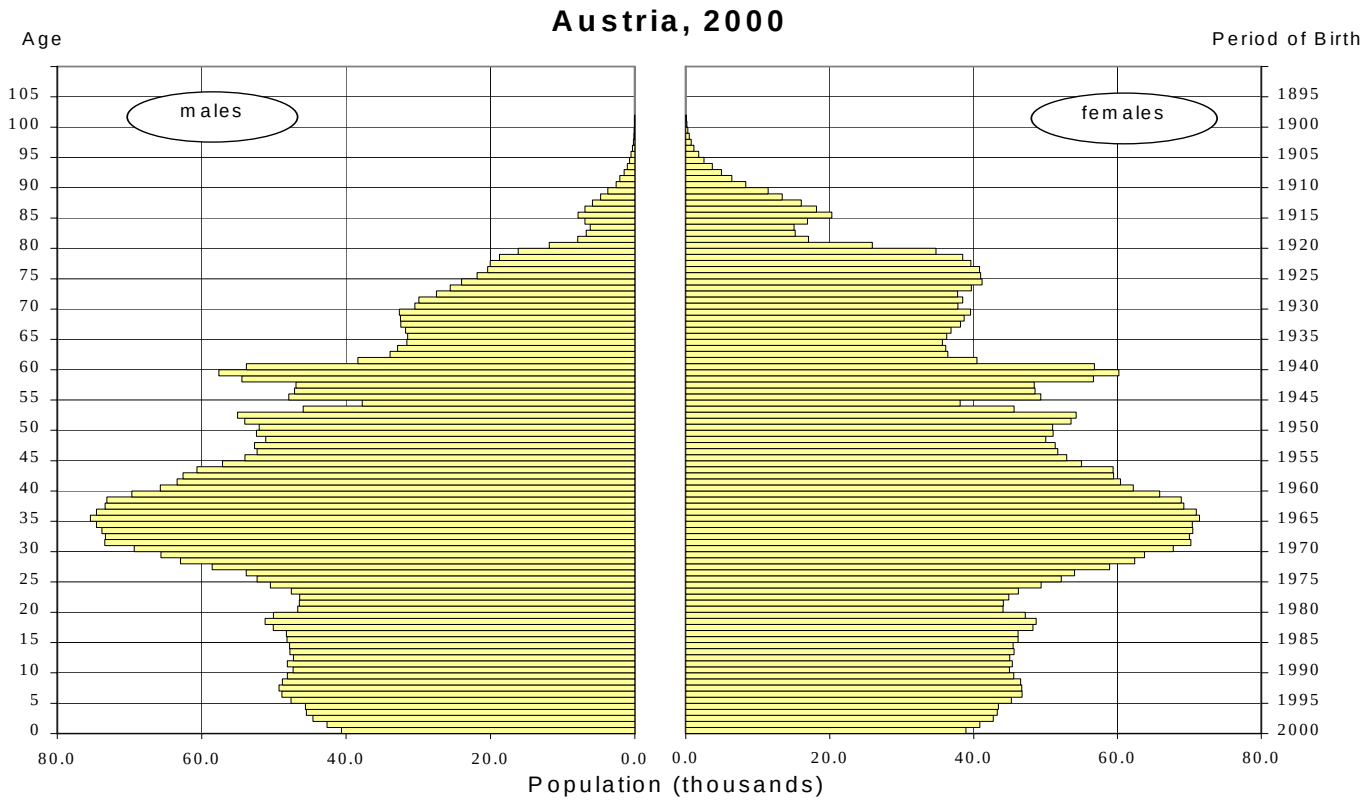
Austria, 2000
Age
Period of Birth
males
females
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
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20
15
10
5
0
1895
1900
1905
1910
1915
1920
1925
1930
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
80.0
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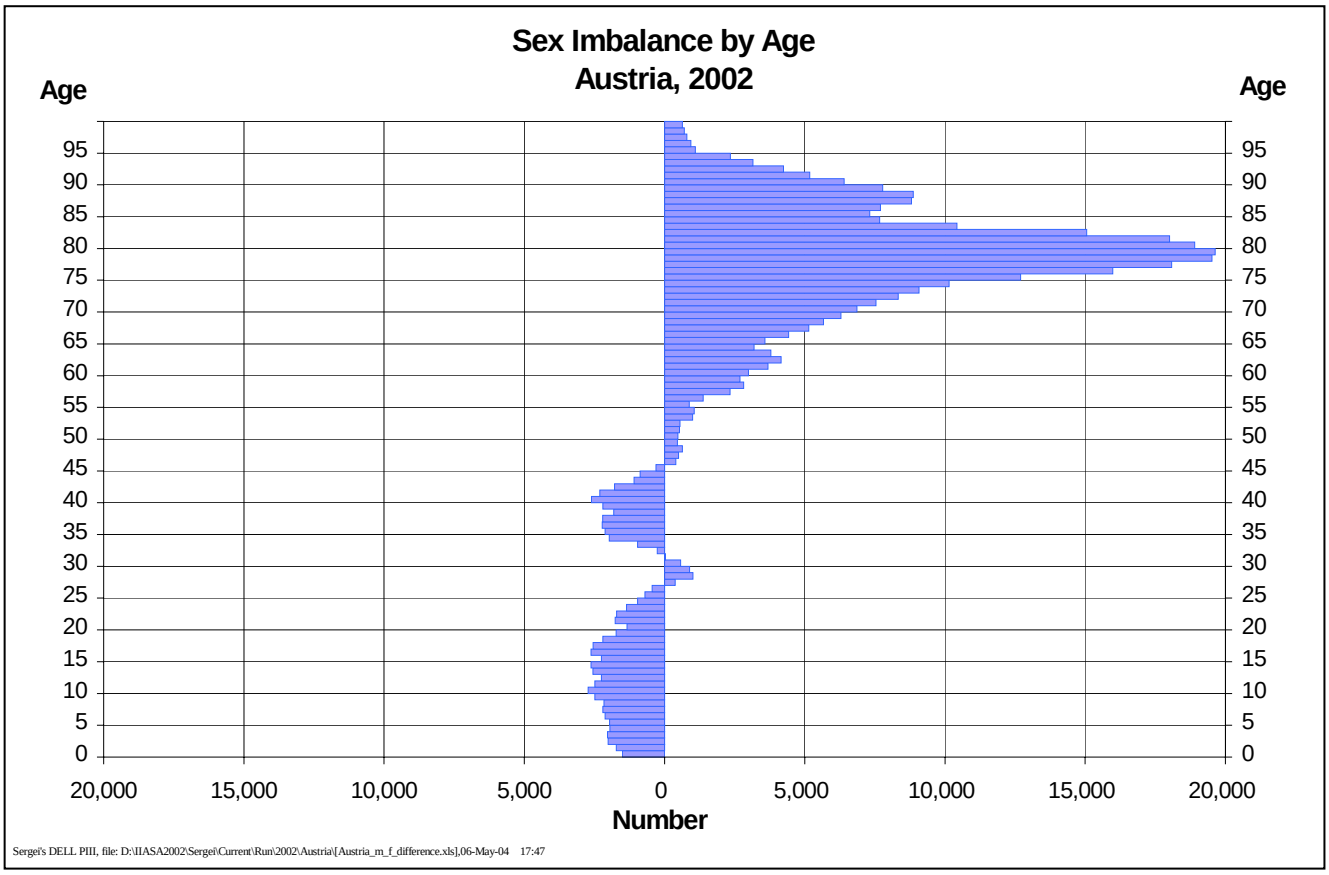
20.0
0.0
0.0
20.0
40.0
60.0
80.0
Population (thousands)


Sex Imbalance by Age
Austria, 2002
Age
Age
95
90
85
80
75
70
65
60
55
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45
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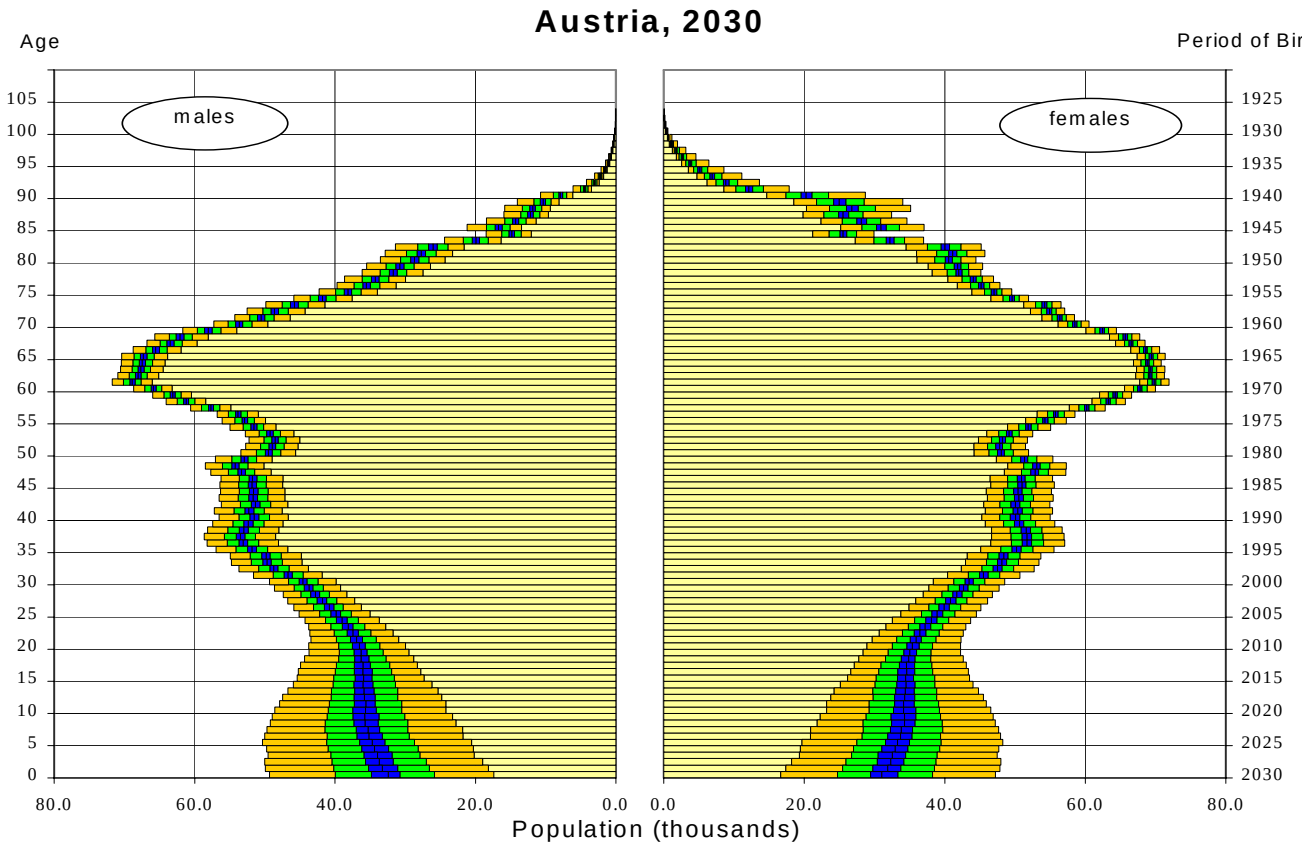
Austria, 2030
Age
Period of Bir
males
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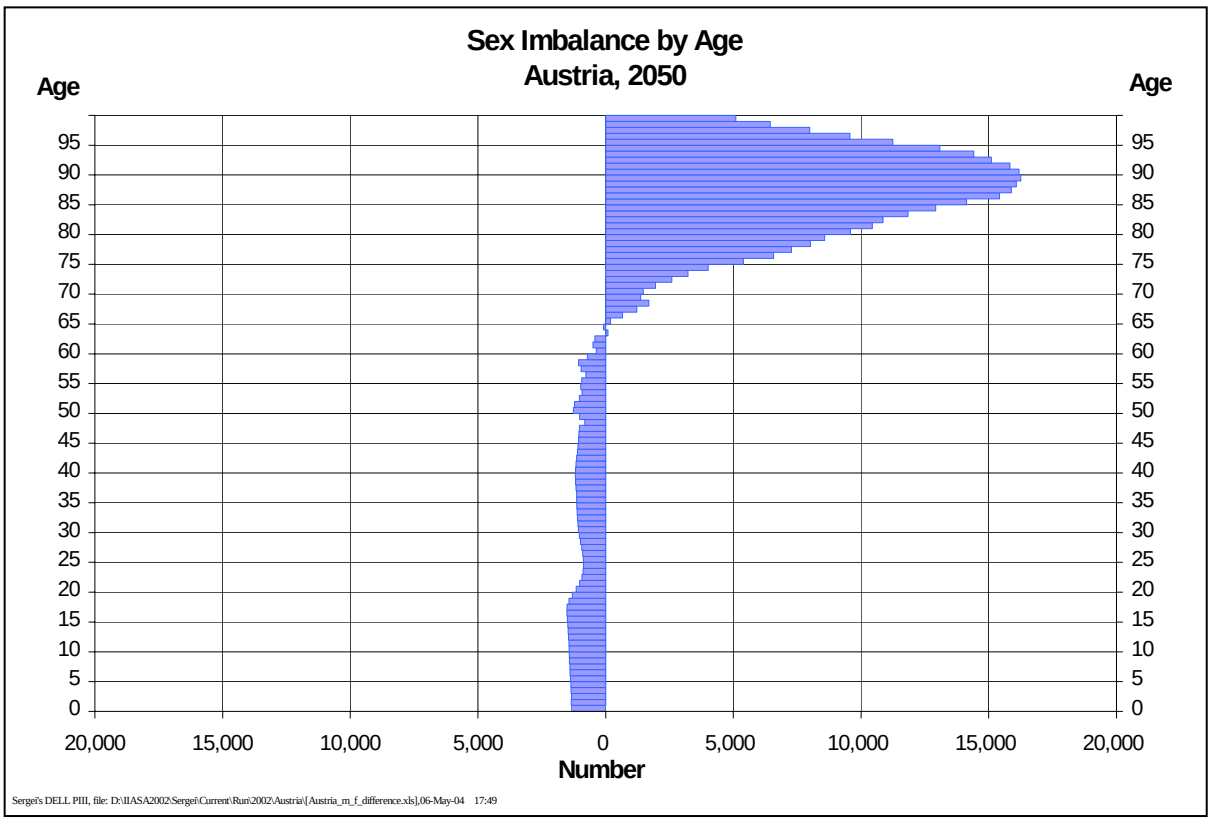
Population (thousands)


Sex Imbalance by Age
Austria, 2050
Age
Age
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Number
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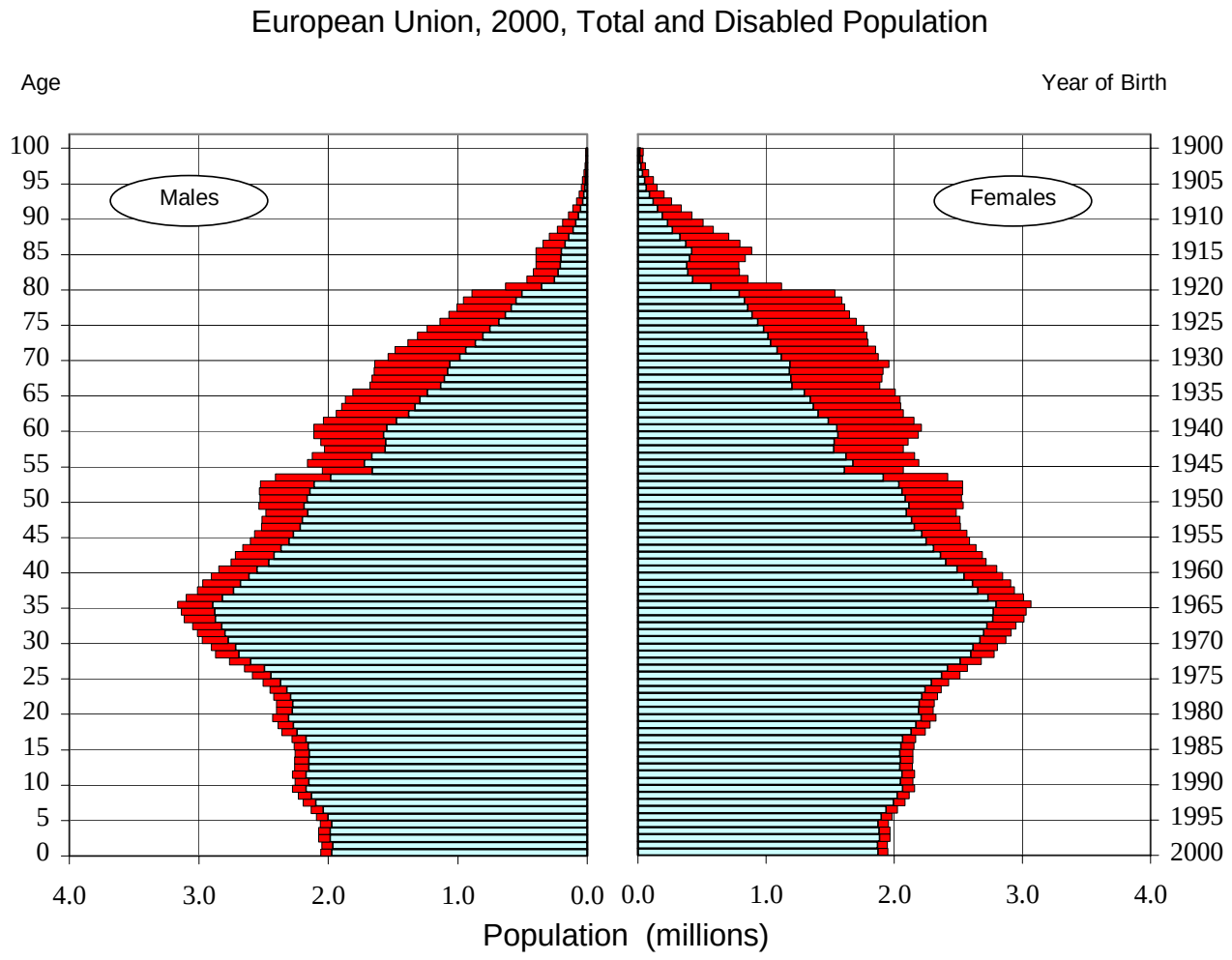
Will the massive population ageing expected for Europe result in a major increase in the population with disabilities and need for special care?

Conventional expectation is: Yes.

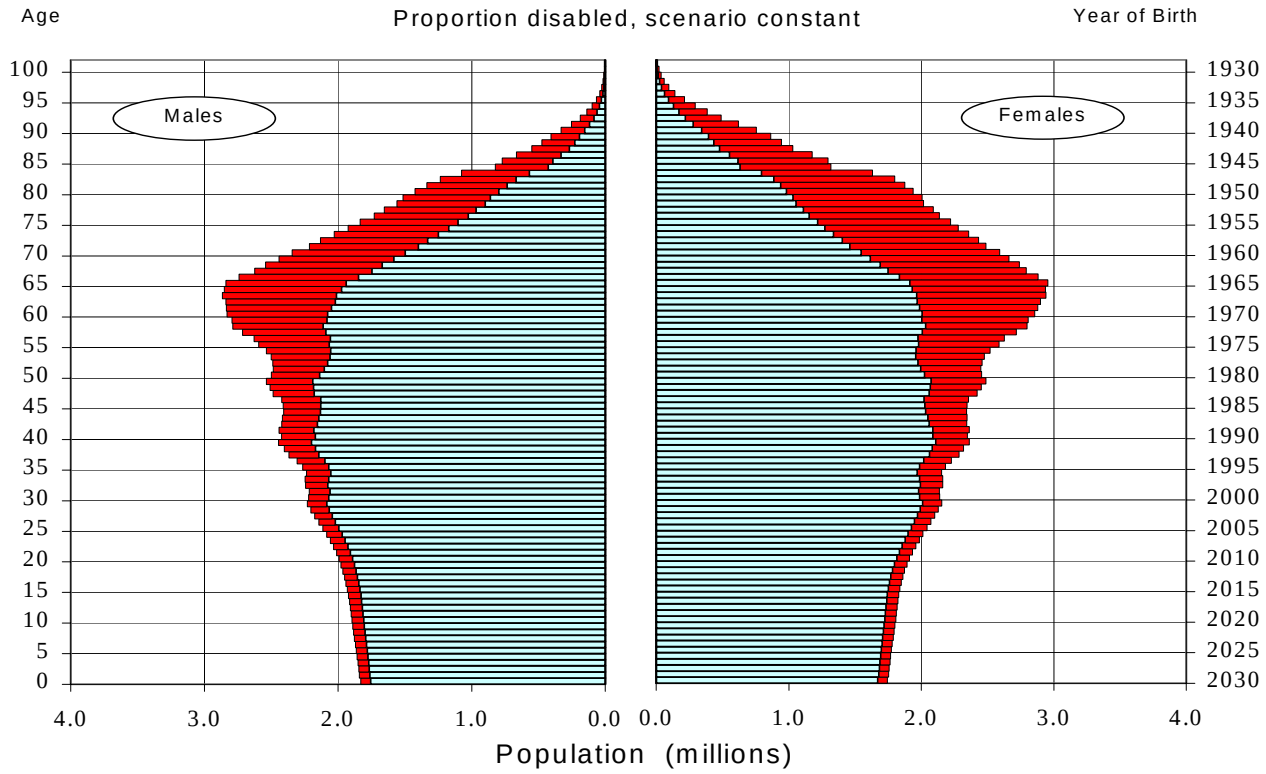
But these expectations combine the current age profile of disabilities with the future age structure.

Hopefully, the age profile of disability will also change in the future.

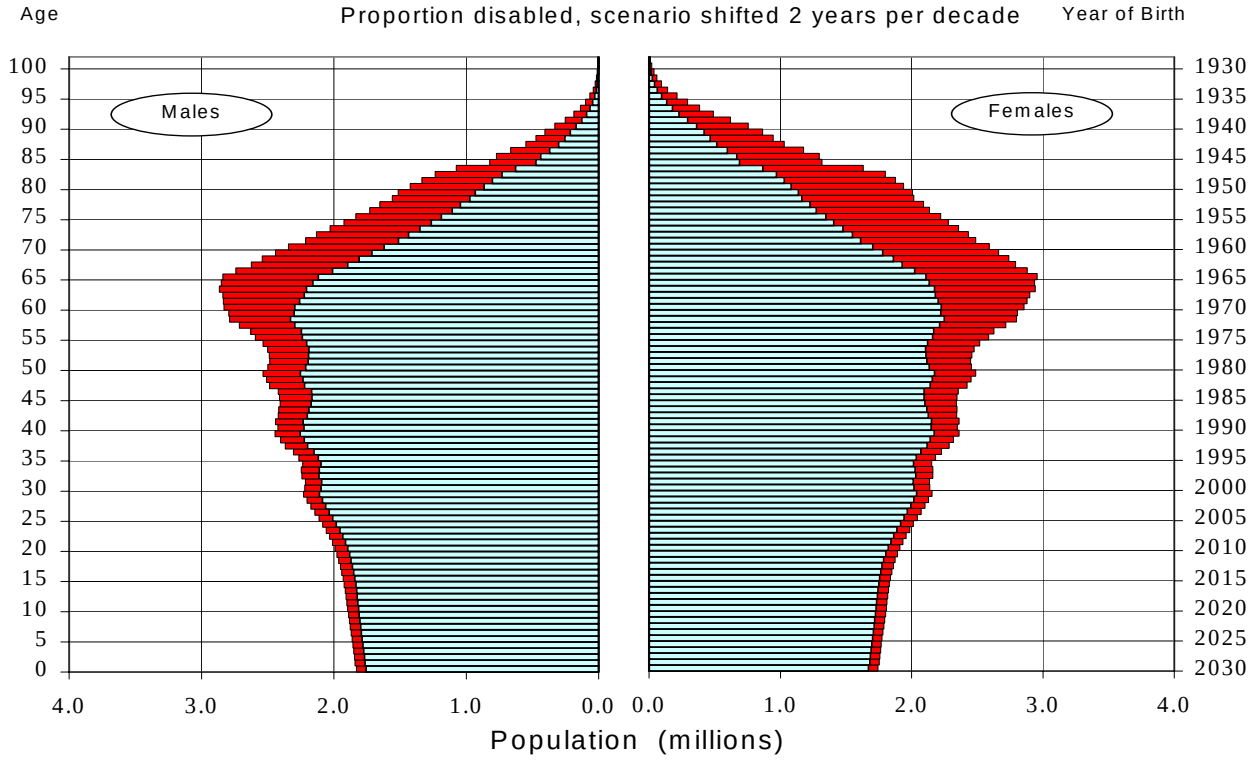
European Union 2000, Proportion with some disabilities by age



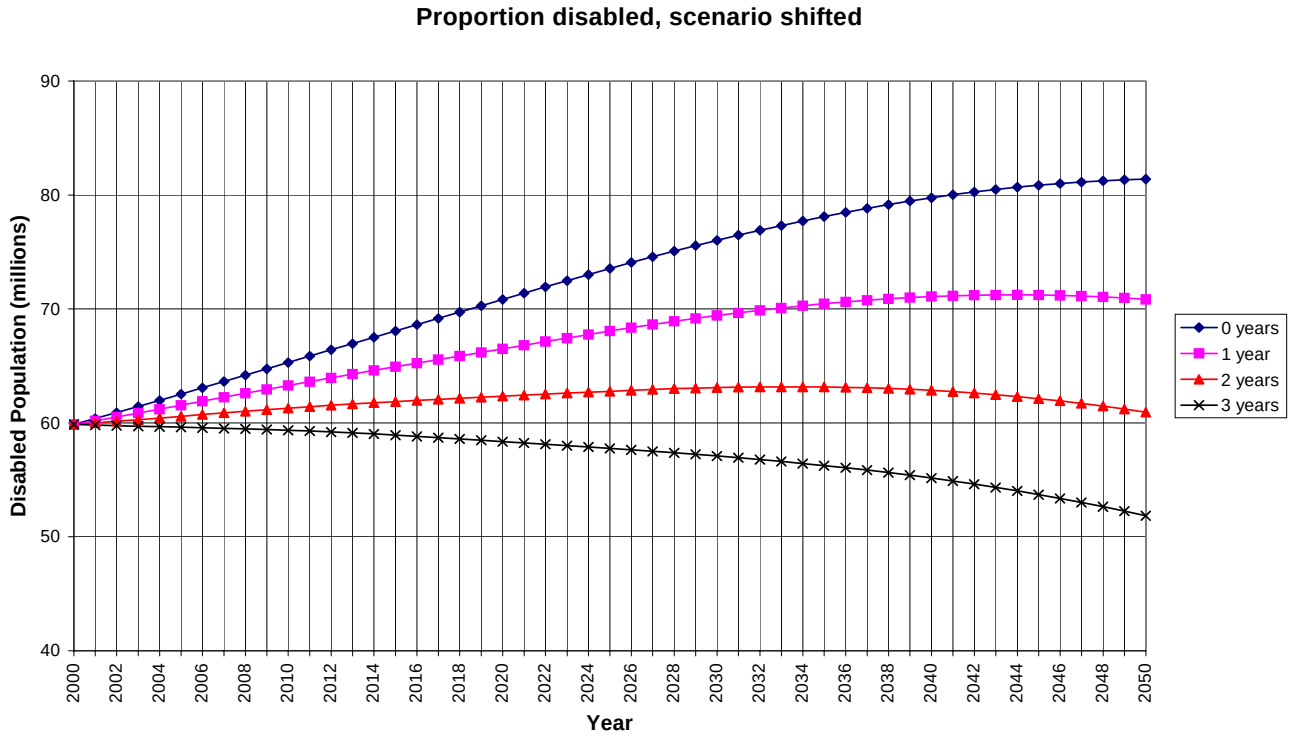
European Union, 2030, Total and Disabled Population

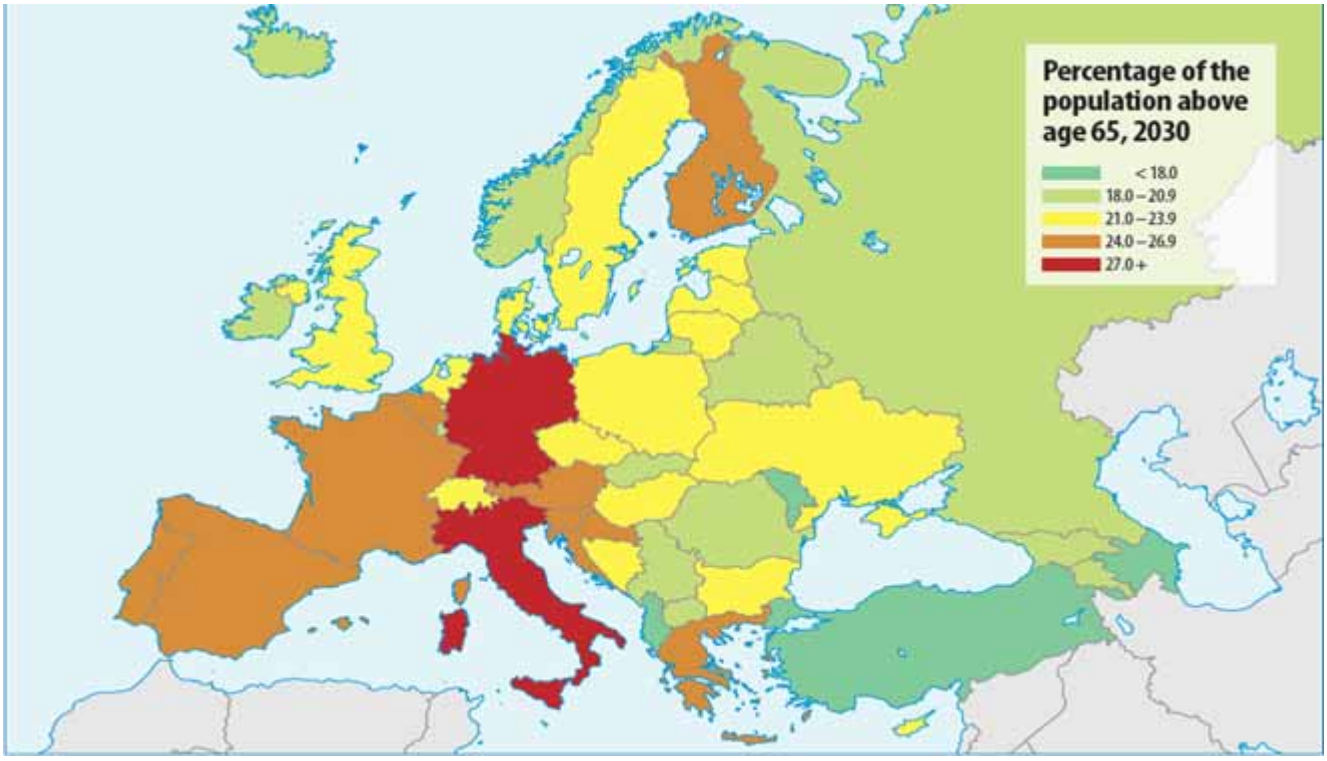


European Union, 2030, Total and Disabled Population



Results of the four alternative scenarios shifting the age profile of disability by 0, 1, 2 and 3 years per decade





4.2 *LifeSpan: A project integrating research into development and ageing

Professor Rudi Westendorp
Leiden University Medical Center, Dept. of Gerontology and Geriatrics, Leiden, The Netherlands - Coordinator of EU-Network of Excellence "LifeSpan"

***Due to document upload size limitations Professor Rudi Westendorp's presentation is available as a separate document at the following website address:**

http://www.era-age.group.shef.ac.uk/documents.php#document_type_3

4.3 Combining biological and social data in population studies of aging – developing European biodemography of ageing

Professor Claudio Franceschi
Department of Experimental Pathology, University of Bologna, Director of the Inderdepartmental Centre "L. Galvani", University of Bologna, Italy
Coordinator of EU-integrated project GEHA

The equation of longevity

L=E+G+S

Longevity-Environment + Genetics + Stocasticity

Longevity is a very complex trait

Genetics and longevity

- **Parents** of centenarians lived longer than people of the same cohort
- **Siblings** of centenarians have a 'risk' to reach 100 years several times higher than that of people of the same cohort
- **Offspring** of centenarians have a lower mortality and are protected from CVD and cancer
- A strong **familiar** component of longevity

Hum Genet (2006)
DOI 10.1007/s00439-006-0144-y

ORIGINAL INVESTIGATION

Jacob vB. Hjelmborg · Ivan Iachine · Axel Skytthe
James W. Vaupel · Matt McGue · Markku Koskenvuo
Jaakko Kaprio · Nancy L. Pedersen · Kaare Christensen

Genetic influence on human lifespan and longevity

Received: 2 December 2005 / Accepted: 6 January 2006

Abstract There is an intense search for longevity genes in both animal models and humans. Human family studies have indicated that a modest amount of the overall variation in adult lifespan (approximately 20–30%) is accounted for by genetic factors. But it is not known if genetic factors become increasingly important for survival at the oldest ages. We study the genetic influence on human lifespan and how it varies with age using the almost extinct cohorts of Danish, Finnish and Swedish twins born between 1870 and 1910 comprising 20,502 individuals followed until 2003–2004. We first estimate mean lifespan of twins by lifespan of co-twin and then turn to the relative recurrence risk of surviving to a given age. Mean lifespan for male monozygotic (MZ) twins increases 0.39 [95% CI (0.28, 0.50)] years for every year his co-twin survives past age 60 years. This rate is significantly greater than the rate of 0.21 (0.11, 0.30) for dizygotic (DZ) males. Females and males have similar rates and these are negligible before age 60 for both MZ and DZ pairs. We moreover find that having a co-twin surviving to old ages substantially and significantly increases the chance of reaching the same old age and this chance is higher for MZ than for DZ twins. The relative recurrence risk of reaching age 92 is 4.8 (2.2, 7.5) for MZ males, which is significantly greater than the 1.8 (0.10, 3.4) for DZ males. The patterns for females and males are very similar, but with a shift of the female pattern with age that corresponds to the better female survival. Similar results arise when considering only those Nordic twins that survived past 75 years of age. The present large population based study shows genetic influence on human lifespan. While the estimated overall strength of genetic influence is compatible with previous studies, we find that genetic influences on lifespan are minimal prior to age 60 but increase thereafter. These findings provide a support for the search for genes affecting longevity in humans, especially at advanced ages.

Introduction

The success in identifying longevity genes in Nematoda, *Drosophila* and mouse has facilitated large scale efforts

we find that genetic influences on lifespan are minimal prior to age 60 but increase thereafter.

. The present study is the first to demonstrate that at population level genetic variants for survival may exist with a pattern compatible with a significant and constant to increasing influence of genetic factors with age

These findings provide a support for the search for genes affecting longevity in humans, especially at advanced ages.

European Journal of Human Genetics (2006) 14, 79–84

www.nature.com/ejhg

ARTICLE

Evidence of genetic enrichment for exceptional survival using a family approach: the Leiden Longevity Study

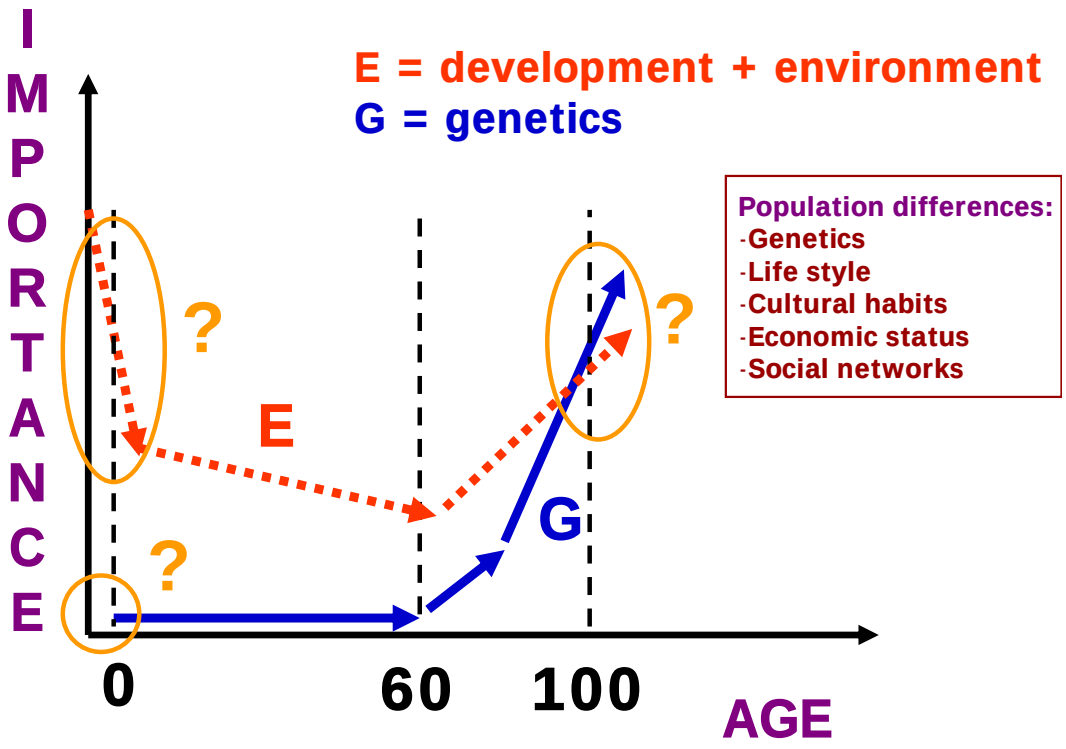
Manja Schoenmaker[1], Anton JM de Craen*,[1], Paul HEM de Meijer[2], Marian Beekman[3], Gerard J Blauw[1], P Eline Slagboom[3] and Rudi GJ Westendorp[1]

Standardised mortality ratios (SMRs) compared with the general Dutch population, were calculated. The SMR for all siblings of the long-living participants was 0.66 (95% CI 0.60–0.73). A similar survival benefit was also observed in the parents (SMR = 0.76, 95% CI 0.66–0.87) and in the offspring of the long-living subjects (SMR = 0.65, 95% CI 0.51–0.80). The SMR of the spouses of the long-living subjects was 0.95 (95% CI 0.82–1.12). The familial clustering of extended survival is unlikely to be caused by ascertainment bias, because in all analyses the long-living participants were excluded. Moreover, it is also unlikely to be caused by environmental factors, because the spouses of the long-living participants had a mortality risk comparable with the general Dutch population, whereas they share the same environment. We conclude that our sample is genetically enriched for extreme survival.

genetics and longevity

The survival advantage of offspring of long-living sibs **is not shared by their spouses** despite the fact that they have shared the same environment for most of their lives.

Thus the strong familiar component of longevity is likely a **genetic** component and **long living sibs should be highly enriched in longevity genes**.



GEHA

Genetics of healthy Aging
Integrated Project of EU 6th FP
7.2M€, 25 partners
Recruitment and Genome Scanning
(nucleur and mitochondrial genomes)
of 2650 90+ sibpairs and 2650 young controls
collected in 11 countries
May 1st 2004 – April 30th 2009

(www.gea.unibo.it)

Coordinator: Prof. Caludio Franceschi
Project Manager: Dr Alessandra Malavolta
Scientific Manager: Dr. Silvana Valensin

The GEHA Consortium
25 partners from 11 European countries and China

Participant name	Short name	Country
CIG - University of Bologna, C. Franceschi	UNIBO	IT
University of Montpellier UM1, J.M. Robine	CRLC	FR
CAU Kiel Centre for Functional Genomics S. Schreiber, A. Nebel	CAU	DE
Foundation Jean Dausset, Hélène Blanché	CEPH	FR
Istituto Superiore di Sanità, A. Stazi	ISS	IT
Leiden University Medical Centre, E. Slagboom, R. Westendorp	LUMC	NL
Max Planck Institute for Demographic Research, J. Vaupel	MPIDR	DE
National Hellenic Research Foundation, E. Gonos	NHRF	GR
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Nencki Istitute for Experimental Biology, E. Sikora	NENCKI	PL
University of Belfast, QUB, I.M.Rea	QUB	UK
University of Calabria, G. De Benedictis	UNICAL	IT
IFOM Institute of Milan, P.G. Pelicci	IFOM	IT
University of Sassari, L. Deiana	UNISS	IT
Catholic University of Louvain, M. Poulain	UCL	BE
Fac. Univ. Notre Dame de la Paix O. Toussaint	FUNDP	BE
University of Newcastle, T. Kirkwood	UNEW	UK
University of Southern Denmark, K. Christensen, B. Jeune	SDU	DK
Tampere School of Public Health, A. Hervonen	TAMPERE	FI
Research Innovation s.r.l. A. Leon	R&I	IT
Istituto Nazionale Ricovero e Cura Anziani L. Spazzafumo	INRCA	IT
University of Aarhus, P. Kristensen	UAAR	DK
Bejing Genomics Institute, L. Bolund, B. Liu	BGI	CN
Eppendorf Array Technologies, J. Remacle	EAT	BE
Institute of Gerontology, V. Bezrukov	Inst. Geront.	Ukraine

EU Integrated Project supported through Priority 1 (Life Sciences, Genomics and Biotechnology for Health) of European Union's FP6
Project Number: LSHM-CT-2004-503270

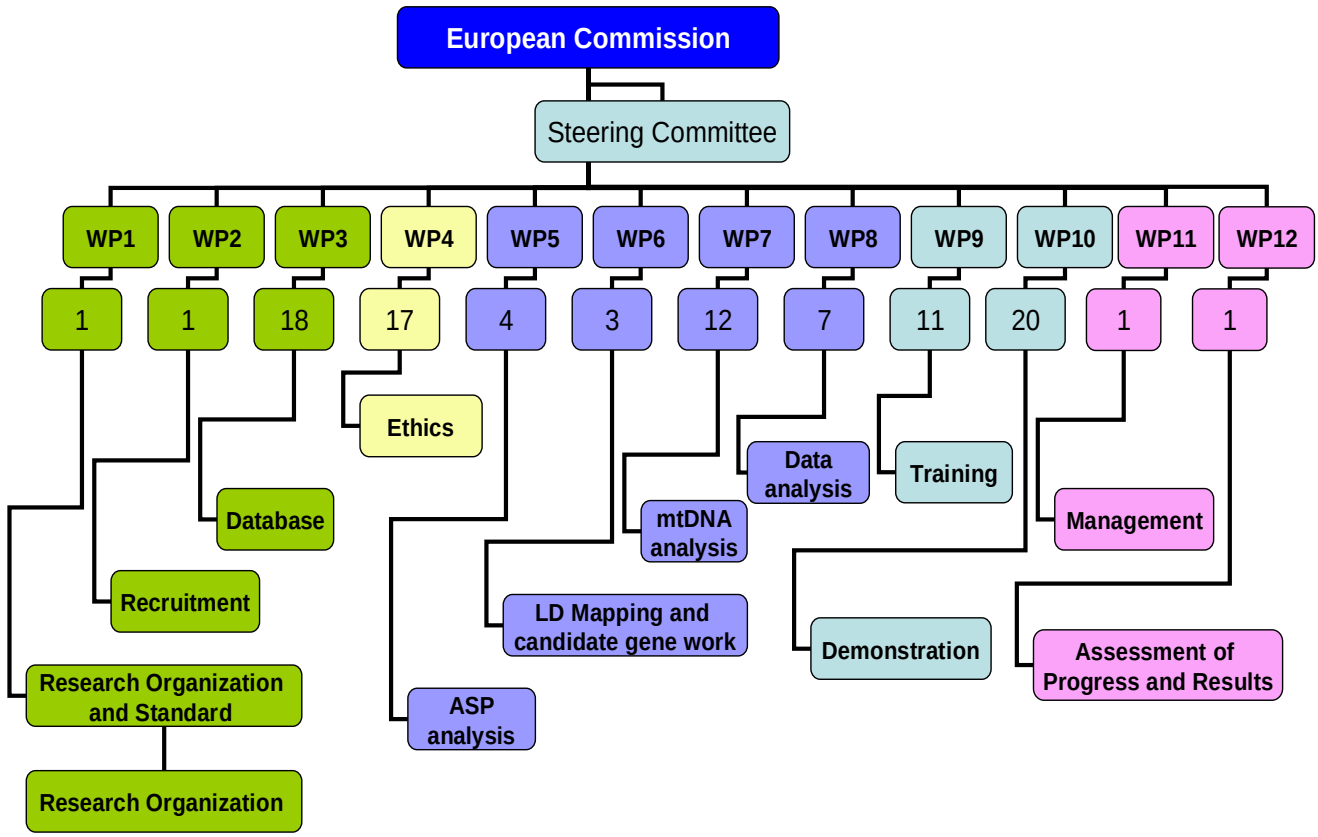
GEHA is the largest project in Europe to study the genetic determinants of human longevity.

The aim of the GEHA is to identify genes involved in healthy aging and longevity in humans, which allows individuals to survive to advanced old age in good cognitive and physical function and in the absence of major age-related diseases and disabilities.

GEHA: A multi-disciplinary project, the Consortium involves:

- demographers
- geriatricians
- geneticists
- genetic epidaemiologists
- molecular biologists
- bioinformaticians
- statisticians

12 Workpackages (WP)



linkage and association studies

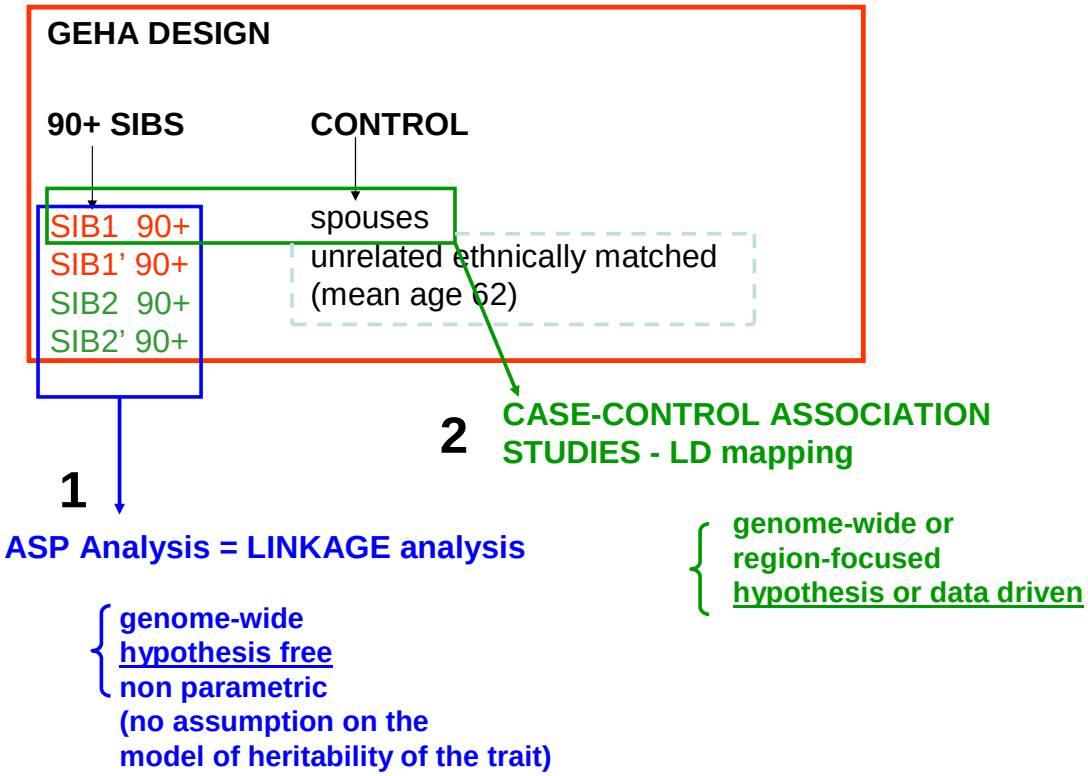
The design of the GEHA Project allows both **linkage and association studies** according to the most advanced genetic approaches.

- linkage studies in large samples of extreme long-lived siblings may be among the best approaches to identify such genes.

- linkage analysis looks for co-inheritance of chromosomal regions with the trait of families. It is more powerful than association analysis for identifying **rare high-risk** disease alleles.

- association studies are an approach to gene mapping that looks for associations between particular phenotype and allelic variation, i.e. for differences in the frequency of genetic variants between **unrelated affected individuals and controls**, with the expectation that the risk-conferring allele (halotype) will be more common in the patients (the long-living people) than the controls (the younger subjects).

- association analysis is expected to be more powerful for the detection of **common** alleles that confer **modest** disease risk.

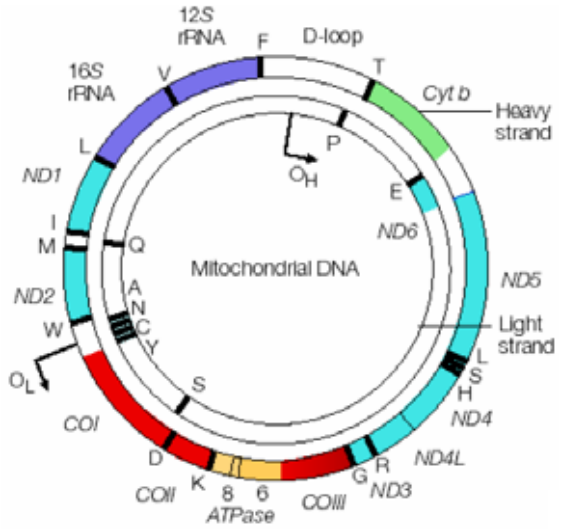


Within an Evolutionary and Systems Biology perspective:

- longevity likely results from the interaction and cross-talk between two genomes – nuclear genome and mitochondrial genome

mtDNA

16569 bp

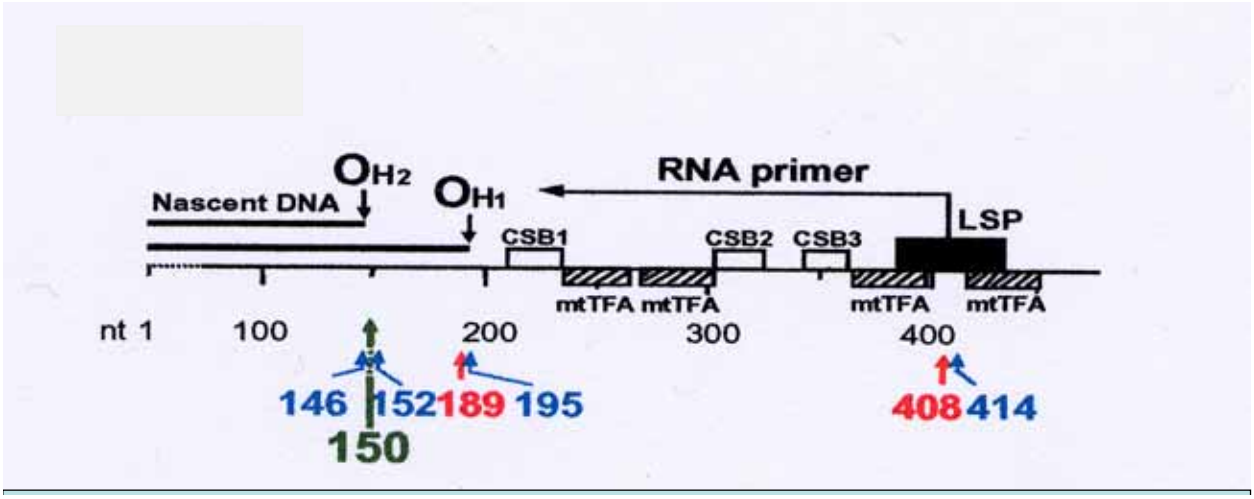


37 genes: 13 OXPHOS subunits
22 tRNA
2 rRNA
D-loop or Control Region (16024-576): regulatory region

- **Maternally inherited**
- **No recombination**
- **High mutation rate (particularly the D-loop)**
- **Several mtDNAs per mitochondrion**
- **Several mitochondria per cell**
- **Homoplasmic status: same mtDNAs per cell, tissue or organ**
- **Heteroplasmic status: different mtDNAs per cell, tissue or organ**

'mtDNA haplogroups (inherited polymorphisms) are associated with human longevity'

(Tanaka, *et al*, 1998; De Benedictus, *et al*, 1998; Tanaka, *et al*, 2000; Ross, *et al*, 2001 ; Dato, *et al*, 2004 ; Niemi, *et al*, 2003, 2005 ; and Santoro, *et al*, 2006)



Positions of the tissue-specific aging-dependant somatic mutations identified in human mtDNA control region

(Zhang et al, PNAS, 100, 1116-1121,2003)

GEHA study of mtDNA inherited variability

- **Resequencing of the entire mtDNA molecule** in 1000 probands and 1000 controls by an innovative technique validated in the laboratory of a GEHA partner
- **mtDNA haplogroups** (by sequencing the D-loop plus RFLP analysis of specific regions of mtDNA in 1650 probands of 90+ sibpairs (one sib per pair) as well as in 1650 controls)

The recruitment unit of the GEHA is a TRIO

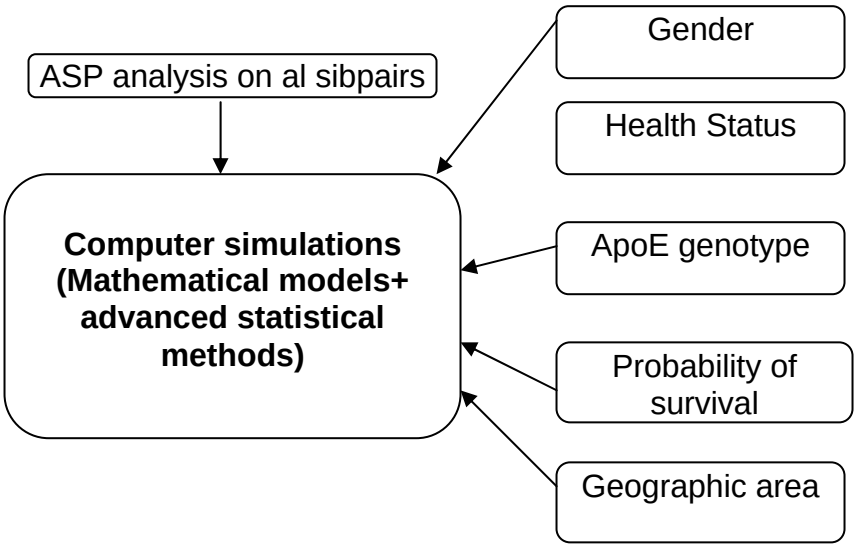
A trio is composed of **a sibpair** where both members are **90 years old or older** (about 0.5% of the EU population) and **a younger ethnically-matched unrelated control** (55-75 years old) recruited in the same geographic area of the sibpair.

We calculated a **50% overall refusal** of the eligible sibpairs.

Information and material collected:

- Informed Consent and Questionnaire:
- health status
- physical and cognitive abilities
- social and economic status
- supporting network
- Blood

GEHA approach to increase the power of the genetic analysis



GEHA LOGISTIC AND SAMPLE SIZE

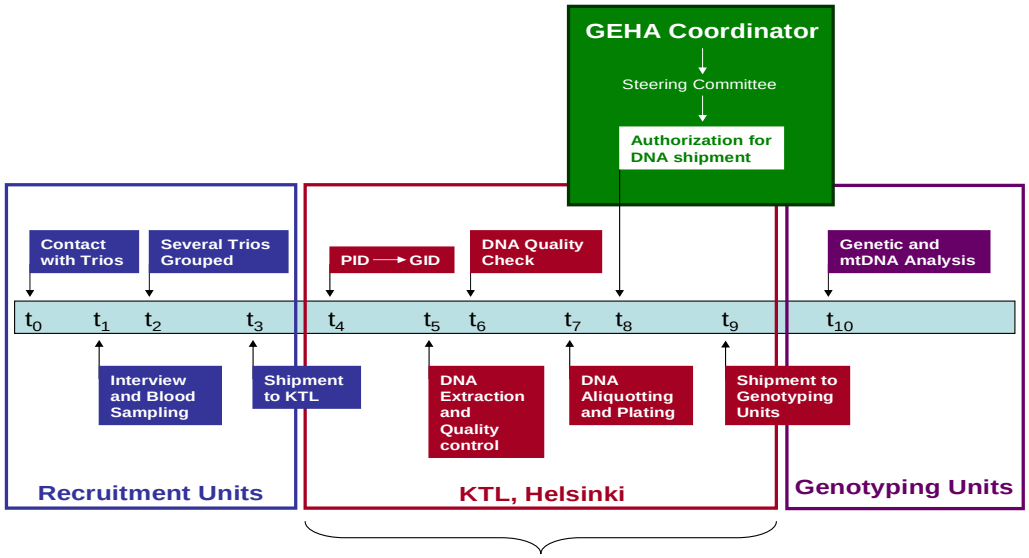
- 2650 sib pairs 90+ years old (for a total of 5300 subects)
- 2650 Younger Controls from the same geographic areas

7950 samples

from 11 European countries

All samples are
Centralized at **KTL in Helsinki** → **DNA { Extraction, Quality control, repository**

GEHA DNA Flow Chart



GEHA infrastructures (www.geha.unibo.it)

Databases :

1. Phenotype database (Odense)
2. Gentoype database (Kiel)
3. mtDNA database (Bologna)

Centralized Facilities for :

- DNA extraction, quality control and banking (Helsinki ans Paris)
- Data analysis, mathematical modeling, advanced statistics (Rostock, Lieden, Rome, Newcastle)
- Genetic analysis (genetic platforms)

The GEHA Consortium -Genetic Platforms

Participant name	**Short name**	**Country**
CIG - University of Bologna, C. Franceschi	UNIBO	IT
CAU Kiel Centre for Functional Genomics		
S. Schreiber, A. Nebel	CAU	DE
Foundation Jean Dausset, Hélène Blanché	CEPH	FR
Leiden University Medical Centre, E. Slagboom,		
R. Westendorp	LUMC	NL
Bejing Genomics Institute, L. Bolund, B. Liu	BGI	CN
National Public Health Institute, L. Peltonen	KTL	FI
University of Calabria, G. De Benedictis	UNICAL	IT
IFOM Institute Milan, P.G. Pelicci	IFOM	IT

- **1800 90+ sibpairs** recruited (in 9% of the cases there are 3 or more 90+ sibs)
- **1800 controls** recruited (ethnically-matched, mean age: 62 years)
- **5000 DNA samples** extracted
- preliminary genetic analysis of chromosomal regions **11p15.5**
- analysis of **mtDNA** variants in several hunder subjects
- contacts with **EU BIOBANK register initiative**
- contract with **similar projects** on the genetics of longevity in Japan and USA

GEHA major goals

1. to overcome the **fragmentation** of the research on the genetics of ageing in Europe
2. to recruit an unprecedented number of **long lived siblings (2650 90+ sibpairs)** from **11 European countries** in **15 geographic areas** for genome wide scanning to identify chromosome regions involved in longevity and healthy ageing
3. to recruit a large number (**2650**) of **younger control** subjects from the **same geographic areas**, necessary for Linkage Disequilibrium (LD) mapping, followed by positional cloning and mutational analysis to fine map the chromosome regions identified by genome wide scanning
4. to perform **bioinformatic, functional genomics and proteomics**, and molecular biology studies on the identified/putative longevity regions/genes and gene variants resulting from ASP analysis and LD mapping
5. to test whether **ethnically different populations** (including those from **Sardinia and Finland**) share the same genes involved in ageing and longevity
6. to verify if the genes involved in longevity and healthy ageing in the European population are the same in an ethnically different population such as **Han Chinese**
7. to ascertain the role played in human longevity by **three candidate chromosomal regions** (D4S1564 in chromosome 4, as well as chromosome 11p15.5 and chromosome 19 around the ApoE gene)
8. to assess in a variety of European populations, and at a large scale, the role of **mtDNA variants** in human longevity, and to study their interaction with the newly emerging longevity nuclear genes
9. to identify **gender-specific genes** differently involved in the healthy ageing and longevity of women and men
10. to stratify the sample according to **APOE genotype**, the only genetic marker which so far has been found to be associated with reduced longevity in a variety of populations
11. to develop **innovative analytical strategies** (based on statistical method and mathematical models) capable of combining all the data collected (clinical, socio-economical, related to life-style, demographic and genetic)
12. to perform **a longitudinal study** to evaluate the importance of genetic factors on the mortality of the recruited long-lived sibpairs

Major milestones

M1. Common/standardised protocol for recruitment (standardised case sheet)
M2. Recruitment of 2650 90+ sibpairs
M3. Recruitment of 2650 young control subjects
M4. Identification and inclusion in GEHA of a new partner from Eastern Europe
M5. Biological bank by each recruiting partner and DNA sample for genetic analysis
M6. Phenotype database
M7. Genotype database
M8, mtDNA database
M9. Chromosomal region(s) harbouring putative genes involved in healthy ageing and longevity identified by ASP analysis
M10. Haplotype structure of candidate regions in chromosome 4, 11 and 19, and in chromosomal regions identified by ASP analysis for the identification of htSNP to be used in large scale LD mapping and association studies
M11. Narrow-refined chromosomal region(s) by LD mapping on the DNA from 2650 90+sibpair probands and 2650 young control subjects harbouring putative longevity gene(s)
M12. APOE genotype of all the recruited subjects
M13. mtDNA analysis of all the recruited subjects
M14. Nuclear and mitochondrial genes associated with successful/unsuccessful ageing
and longevity in Han Chinese
M15. Biological role and function of identified/putative gene variants associated with successful/unsuccessful ageing and longevity
M16. Innovative analytical strategies
M17. *ad hoc* microarray for human ageing and longevity
M18. Report of the longitudinal study regarding the mortality of the recruited 90+ sibpairs
M19. Training
M20. Ethics, legal issues and IPR
M21. Establishment of a fully functional Management

4.4 *The ageing cellular power plant, how can it influence longevity

Professor Heinz Osiewacz
Johann Wolfgang Goethe University of Frankfurt, Dept.of Molecular Developmental Biology and Biotechnology, Frankfurt, Germany
Coordinator of EU-integrated project MiMAGE

***Due to document upload size limitations Professor Heinz Osiewaczs' presentation is available as a separate document at the following website address:**

http://www.era-age.group.shef.ac.uk/documents.php#document_type_3

4.5 Changes in the structure and function of cells, how do they affect lifespan?

Professor Brian Clark
University of Aarhus, Dept. of Molecular Biology, Aarhus, Denmark
Coordinator of EU-integrated project PROTEOMAGE

proteomics and functional genomics of ageing

history

4.1 Molgeron (CAP) (12)
4.1 Genage (SCA) (4)
4.1 Protage (SCA) (7)
4.1 Functionage (SCA) (5)

functional genomics

- Comparative genomics
- Structural genomics
- Bioinformatics
- RNAomics – gene expression
- Proteomics – protein profiling
- Metabolomics
- Physionomics
- Functional determination

definition

The most useful definition of proteomics is likely to be the broadest:

Proteomics represents the effort to establish the identities, quantities, structures, and bio-chemical and cellular functions of all proteins in an organism, organ, or organelle, and how these properties vary in space, time and physiological state.

Proteomics is thus a huge, long-term task, much more involved than sequencing the genome.

Molecular and Cellular Proteomics

Functional analysis of evolutionarily conserved mechanisms of ageing based on advanced proteome analysis.

Proteomage

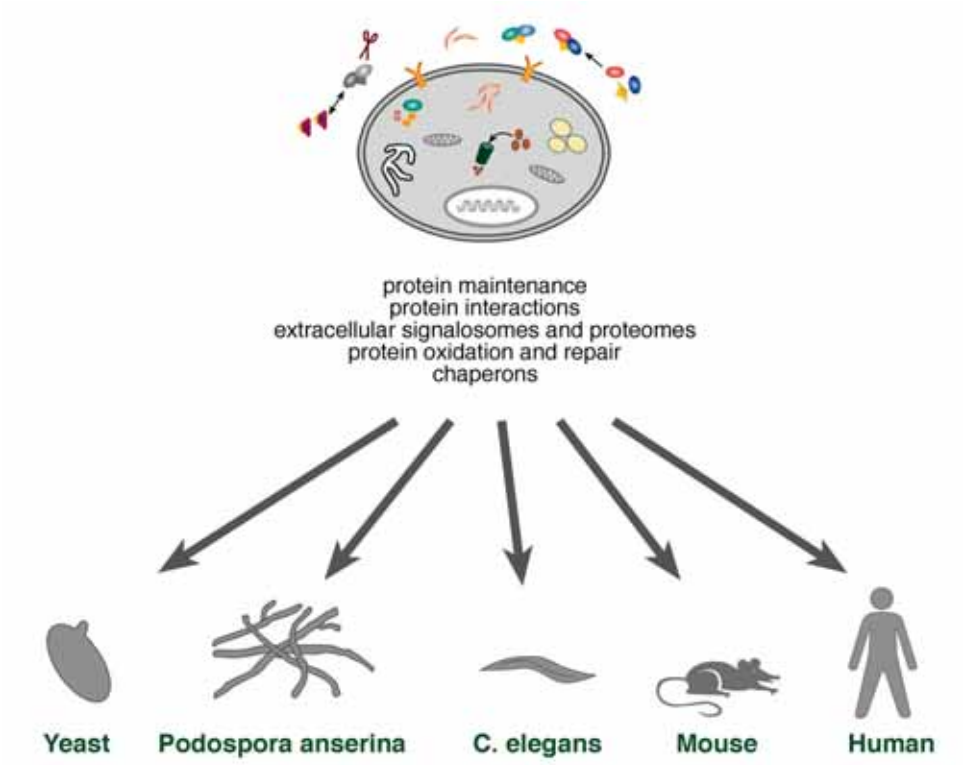
the project

Studies to gain novel insight into **molecular mechanisms of healthy ageing**. Based on proteomic analysis of ageing processes in a variety of ageing models including **model organisms** and **model systems** (e.g. human cell cultures), we will address how

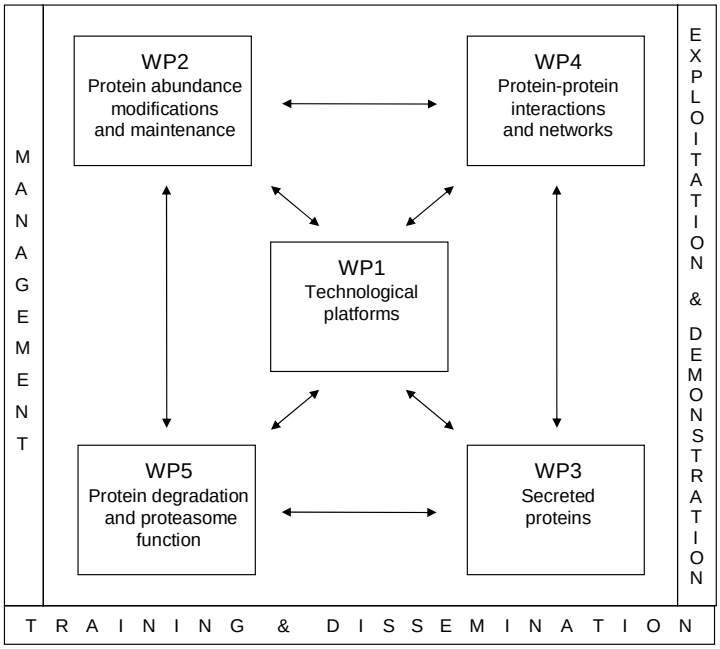
1. changes in **protein concentration and protein modification**,
2. **protein-protein interactions** and protein networks,
3. **signalling** mediated by **extracellular proteins**,
4. **protein turnover and degradation** via the **proteasomal system** play a **functional role** in the ageing process.

aim

- To investigate changes in protein concentration, protein-protein interactions, and post-translational modifications of proteins during ageing in humans and model systems



PROTEOMAGE



Applications

- Novel technology will also allow identification of age-associated port-translational modifications and cleavage events that are known to influence greatly the activity of proteins and also Biomarkers of ageing.
- Trans-species comparisons will reveal candidates for proteins that play a functional role in driving ageing processes, allowing for the first time a delineation of cause-effect relationships (instead of mere correlations) governing proteome changes that lead to age-associated phenotypes.
- The work described above will also lead to new protocols for early **diagnosis** and **prevention of age-associated dysfunctions**, based for example on strategies to reactivate proteasome activity in senescent cells

4.6 European coordination of funding for ageing research

Professor Alan Walker
University of Sheffield, Dept. of Sociological Studies, Sheffield, UK
Director of the European Research Area in Ageing (ERA-AGE)

road map

- The Need for European Co-ordination
- The European Forum on Population Ageing Research
- The European Research Area on Ageing
- After ERA-AGE?

ageing is a major policy priority yet…

- No systematic linkages between centres of excellence
- Absence of concerted European perspective
- Wastage of resources
- Little added value

building blocks in the Europeanisation of ageing research

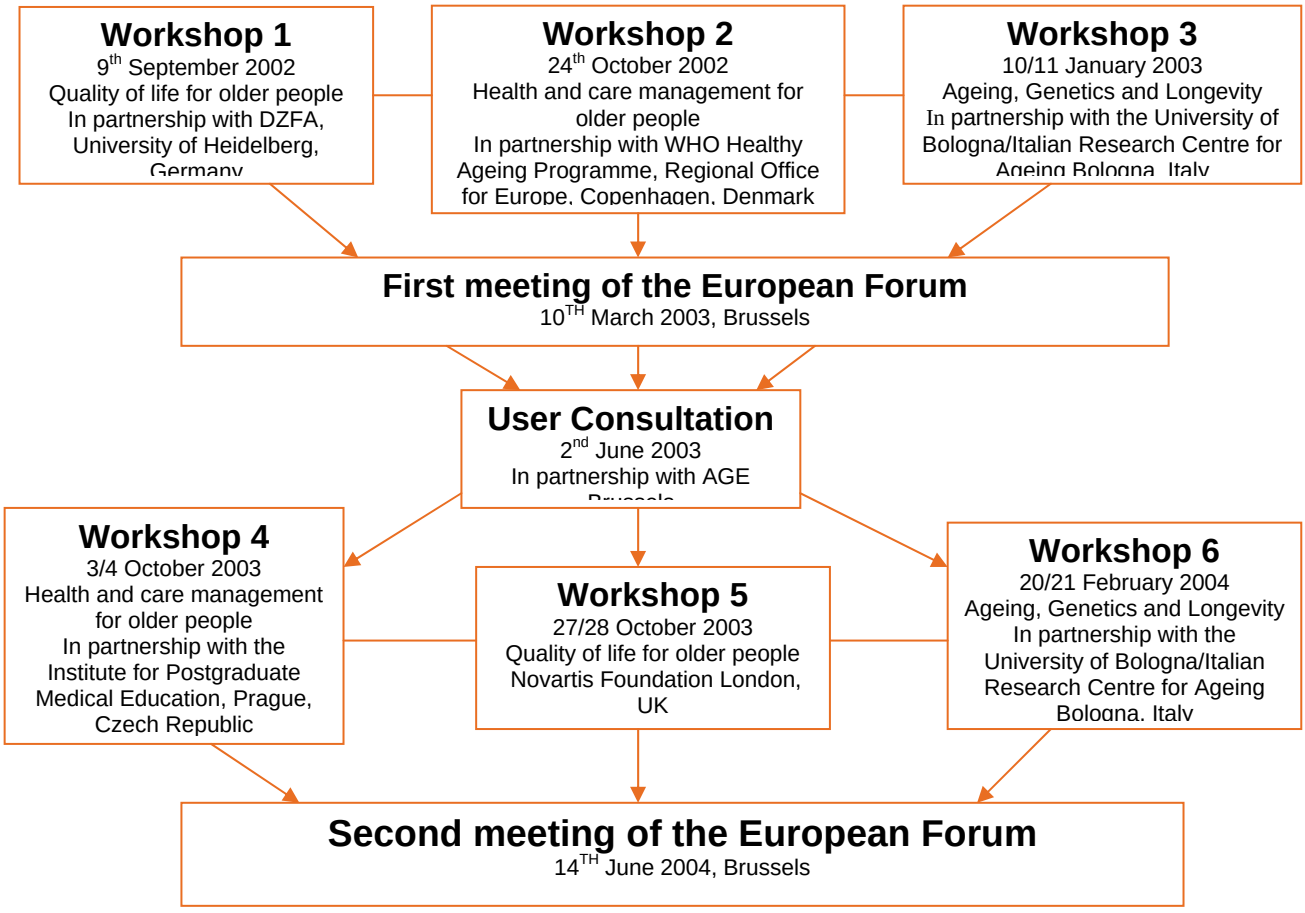
1991	European Observatory on Ageing and Older People
1992	Eurobarometer
1993	European Year of Older People and Solidarity Between Generations
1999	UN Year of Older People (the society for all ages)
1998-2002	FP5 Key Action 6
2000	First European Forum of Ageing Research
2001	FORUM
2004	ERA-AGE

European Forum on Population Ageing Research

objectives

- To promote European co-operation in ageing research
- To develop synergies between national and international programmes
- To improve channels of communication
- To stimulate interdisciplinary research
- To promote improved public awareness

European Forum on Population Ageing Research: Timeline of Events



	INSTRUMENTS	STRUCTURAL LIMITATIONS	METHODOLOGICAL ISSUES	RESEARCH PRIORITIES
QUALITY OF LIFE	1) Consensus on how to understand, measure and define QoL – both standardised and culture specific. 2) Predictors of active ageing. 3) Assess environmental measures to understand how to improve the lives of older people.	1)Developing gerontology researcher capacity in quantitative and financial expertise. 2) Health issues have taken priority to the detriment of other aspects.	1) Biographical and older person centred perspectives. 2) Involving older people in research. 3) Theoretical development that integrates findings across the domains of QoL. 4) Examination of societal level as well as the individual – including provision, providers and recipients. 5) Targeting of research on 50-67 year olds – 'tomorrow's older people'.	1) Data on wealth and goods in kind and individual as a unit as well as household. 2) Little is known about the causal factors of inequalities between countries and social groups. 3) How income needs and perceptions of older people change as they age. 4) Investigate expectations and normative belief systems of older people. 5) Investigate cross-cultural definitions of QoL.
HEALTH AND SOCIAL CARE MANAGEMENT	1) More effective quality assurance of e-health and e-care services. 2) All interventions should be tested amongst the 'oldest old'.	1) Expand research beyond the dominant perspectives and the limitations created by commercial priorities. 2) Fund more research into non-medical interventions.	1) Methodologies need to keep up with the rapid evolution of knowledge – i.e technology, modelling, representativeness, culture. 2) User involvement is underdeveloped and under-utilised. Need for more flexibility and clarity about how and why to involve users.	1) What e-health and e-care services are available, what services do older people want & how do these services interact with others? 2) How to get people on low income and with low education to use these services – greater accessibility. 3) Extensive European longitudinal study that begins by reviewing existing longitudinal studies and their methodologies and variables.
GENETICS, LONGEVITY DEMOGRAPHY	1) No international standard co-morbidity index 2) how to measure and define health and frailty in the oldest old is controversial.	1) The challenge is how to identify bridges between disciplines and integrate their understandings of longevity and ageing.	1) Nonagenarians are under-researched in longevity studies. 2) Co-ordinated approach regarding what biological samples and data should be gathered. Statistics should help define this**.**	1) Better define the phenotype 'longevity' from a biochemical and physiological perspective. 2) Investigate relationship between diseases and longevity to define which genes to study. 3) Focus on what happens before mortality, why people survive with co-morbidity and what can be changed by what interventions. 4) Researchers should try to answer: a) can we attain a robust common measure of individual biographical frailty? b) Can we use this measure to identify genetic, lifestyle, psychological, social and environmental factors that influence the onset of critical frailty?

FORUM priority recommendations

- European Collaboration
- National Funders / Policy Makers
- European Funders / Policy Makers
- Scientific Research Agenda
- Methodology

FORUM priority recommendations top 5

- Use recommendations to plan FP7
- Establish a European Institute on Ageing
- Work together to develop European and interdisciplinary collaboration
- Commitment to user involvement
- Attract and support new researchers

European Research Area in Ageing (ERA-AGE)

www.shef.ac.uk/era-age

Partner Countries:

Austria, Finland, France, Germany, Israel, Italy, Luxembourg, Netherlands, Norway, Romania, Sweden, UK (coordinator)

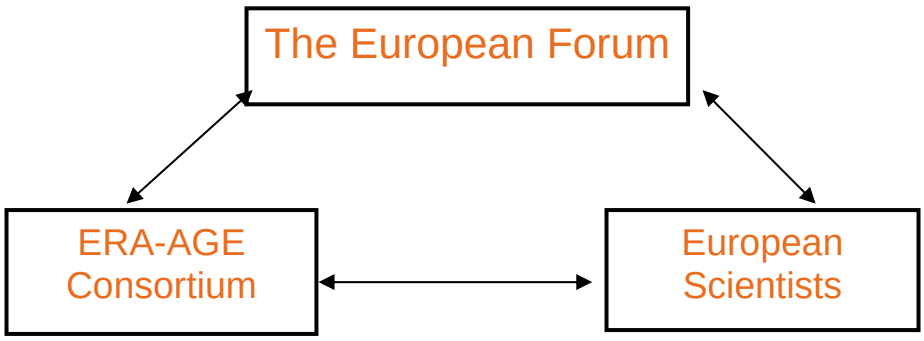
Associate Partner Countries:

Latvia, Spain

Objectives:

- To facilitate coordination of existing ageing research programmes
- To promote interdisciplinary research activities between countries
- To share good practice in coordination and management of ageing programmes
- To support the production of European priorities for ageing research programmes
- To help break down the barriers between ageing research programmes and policy and practice

Key Elements:



Collaboration: Making a Start

- Developing a Virtual European Institute
- Coordinating European Databases
- Good Practice Workshops
- Future Leaders of Ageing Research in Europe (FLARE)

European Coordination of Funding for Ageing Research

- The Need for European Coordination
- The European Forum on Population Ageing Research
- The European Research Area on Ageing
- After ERA-AGE?
- Conclusion

4.7 Developing effective multidisciplinarity in ageing research

Professor Tom Kirkwood
Co-Director of the Institute for Ageing and Health, University of Newcastle, Newcastle upon Tyne, UK

Unfortunately, Professor Kirkwood was not able to get to Innsbruck in time to join the workshop, but he kindly provided his talk to be put into the attendees' conference packs.

Ageing and Inter/Multi-Disciplinarity

- The ageing process is biological (BBSRC)
- Ageing is experienced in a social context (ESRC)
- Ageing has major interactions with health (MRC)
- The social impacts on ageing are modulated by the physical environment (EPSRC)

So

- Human ageing cannot properly be understood without a multidisciplinary approach.
- Interdisciplinary collaboration is of primary importance in addressing the challenges of population ageing.

Engagement, translation

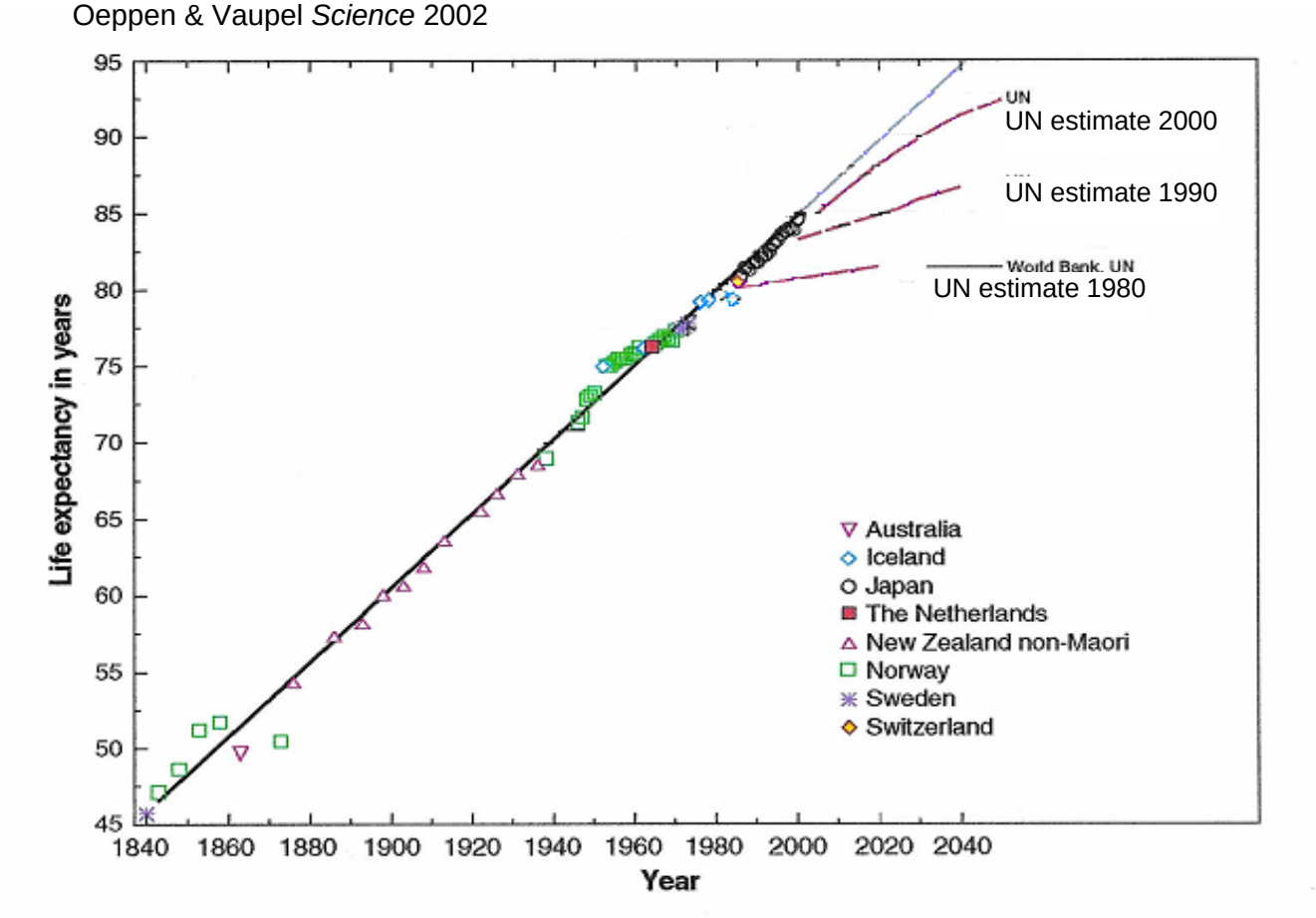
- New understanding of the complex interactions underpinning healthy ageing and longevity.

- Multidisciplinary approaches to intervention – exploiting the intrinsic malleability of ageing.

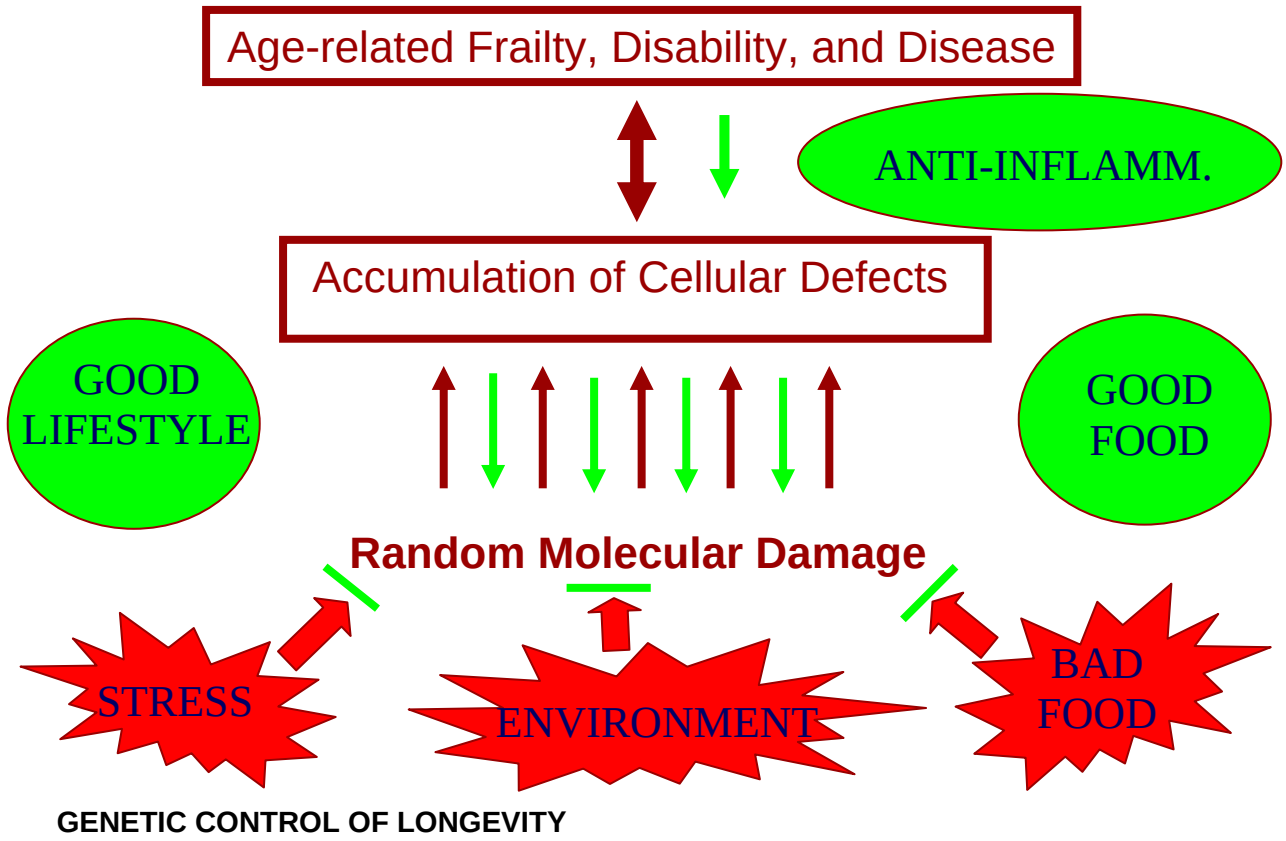
- Overcoming the obstacles.

The Continuing Increase in Life Expectancy

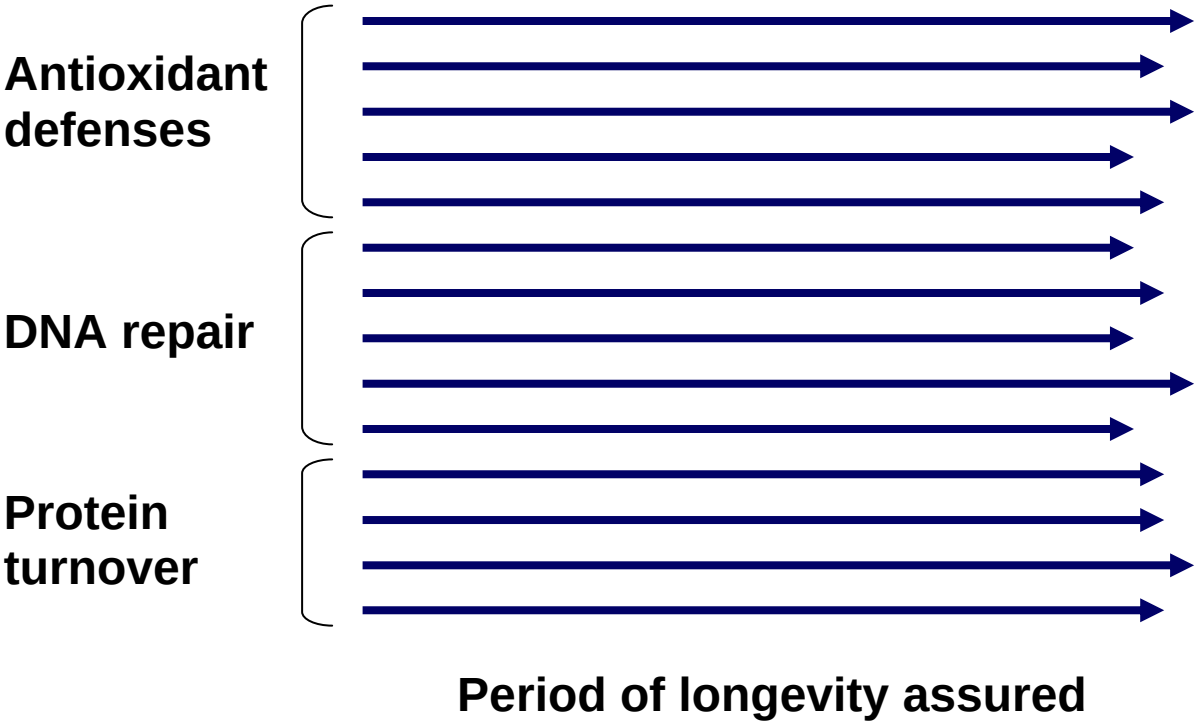
Oeppen & Vaupel *Science* 2002



The Ageing Process Kirkwood *Cell* 2005



GENETIC CONTROL OF LONGEVITY



Period of longevity assured

Human Ageing is Malleable

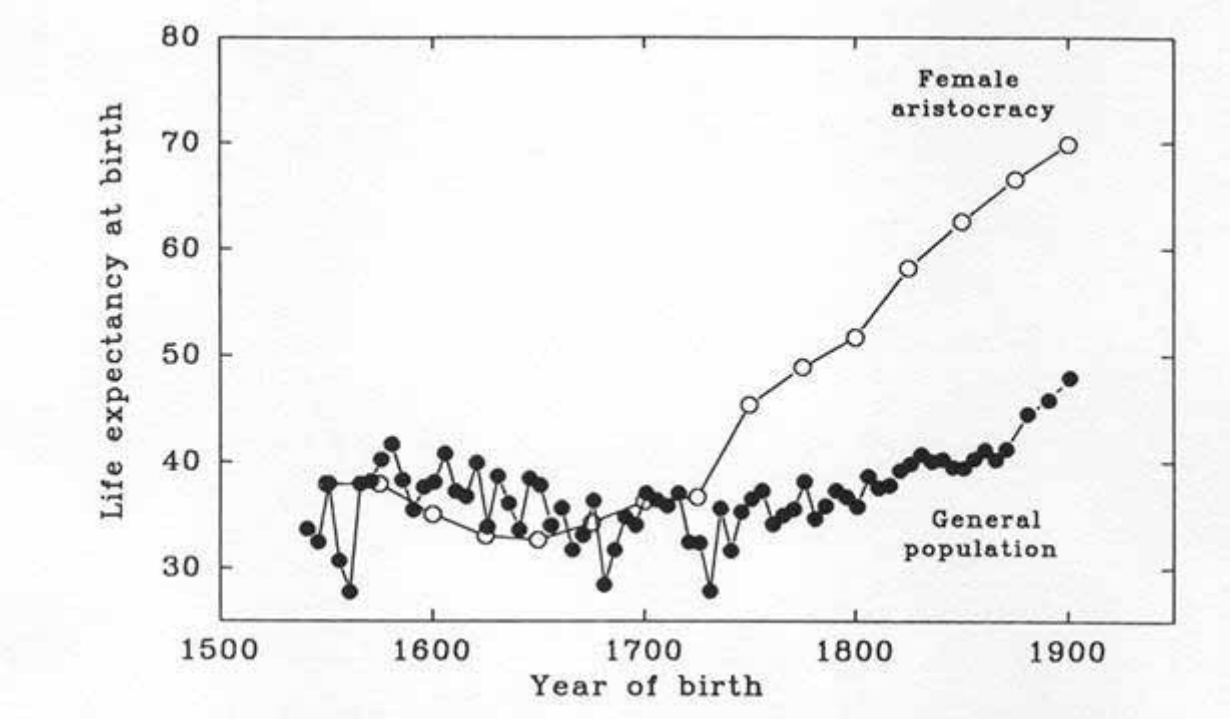
- By decreasing exposure to damage
  - Improved nutrition
  - Improved lifestyle
  - Improved environment

- By enhancing natural mechanisms for protection and repair
  - Improved nutrition
  - Novel drugs, etc

Factors Influencing Longevity and Health Span

- Genes
- Nutrition
- Lifestyle
- Environment
- Socioeconomic status
- Attitude
- Chance

Wealth and Expectation of Life



Differences in Life Expectancy across Local Authorities in England & Wales 1999-2001

	Local Authority	Life Expectancy
High	North Dorset	79.3
	Christchurch	79.3
	S. Cambridgeshire	79.0
	Horsham	78.6
Low	Merthyr Tydfil	72.8
	Middlesbrough	72.7
	Liverpool	72.0
	Manchester	69.8

Source: National Statistics, 27 Feb 2003

Meeting the Interdisciplinary Challenge

- Creating the necessary partnership
- Underpinning individual disciplines
- Motivating researchers to invest time in interdisciplinary research
  - Funding
  - Career recognition and advancement
- Knowledge transfer and translational research

Barriers to be Overcome

- Peer review – multiple jeopardy
- Differences in basic skill sets and priorities
- Differences in criteria for career advancement
- Tribalism and the problem of 'where do I belong?'
- Creating enough time together
- Sustaining multi-level networking (seniors and juniors)
- Active management of interdisciplinary integration

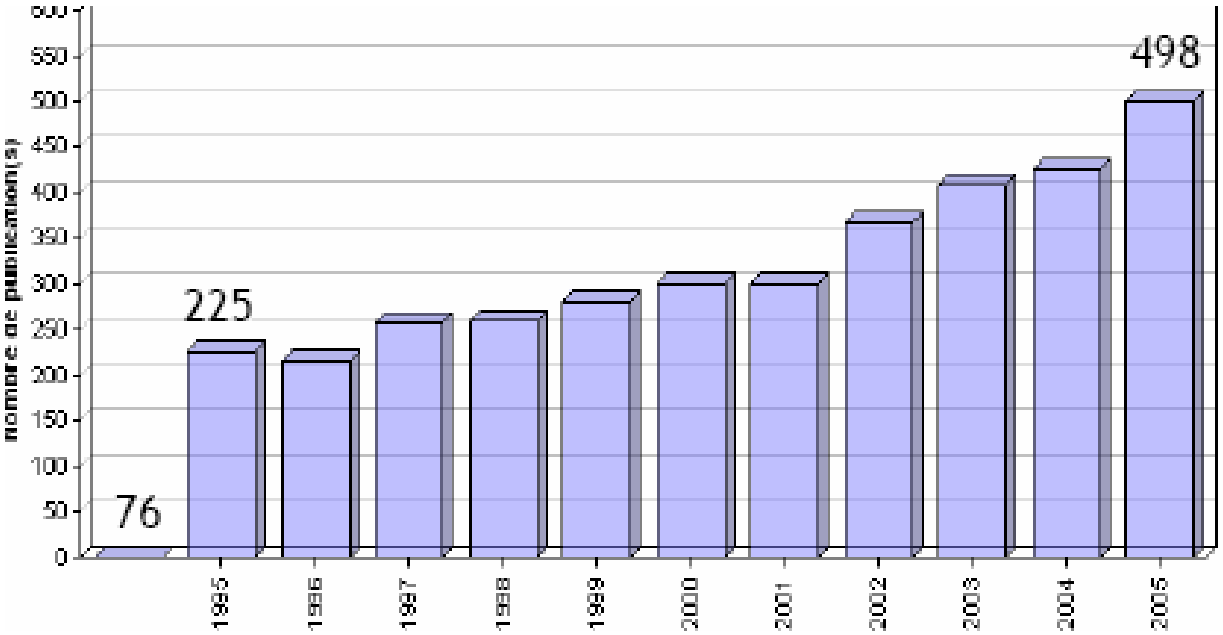
4.8 Choosing biogerontological research topics of industrial relevance

Daniel Asselineau
Head, Skin and Ageing Life Science Research, L'Oréal, Clichy, France

AGEING

= **Extrinsic Ageing Extrinsic Aging** (external influences) + **Intrinsic Ageing** (mostly genetic factors)

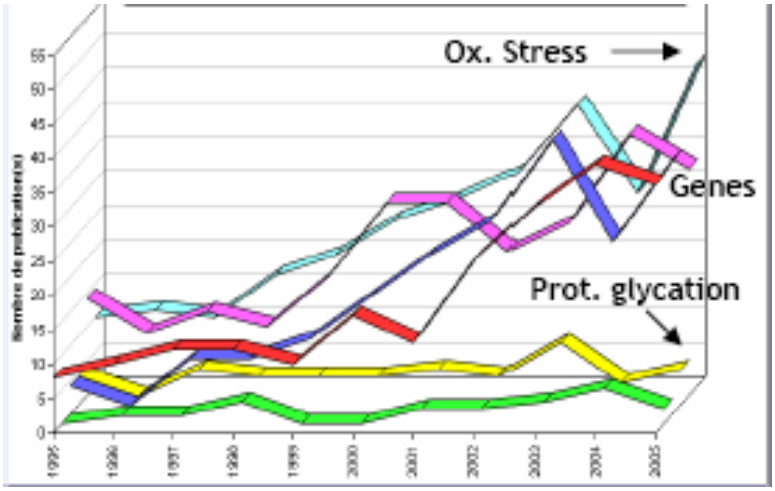
= A domain characterized by:
• Growing importance (Human life expectancy)
• Growing scientific interest (Publications)



Scientific Background

Theories – Molecular Mechanisms

- Oxidative stress
- Alteration of the genome / mutations
- Error catastrophe (L.E Orgel 1963)
- Programmed aging genetic clock
  - Limited replicative potential (Hayflick 1966) (telomere shortening)
- Auto immune responses; deterioration of the immune system
- Accumulation of toxic metabolites
- Formation of cross links



Proposed modern interpretation of Proposed modern interpretation of « old theories

The Bare Essentials

A few major categories of mechanisms:

Oxidative stress : DNA, Proteins, Lipids, Mitochondria, UV

DNA

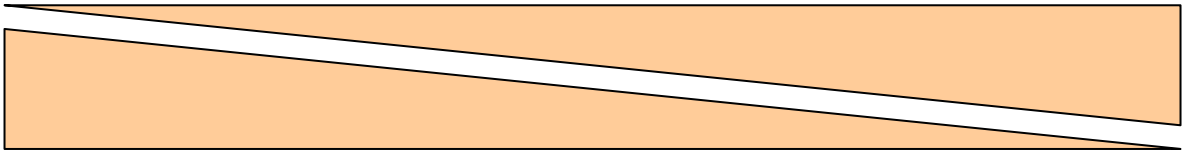
- Repair (mutations)
- Function (expression)
- Replication (telomere length)

PROTEINS

Structure and function post translational modifications

- Glycation (AGE, cross Glycation (AGE, cross-links) links)
- Transglutaminase (cross Transglutaminase (cross-links) links)
- Farnesylation Farnesylation
- Methylation

etc ….
These mechanisms are not independent
Models and experimental approaches



Human Ape | Mouse | Fruit fly (Drosophilia) | Worm (C. elegans) | Yeast

Environmental Approach
(multiparameter)

- Social sciences

  gerontology
  medicine

- Genetics
  centenarians
  diseases (premature aging)

- Biology
  organotypic cultures
  reconstructed tissues

Focal Approach
(a single parameter)

= Molecular biology - Genetics

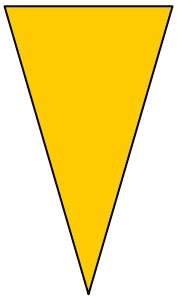
- Transgenic animals
- Transfected cells

Longevity genes

Species		Gene / Function	Genetic Modification used	Human homolog / Human gene
Yeast		SIR2 Deacytylase - NAD	Mutation Overexpression	Sirt 1 Sirt 6 (Sirtuins (↗)
Caenorhabditis elegans		DAF2	Homolog to human Insulin receptor	IGF -1 / insulin receptor (↘)
Drosophila melanogaster		Superoxide dismutase catalase	Overexpression	
Humans	Werner			Helicase
	Progeria			Lamin A (Progerin)
	Xeroderma			XP genes
Cultured Human Cells Replicative senescence		Tert / Telomerase	Overexpression	

Industrial background

Large Companies



Small Companies

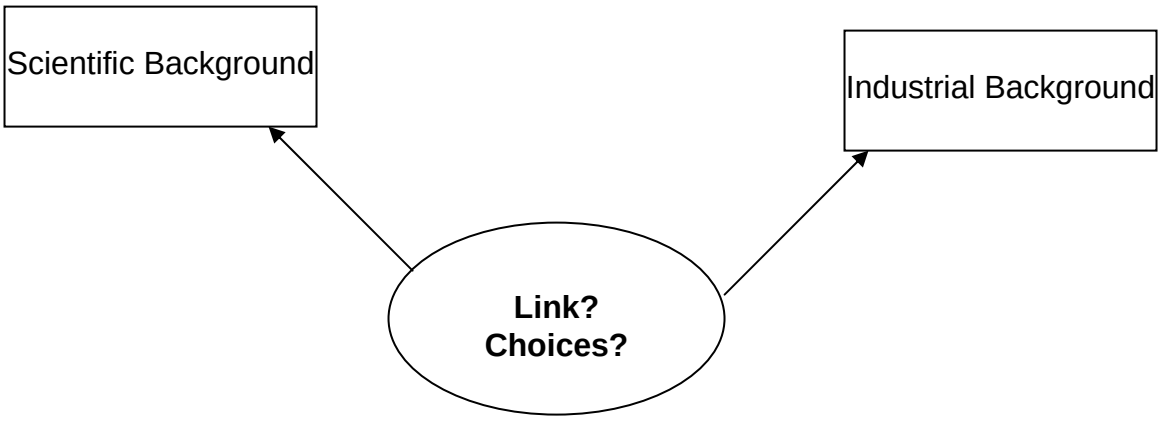
All with a common logic of industry

- **To consider**

  The market | size
  severity / importance

- **For**

  Benefit | to make money
  to grow bigger



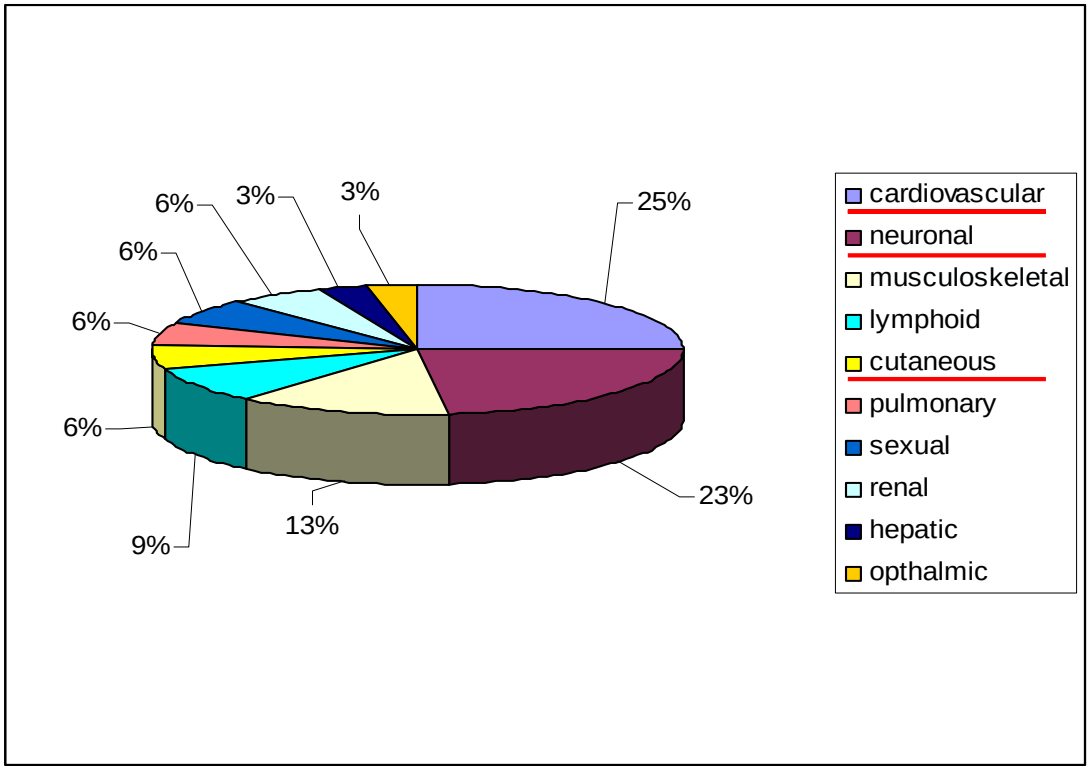
Industrial Relevance

1/ Classical views

2 extremes situations

- Pharmaceutical companies

→ Major domains and targets for new molecules / treatment



- Biotech / start -up companies

  - a finding / concept / mechanism
  - a single therapeutical goal
  - search for new development

Ex : Genetic studies in yeast (L. Guarente)

Life span mutants
SIR genes
Sirt genes in humans (sirtuins)
Sirtris pharmaceuticals for activators like resveratrol

Or replicative senescence in culture

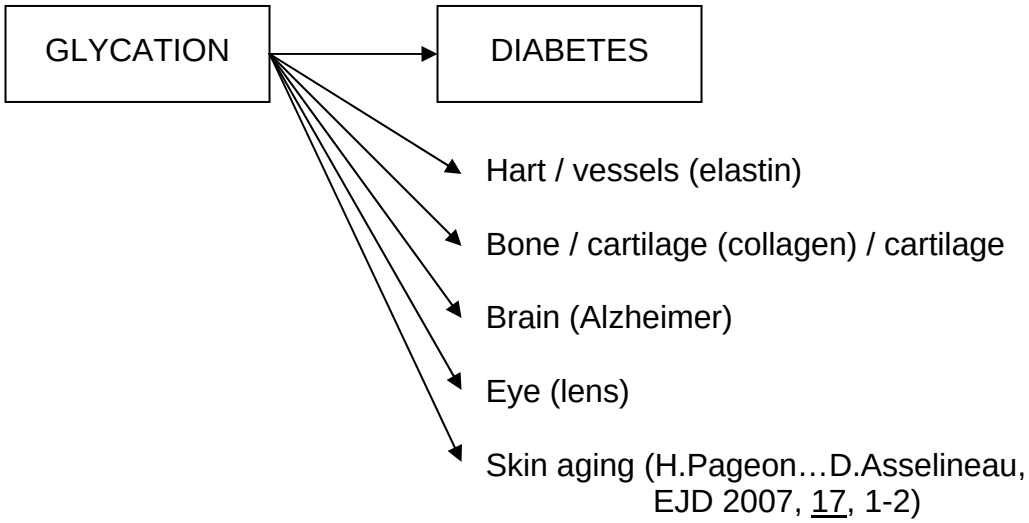
telomerase

GERON

Industrial Relevance

2/ New Developments?

Example 1: Glycation, a recognized mechanism of aging with growing interest



Biotech:

- Alteon
- Farrington
- Dynamis
- Vasix

Cosmetic Industry:

- E. Lauder
- L'Oréal

Longevity → Pentosidine accumulation/Lifespan in species (D. Sell, V. Monnier PNAS, 1996, 93, 485-490)

RAGE soluble receptor in plasma

Example 2: Premature ageing

Hutchinson-Gilford Progeria Syndrome (HGPS)

- Hugely severe genetic disease
- Hugely rare (10 individuals = no market)
- Alteration of a nuclear membrane protein = Lamin A (Progerin)
- Defect in farnesylation - processing (lethal)

Considerations:

1/ low levels of farnesylated lamin A in normal (aging) cells?
2/ Farnesyl transferase inhibitors in culture cells → return to normal nuclei

→ **GENERAL VALUE?**

Xeroderma Pigmentosum

- Very severe
- Very rare (< 100 in France)
- Appearance of multiple skin tumours early in life (lethal) provoked by sun/UV exposure
- Defect in DNA repair

Considerations:

XP = DNA repair model
= model for UV hypersensitivity

→ A new way to investigate (normal) photoaging?

Question = Pathology → Physiology (normal ageing) ?
(diseases of general interest of opposed to Cutis laxa specific for skin)

3/ Breakthrough?

Example 1 : Stem Cells

- A rapidly growing field in biology
- Recent findings about flexibility of cells in adult tissues

Application : Tissue regeneration (ex : Osiris)

Questions:

- Do stem cell age?
- Does the stem cell pool decline?
- Common / specific to each type?
  (epithelium cells vs. mesenchymal cells)

→ **A new view of Cellular Ageing**

= maintenance and/or replacement of specific populations

= Activation of resident stem cells

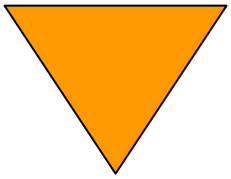
After A. Caplan, Clin. Plast. Surg., 1994, 21, 429-435

3/ Breakthrough?

Example 2 : Skin, a field of increasing interest

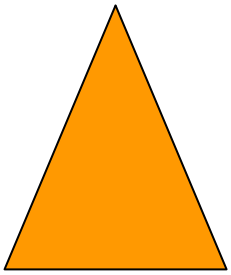
- Skin is the most important organ (quantitatively)
- Skin is the most exposed organ both no extrinsic (UV) or intrinsic aging
- Skin reflects like a mirror apparent and actual ageing (AGE) and health

IMPORTANCE **REQUEST**



- To live longer
- To age later = to stay young
- To remain healthy
- To remain attractive

RELEVANCE **RESPONSE**



- Medicine (HEALTH)
- Pharmacy
- Dermatology
- Cosmetology (BEAUTY)
- Food Industry
- Prevention

Conclusions

The industry is cautions and favours predictable situations

However, the industry should also consider less predictable situations by considering:

- New fields (defined by scientific progress like stem cells)
- New needs (defined by social evolution like skin care)

Contributions:

- M. Kermici and C. Muller
- L. Mery

Acknowledgements:

- C. Olivry

4.9 How can present research initiatives in biogerontology bring maximal added value for Europe?

Professor Stathis Gonos
Director of Research National Hellenic Research Foundation, Dept. of Molecular & Cellular Ageing, Athens, Greece

EU funded projects on Biogerontology

Coordination projects:	MOLGERON (1995) et al.
Research projects (FP-5)	GENAGE (1998) et al.
Research projects (FP-6)	GEHA (2004) et al.
	Zincage (2004) - FOOD

National Centres on Biological Ageing Research in Europe

Inst. Of Biomedical Ageing Research, Innsbruck, Austria

Danish Centre for Molecular Gerontology, Aarhus, Denmark

Italian National Centre of Ageing Research, Ancona, Italy

Institute of Ageing and Health, Newcastle, UK

"Coordination of Ageing Research in Europe (CARE)" Workshop
a joint meeting with "LINKAGE"

Island of Spetses, Greece, May 20-23, 2006
Chairman: Dr. Stathis Gonos

Coordination of EU/FP-6/Health Projects on Biological Ageing (GEHA, MIMAGE, PROTEOMAGE & LIFESPAN)

Aims:

- Coordination of research activities on ageing at European level
- Establishment of virtual "European Institute of Ageing Research"
- Attracting and training young scientists in the field of Biogerontology

Topics covered by the "CARE" workshop:

a. perspectives for FP-7
b. potential of translational ageing research
c. infrastructures, high throughput platforms
d. data bases & biological banks
e. model systems
f. training
g. dissemination activities & ethics
h. future politics on ageing research in Europe
i. future planning for spreading of excellence
j. future planning for funding

LINKAGE:
Coordinator: Dr. Olivier Toussaint, Namur, Belgium

Aims:

a. to identify and help implement common research strategies that generates critical mass and added value from European biogerontolgy research
b. to establish a process that helps bring new researchers into the field from new geographical regions within the wider European community
c. to establish a framework that allows effective integration of research on different species
d. to maximise the opportunities for synergy and interaction between researchers working on such species

Establishing a European Institute for Ageing Research : An Article 169 Initiative?

What is planned already

AGEACTION:
identifying research links & promoting public awareness

12th I.A.B.G. CONGRESS:
promoting communication of scientific excellence

LINKAGE SUMMER SCHOOL:
Promoting training of young scientists

AGEACTION

Aims:

a. develop a stronger sense of common purpose to deliver the knowledge base that will extend health, reduce dependency and improve quality of life for Europe's older people
b. identify links between biological ageing research and various social factors
c. stimulate closer engagement between biological ageing research and industry
d. create closer interactions between biological ageing research and those involved in financial planning
e. provide for Europe's policy makers a clearer understanding of the nature of the ageing process

Newcastle, UK, April 23rd, 2007
Chairman: Prof. Tom Kirkwood

12th Congress of the International Association of Biomedical Gerontology (IABG)

"Molecular Mechansims and Models of Ageing"
Spetses Island, Greece 20-24 May 2007

Chairman: Stathis Gonos (National Hellenic Research Foundation)

Deadline for abstract submission: 08 December 2006

Deadline for registration/accommodation: 09 March 2007

Scientific Programme and on-line application at:
http://www.eie.gr/nhrf/institutes/ibrb/spetses-2007/home.html

Contact: Katerina Theodorelou National Hellenic Research Foundation,
48 Vas. Constantinou Ave.,
Athens 11635, Greece
Email: 12iabg@eie.gr

LINKAGE SUMMER SCHOOL

18-22 September 2007
Les Diablerets, Switzerland
Chairman: Dr. Olivier Toussaint
Organisers: Markus Bucher & Béatrice Rayet

SECTION 5

WORKING GROUP THEMES AND RECOMMENDATIONS

5.1 Working Group Themes

Participants attended one of three working groups which were themed as follows:

Group 1
How can demography profit from biogerontology and *vice versa*?

Chair: Beatrix Grubeck-Loebenstein (Institute for Biomedical Aging Research of the Austrian Academy of Sciences, Innsbruck, Austria)

Note taker: Ourania Kovaiou (Institute for Biomedical Aging Research of the Austrian Academy of Sciences, Innsbruck, Austria)

Participants: Jos Even, Amiela Globerson, Bernard Jeune, Marja Jylhä, Wolfgang Lutz, Michel Poulain, Jean-Marie Robine, Emanuele Scafato, Rafael Solana, and Alan Walker

Group 2
Longevity: How can parameters which affect longevity be defined?

Chair: Pidder Jansen-Dürr (Institute for Biomedical Aging Research of the Austrian Academy of Sciences, Innsbruck, Austria)

Note taker**:** Sam Taylor (University of Sheffield, UK)

Participants:Luc Bonneux, Brian Clark, Eino Heikkinen, Marc Luy, Fiorella Marcellini, Heinz Osiewacz, Graham Pawelec, Beatrice Rayet, Christoph Rott, Olivier Toussaint

Group 3
Genetics: Genes or environment: which is the determining factor to achieve healthy longevity?

Chair: Claudio Franceschi (University of Bologna, Italy)

Note taker**:** Maeve Rea (Queens University of Belfast, Ireland)

Participants:Vladimir Anisimov, Daniel Asselineau, Harry Finke, Stathis Gonos, Antti Hervonen, Eugenio Mocchegiani, Sarah Lewis, Almut Nebel, Ewa Sikora, Antonia Stazi, Cornelia van Duijn

5.2 Working group questions

Working group 1 focused on potential new ways of communication between demographers and biogerontologists. The following question and subquestions were considered:

"How can demography profit from biogerontology and *vice versa*?"

a) Define research topics in which a close interaction between demographers and biogerontologists is of advantage
b) Biogerontologists usually do not know much about methodological approaches and goals in demography and *vice versa*: How can this gap be bridged?
c) How can potential steps defined under (b) be implemented?
d) How can joint studies be funded?
e) Would a joint / central platform administering data bases accessible to both groups of scientists be a useful tool?

Working group 2 focused on the definition of parameters which affect longevity and discussed the design of interdisciplinary research projects on this subject:

"Longevity: How can parameters which affect longevity be defined?"

a) Definition of biological parameters of potential significance for longevity
b) Definition of social parameters of potential significance for longevity
c) Which age groups should be studied?
d) How can factors predicting healthy longevity be defined?
e) Are longitudinal studies a useful tool and how can they be organised using an interdisciplinary approach?
f) Would a platform for data collection and documentation be a good tool?

Working group 3 focussed on the role of genes vs. environment to determine healthy longevity while addressing the following main and subquestions:

"Genetics: Genes or environment: which is the determining factor to achieve healthy longevity?"

a) What is the impact of genes?
b) How useful are animal models to define longevity genes?
c) Definition of environmental factors which influence longevity

d) How can measures, which change the environment of an individual, overrule the influence of genes on longevity?

e) How can such measures be tested, what type of studies are needed?

f) Do we need gene banks for studies on healthy longevity?

5.3 Working group recommendations

The three working groups provided the following recommendations which were presented at the concluding plenary session.

5.3.1 Summary of working group 1 recommendations

5.3.1.1 Definition of research topics in which a close interaction between demographers and biogerontologists are of advantage

- Identify the causes of longevity and understand why some people live longer and in better health than others. This question can be explored at the individual and population level. It is extremely difficult for biologists to study biological markers in populations which is mainly due to the cost of longitudinal studies. However, demographers can provide information to help biologists define their study-groups and collect samples that better reflect population dynamics.

- Nowadays demographers base their work mainly on social predictors. However the effect of biological factors on populations is very important. There is a need to move from demography to bio-demography, which will validate data from other disciplines, i.e. biology

- New parameters can be included in addition to age, sex and health status such as nutrition, education, productivity, labour force participation and biological markers

- Evaluate disability.

5.3.1.2 *Biogerontologists usually do not know much about methodological approaches and goals in demography and vice versa: How can this gap be bridged?*

- Attract and educate newly established scientists: provide adequate training at postgraduate level (Master), have a joint curriculum and promote interdisciplinary interactions

- Organise meetings, workshops and seminars to bring the various disciplines together.

5.3.1.3 *How can potential steps defined under (2) be implemented?*

- A central coordinator; person or institute, i.e. European Institute of Ageing, is needed which could eventually provide education, coordination, financial support

- Multidisciplinary / Holistic approach; demographers could bridge the gap between biomedical and social scientists

- Interdisciplinary longitudinal studies in Europe including participation of demographers, epidemiologists and biogerontologists

- Bridge the gap between studies in animal models and human studies. However not every research topic which uses animal models can be studied in humans and vice versa. Care must be taken when extrapolating data.

5.3.1.4 *How can joint studies be funded?*

- Common projects; define aims, show politicians and funding organisations the impact of new scientific knowledge to society

- Conference with policy makers

- Centres of Excellence

- Lessons from US funding system

- Road map for Coordination and Support action

- Longitudinal studies

5.3.1.5 *Would a joint/ central platform administering data bases accessible to both groups of scientists be a useful tool?*

- Yes.

5.3.2 Summary of working group 2 recommendations

5.3.2.1 *Definition of biological and social parameters of potential significance for longevity*

Biological parameters

- Biological (functional) age versus chronological age. Scientists want to define healthy functional ageing hence there is a need for bio-markers. However, there are many risk factor issues that are not yet addressed. We can't say bio markers are useful at present since they need to be developed.

- It would help politicians to talk about functional age

- There is a difference between wellness (good physical shape) and well-being (including self estimation and other psychological parameters)

Social parameters

- Lifestyle, nutrition, socio economic conditions and their role for life expectancy and life span

- Should have voices from social sciences

- Life style – behaviours such as smoking, alcohol, psychological factors such as stress of the individual

Psychological parameters

- Society and social interactions between members of the population influence the longevity phenotype, in addition to the biological make up of individual members

5.3.2.2 *Interaction between biological, psychological and social parameters*

Status quo

- We talk about healthy ageing but it is better to separate e.g. psychological, mental and physical fitness. It is very difficult to determine social biological and psychological parameters – there is a need to study how they change later on in life and consider what this means. Do they travel together or apart? How is well being linked to genetics?

Critical evaluation of status quo: open questions

- There are 2 levels
  (i) society and its make up impact on levels of society involving concepts such as social networks, social capital and the individual level;
  (ii) behavioural psychological issue involving the two aspects of behaviour and free will (personality and life style) biological level – diseases etc.

- There is a need to move to causal explanations

- Need more precise definitions of biological and social indicators and their interplay

- Parallel or non-parallel ageing of the body and brain – is it coupled or non-coupled – interesting study. Talking about psychological issues and what really happens in the brain contributes to the puzzle of ageing – good window of opportunity. This is clearly linked to biology of ageing

- Many different parameters impacting on longevity e.g. Self estimation, genes – must connect them in some way the question is how? Why do you become very old?

- More complicated physical fitness is measurable but sometimes they don't go in parallel

Proposed future actions

- Define parameters then bring them together with biology – psychology and biology

- Not sure we are ready to do this – we need to talk to each other and end up with not more than 10 parameters

- Coping, networks, lifestyle, income, education, gender issues. May have huge impact on longevity along with biological factors. Problem to compare different factors since they have not been studied in this way.

- Need longitudinal study to enable comparisons – to identify which factors are more important

- Need pilot project then compare with other disciplines

- Lots of different issues that we can take into account but in order to end up with important parameters we need longitudinal studies

- Interdisciplinary project is needed with physical and psychological aspects

5.3.2.3 *Which age groups should be studied?*

- The age range that should be studied depends on the design and goal of individual studies
- It is better to study very old people but prevention studies need to start early – both groups are equally important
- People are living longer which poses a problem for longevity studies
- Should study in accordance to functional issues rather than age groups – we therefore need valid bio-markers
- Ageing starts at inception

5.3.2.4 *How can factors predicting healthy longevity be defined?*

- Factors can be defined by a well prepared interdisciplinary longitudinal study
- Interaction of socio and biological aspects need to be included and given careful consideration during the design stage

5.3.2.5 *Are longitudinal studies a useful tool and how can they be organised using an interdisciplinary approach?*

- Longitudinal studies are a useful tool.
- The group proposed a 2 stage model – A pilot study on multidisciplinary interactions should be carried out which aims to define the terms of interaction between disciplines and to assess the quality of potential outcomes

5.3.2.6 W*ould a platform for data collection and documentation be a good tool?*

- A platform for data collection is an essential tool but its design requires additional thought
- There may be pre-existing knowledge and precedence of the design of the proposed pilot study that needs to be investigated further.

5.3.3 Summary of working group 3 recommendations

5.3.3.1 *What is the impact of genes?*

- Early studies suggested an apparent 25% effect of genes on ageing
- Recent papers (Westendorp and Christensen, 2006) support a consistent effect of genetics in ageing in humans
- In oldest old, genes may have a greater effect, as suggested from twin studies, but power may be affected since numbers are limited
- One problem is the population in which genes are studied. Heritabilty of longevity is much higher in aristocracy than in those in lower social classes.
- Gene effect is context specific
- We should also ask, 'What are longevity genes doing in younger people? And what are pathways doing in younger people? Is there altered functional activity?'

5.3.3.2 *How useful are animal modes to define longevity genes?*

- Animal models can help us to understand genes which may be important in ageing. But fixed environments in which animals are kept or specific strains of animals bred for fecundity for example, are unlikely to demonstrate the complex systems which exist in humans.
- IGF1 seems important in animals but studies have been less impressive and not really replicated in humans
- Immune studies in humans can not fix a static environment as is the case for laboratory animals

5.3.3.3 *Definition of environment factors which influence longevity*

- Gene studies must take into account our environment, since our new non non-harsh environment may alter gene up-regulation. In Russia, life style is affecting life expectancy within a short time frame.
- Laboratory mice selected for fecundity and rapid generational studies may have gene pools which are not typical
- Hirokawa said laboratory mice live in conditions where the genotype may be fixed and the environment is fixed and therefore not typical of wild state

- Mocchegiani - Contradictory data exist in gene studies so basic phylogenetic genes should be considered most important (public genes) and also used to guide major pathway studies.

- Gonos - Although genes in humans were not selected for either ageing or longevity, they do have an impact. Genes therefore may have a role later in life, say after the age of 60 years.

- Animal model systems may point us to genetic or public pathways involved in longevity but these are not necessarily genes which are involved in humans.

- There are not many parallels between animal models and human systems at present

- Mitochondrial and nuclear genes work together and should not be considered in isolation. Also haplotype blocks of genes work together and these may affect protein expression. So gene combinations are likely to be important in longevity.

- In addition epigenetic changes may be important but are hard or impossible to study in humans

- Post mitotic cells help us to produce memory but this means that humans risk damage. Some animal models such as C. Elegans and Drosophila are post mitotic organisms and therefore may not be very useful as mirrors of the human model.

- Environment in humans is the driving force for change and therefore we can expect to find population-specific genes especially in the mitochondrial haplotype

- It is important to remember that today's centenarians have lived in a very different environment

- Genes of today's centenarians may not be the genes useful to study in future human ageing but may be useful for emerging populations such as in Africa

- Today in one lifespan the genetic background has changed from what it was at age 10 years compared with present day 80 year olds

- We do not know if these cohort genes are the longevity genes of the future

- Beneficial or conversely damaging genes also may depend on a dose effect

- Supercentenarians in East and West Germany have equalised life expectancy in 10 years. The separation of Germany is a natural experiment. What is the effect, is it environmental ? Or are there social effects or both?

- Circadian cycle or clock genes produces different effects on genes in old and young animals. Too much light is harmful. Old mice die when exposed to eastern jet lag. 'Go west, old mouse'!

5.3.3.4 *Measures which change the environment of an individual overrule the influence of genes on longevity?*

- Change of immune status due to nutrition, e.g. olive oil can change/modify the immune phenotype of an individual.
- Strong gender effect which is largely still unexplained
- Offspring of centenarians from Boston show a cardiovascular risk profile which is better (also BP and lipid level) suggesting that life style factors such as exercise, obesity and smoking control should be first measures of control. Not yet shown that exercise can increase lifespan
- Good phenotype is important
- Light environment alters life span and is shorter in constant light.
- Genes which previously were beneficial in harsh life conditions may not be helpful in today's conditions, but effect may change with age ie grelin in famine/obesity.

5.3.3.5 *How can these measures be tested?*

- Biomarkers for ageing and individual differences are needed but can we identify these factors and use them to modify the role of genes?

Effect of BP control, exercise and smoking are highly important and can be measured

- Different countries' models may be able to demonstrate the effect of caloric restriction
- It is more likely that nutrition can be altered and affect genes.
- Easier to change exercise role and control smoking

Use of artificial//natural compounds

- Companies are interested in looking for calorific restriction mimetics ie metformin

- Restraverol, seems useful in animals, but would we be able to use it in human studies – equivalent dose is 10 bottles of wine!

Other tools

- Follow-up studies should be looking for biomarkers to help inform us for future studies
- Offspring studies already in place may help and maybe proteomics could be useful and could guide us for future biomarkers
- ECCHE studies in twins can help guide gene/environment studies and biomarkers
- It may be fruitful to analyse cancer/gene environment to help model ageing genes, as in Doll and Peters book of 20 years ago. Similar models and pathways may exist between ageing and cancer.

5.3.3.6 *Biobanks for studies on healthy longevity*

- Pooling for existing resources in other longitudinal studies would save money and stop re-inventing the wheel
- Many compounds are known to modify the proteosome, which can either speed up or reduce cellular effective metabolism. Could such modifying compounds be used in a pilot and in parallel with a longevity follow-on study?
- Signatures of medical conditions could be identified in cohorts within longevity studies by using microarrays but could also be found by studying gene/phenotype questionnaire information and which would provide valuable information
- Negative genes in longevity should be explored and the opportunity used to compare the environment in those individuals who live long and ask questions as to what differences exist?

Appendix A

LIST OF PARTICIPANTS

NAME	ORGANISATION	ADDRESS	COUNTRY
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Appendix B

LIST OF PARTNERS AND NATIONAL COORDINATORS

NAME	ORGANISATION	COUNTRY
Dr Kenneth Abrahamsson	Swedish Council for Working Life & Social Research	Sweden
Dr Irit Allon	Israeli Ministry of Health	Israel
Dr Claudine Attias-Donfut	Caisse Nationale D'Assurance Viellesse	France
Dr Martin Barth	Projektträger im DLR (PT-DLR)	Germany
Kerstin Carsjo	Swedish Council for Working Life & Social Research	Sweden
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Appendix C

GLOSSARY OF DEFINED ACRONYMS

AGE	-	Advanced Glycation Endproducts
AGEACTION	-	Changing Expectations of Life
APOE	-	Apolipoprotein E Genotyping
ASP	-	Affected Sib Pair
ATP	-	Adenosin-triphoshate
BBSRC	-	Biotechnology and Biological Sciences Research Council
EPSRC	-	Engineering and Physical Sciences Research Council
ERA-AGE	-	European Research Area in Ageing
ESRC	-	Economic and Social Research Council
FLARE	-	Future leaders of Ageing research in Europe
FP6	-	Framework Programme 6
FP7	-	Framework Programme 7
GEHA	-	Genetics of Healthy Ageing
GENAGE	-	Cloning and expression of genes involved in human senescence and longevity
IABG	-	Congress Of The International Assocation Of Biomedical Gerontology
IPR	-	Intellectual Property Rights
LD	-	Linkage Disequilibrium
LINKAGE	-	Coordination and consolidation of European biogerontology: en route towards formation of a European college of biogerontology

MIMAGE	-	Role of Mitochondria in Conserved Mechanisms of Ageing
MOLGERON	-	Molecular Gerontology
MRC	-	Medical Research Council
MTDNA	-	Mitochondrial DNA
PROTEOMAGE	-	Molecular Mechanisms of Healthy Ageing
QOL	-	Quality of Life
RAGE-	-	Receptor for Advanced Glycation Endproducts
SIR	-	Silent Information Regulator
SMR	-	Standard Mortality Ratio
XP	-	Xeroderma Prigmentosum