Diagnostics and Healthy Ageing

Graham Armitage
on behalf of Michael Catt

Wednesday, 3 Apr 2019: 10:40 – 11:00
Level 1 Conference Arena

European Photonics Roadshow Newcastle
3 Apr 2019 - 4 Apr 2019 / Newcastle-upon-Tyne, United Kingdom

https://photonics-roadshow-newcastle.b2match.io/agenda
Grand Challenges

- Harness the power of innovation to help meet the needs of an ageing society.
- Put the UK at the forefront of the artificial intelligence and data revolution;
- Maximise the advantages for UK industry from the global shift to clean growth;
- Become a world leader in shaping the future of mobility
Healthy Ageing Mission

“Second, through our healthy ageing grand challenge, we will ensure that people can enjoy five extra healthy, independent years of life by 2035, whilst narrowing the gap between the experience of the richest and poorest”.


www.ncl.ac.uk/nica
**Broken Limits to Life Expectancy**


http://www.nature.com/scitable/content/19786/10.1038_451644a-f1_full.jpg

www.ncl.ac.uk/nica
Figure 0-1: Estimated and projected age structure of the United Kingdom population, mid-2012 and mid-2037

## Consumer perceptions of Health Related Changes with Age

### Table 3: Participant Experience of Health-Related Changes and Attribution of Experienced Changes to Aging (n = 2,033)

<table>
<thead>
<tr>
<th>Health-related change</th>
<th>Frequency (%)</th>
<th>Have experienced health-related change</th>
<th>Attributed experienced change to aging</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Weight problems</td>
<td>28.2</td>
<td></td>
<td>13.1</td>
</tr>
<tr>
<td>2) Sleep problems</td>
<td>35.7</td>
<td></td>
<td>19.8</td>
</tr>
<tr>
<td>3) Back problems or slipped disc</td>
<td>29.5</td>
<td></td>
<td>14.2</td>
</tr>
<tr>
<td>4) Painful joints</td>
<td>55.4</td>
<td></td>
<td>40.8</td>
</tr>
<tr>
<td>5) Not being mobile</td>
<td>27.0</td>
<td></td>
<td>19.5</td>
</tr>
<tr>
<td>6) Loss of balance</td>
<td>20.4</td>
<td></td>
<td>12.8</td>
</tr>
<tr>
<td>7) Loss of strength</td>
<td>44.5</td>
<td></td>
<td>39.3</td>
</tr>
<tr>
<td>8) Slowing down</td>
<td>71.0</td>
<td></td>
<td>65.4</td>
</tr>
<tr>
<td>9) Cramps</td>
<td>25.0</td>
<td></td>
<td>17.6</td>
</tr>
<tr>
<td>10) Bone or joint conditions</td>
<td>42.8</td>
<td></td>
<td>31.6</td>
</tr>
<tr>
<td>11) Cardiac problems</td>
<td>24.8</td>
<td></td>
<td>13.1</td>
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<tr>
<td>12) Ear or hearing problems</td>
<td>25.6</td>
<td></td>
<td>18.8</td>
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<tr>
<td>13) Vision and eye sight changes</td>
<td>44.4</td>
<td></td>
<td>37.4</td>
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<tr>
<td>14) Respiratory problems</td>
<td>20.3</td>
<td></td>
<td>12.2</td>
</tr>
<tr>
<td>15) Foot problems</td>
<td>19.3</td>
<td></td>
<td>12.2</td>
</tr>
<tr>
<td>16) Depression</td>
<td>13.9</td>
<td></td>
<td>6.6</td>
</tr>
<tr>
<td>17) Anxiety</td>
<td>16.2</td>
<td></td>
<td>7.7</td>
</tr>
</tbody>
</table>

Perceptions associate with common biomarkers that change with age

### Table 1: Sample Characteristics (n = 2,033)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean Age (years) (SD)</th>
<th>Gender (%)</th>
<th>Marital status (%)</th>
<th>Functional Disability (HAD-Q-D) (M ± SD)</th>
<th>Depression (HADS-D) (M ± SD)</th>
<th>Comorbidity Index (CM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>74.1 (6.8)</td>
<td>43%</td>
<td>44%</td>
<td>0.50 (0.77)</td>
<td>5.54 (2.85)</td>
<td>0.79 (0.95)</td>
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</tbody>
</table>

**Perceptions in community dwelling Irish adults**

*BMC Geriatrics 2007, 7:9*
Our experience of the world changes ...

**Mental Performance**

- Extended Cognitive Assessment: F.A. Huppert et al 2005

**Accommodation**

- Accommodative Amplitude (D)
  - $y = 0.26x + 12.99$
  - $r^2 = 0.63$, $p < 0.05$
  - $n = 66$

**Hearing**


**Touch**

- 30 Hz

**Grip**

- Grip Strength

**Olfaction**

- Small identification test scores

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driven by random molecular damage
Healthy tissues

Compromised tissues

Protection

Genetics

Repair

Hygiene
Healthy diet
Physical activity
Relaxation & sleep
Weight control

Damaging Environment
Infection, pollution
UV irradiation
Stress
Unhealthy diet
Overweight
Poor lifestyle
Smoking

Cognition
Neural
Digestion
Renal
Endocrine
Cardiovascular
Sensory
Musculoskeletal
Respiratory
Immune
Reproductive
Skin / Barrier
Microbiome?

www.ncl.ac.uk/nica
Healthy Diet
Adequate Physical Activity
Good sleep

Low Stress
Good Emotional Wellbeing
Good Hygiene, moderate alcohol

Smoking
Poor Diet
Poor Hygiene
Sedentarianism
Excessive Alcohol
Lack of sleep

High Stress
Poor Emotional Wellbeing

‘Healthy Homeostasis’

‘Homeostatic Drift’/
Reduced Responsiveness

Metabolic Dysregulation

Metabolic Disease

Inflammation
Oxidative Stress
Impaired Repair
/Regeneration
Altered Energy Metabolism
Elevated Fasting Glucose

Elevated
Blood Pressure
Blood Cholesterol
LDL, TG
Glucose Intolerance
Chronic Inflammation
Mitochondrial Dysfunction

Hypertension
Hyperlipidaemia
Hyperglycaemia
Sarcopenia
Osteopenia
Endothelial Dysfunction

Unhealthy Appearance
Lack of Energy
Stress
Lowered Immunity

Accelerated Ageing
Muscle/Bone Loss
Low Grip Strength
Accelerated Loss of
Cognitive Performance
Sensory/Functional Capability
Obesity

CVD
Dementia
Diabetes
Frailty
Stroke
AMD
Osteoporosis
. . .

**not a one-way street!**
**But biomarkers can/must inform action**

*biomarkers of multisystem function?*
As we can see from this diagram published in the Lancet, people can accumulate a number of health issues over the life course. By the age of 50, 50% of us will be living with at least one condition, 20% with 2 conditions, and around 10% living with three. But by the age of 80, the proportions jump considerably – 90% of 80 year old’s will be living with at least 1 condition, 30-40% are living with 3 or more. But there will still be around 10% of people over 85 who do not have any health conditions at all.
No one has perfect medical health at age 85. Yet, 78% rated their health compared with others of the same age as “good” (34%), “very good” (32%) or “excellent” (12%).

Collerton et al *British Medical Journal* 2009
## Lifestyle factors driving multimorbidity

<table>
<thead>
<tr>
<th>Percentage of patients with the row condition who also have the column condition</th>
<th>Percentage who only have the row condition*</th>
<th>Mean No of conditions in people aged &lt;65 years with row condition</th>
<th>Mean No of conditions in people aged ≥65 years with row condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease</td>
<td>8.8</td>
<td>3.4</td>
<td>4.4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>21.9</td>
<td>2.5</td>
<td>3.6</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2.8</td>
<td>3.9</td>
<td>5.6</td>
</tr>
<tr>
<td>Stroke/transient ischaemic attack</td>
<td>6.0</td>
<td>3.6</td>
<td>4.8</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>6.5</td>
<td>3.3</td>
<td>5.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17.6</td>
<td>2.9</td>
<td>6.5</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>14.3</td>
<td>2.8</td>
<td>4.5</td>
</tr>
<tr>
<td>Painful condition</td>
<td>12.7</td>
<td>3.1</td>
<td>4.3</td>
</tr>
<tr>
<td>Depression</td>
<td>25.4</td>
<td>2.6</td>
<td>4.9</td>
</tr>
<tr>
<td>Dementia</td>
<td>5.3</td>
<td>4.1</td>
<td>4.6</td>
</tr>
</tbody>
</table>

* Percentage who do not have one of 39 other conditions in the full count

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**Need for integrated care and integrated biomarker assessment?**
Closed Loop Medicine Ltd

• A 21st century approach to patient care would capitalise upon our understanding of drugs, diagnostics, precision medicine, remote monitoring and digital health, combining these with a real-time feedback process to optimise patient outcomes.

• This is fundamentally required as we move to from Products → Solutions and from paid interventions towards value based and outcomes based pricing.

• Care pathways of the future will require integration across different modalities
Remainder of this talk will focus on biomarkers relevant to prevention...
NICA BRC: Sustaining Independence?

*Based on continuing research carried out at the Newcastle University Institute for Ageing
© 2014 Core/Johnson/Jagger
A few minutes on the metro

Expected age at disability onset for 55 yr old

74.6
66.1
72.2
69.1
72.7
64.5
Factors across life associated with remaining free from functional limitations despite lifelong exposure to socioeconomic adversity.

<table>
<thead>
<tr>
<th>Prevalence of functional limitations in</th>
<th>high,</th>
<th>intermediate</th>
<th>low adversity</th>
</tr>
</thead>
<tbody>
<tr>
<td>men</td>
<td>44%,</td>
<td>30%</td>
<td>23%</td>
</tr>
<tr>
<td>women</td>
<td>61%,</td>
<td>55%</td>
<td>49%</td>
</tr>
</tbody>
</table>

Compared with the other high adversity group, the resilient group had a lower prevalence of childhood illness (12% vs 19%) obesity throughout ages 43-64 (70% vs 55%).

Partially adjusted models also showed
  higher adolescent self-management,
  lower neuroticism,
  higher prevalence of volunteer work and physical activity (age 60-64)
and lower prevalence of smoking (age 43) in the resilient.

Marital status and contact frequency were not associated with resilience.

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What leads to exceptional healthy survival?: mid-life risk factors

Contribution of six mid-life factors for healthy survival to old age, free of cancer, CVD, COPD, Parkinson, DM, cognitive and physical impairment.

**Mid-Life Risk Factors**
- Hyperglycaemia
- Hypertension
- Overweight
- High triglyceride
- High alcohol intake
- Ever smoker
- Low grip strength
- Low education
- Unmarried (male)

*Figure 2. Probability of Exceptional Survival by Age at Follow-up*

All participants were Japanese American men followed from baseline (1965-1968) to the end of 2005. Among those alive at a specified age, exceptional survival was defined as absence of 6 major chronic diseases and absence of physical and cognitive disability. Survival risk score indicates number of risk factors (hyperglycemia, hypertension, high alcohol consumption, low education, overweight, high triglyceride level, low grip strength, ever smoker, and unmarried). Error bars indicate likelihood ratio-based 95% confidence intervals.
AAIC: Lancet Commission reveals a third of cases of dementia may be preventable – Alzheimer’s Society comment

Dementia prevention, intervention, and care


The Lancet Commissions
http://www.thelancet.com/commissions/dementia2017
A proposed panel of biomarkers of healthy ageing

Jose Lara, Rachel Cooper, Jack Nissan, Annie T Ginty, Kay-Tee Khaw, Ian J Deary, Janet M Lord, Diana Kuh and John C Mathers

Fig. 2 Proposed panel of biomarkers of healthy ageing

Fig. 4 | Ageing is characterized by mechanistic hallmarks that contribute to ageing to different extents in different organisms, and in different cell types within an organism. Hallmarks can influence each other both within cells and at a distance. Different interventions to prevent or ameliorate symptoms of ageing can affect different groups of hallmarks, and different groups of hallmarks can contribute to the aetiology of specific age-related phenotypes and diseases.
### Genetic loci and age related phenotypes

| Loci emerging from GWAS of discrete and continuous lifespan-related phenotypes in human studies | Replication |
|---|---|---|---|---|
| **Closest gene(s)** | **Discrete phenotypes** | **Continuous phenotypes** | **Within publication** | **Between publications** | **Associations with age-related diseases** |
| **APOE**<sup>141-145</sup> | Age ≥ 99th percentile; age ≥ 90 years; age ≥ 100 years; parental age ≥ 90th percentile | Parental lifespan; age attained by parents | Yes | Yes | Multiple |
| **CHRNA3 and CHRNAS**<sup>143,144</sup> | Parental age ≥ 90th percentile | Parental lifespan; age attained by parents | Yes | No | Cancer |
| **LPA**<sup>143,144</sup> | Parental age ≥ 90th percentile | Parental lifespan; age attained by parents | Yes | No | Multiple |
| **CDKN2A and CDKN2B**<sup>143</sup> | Parental age ≥ 90th percentile | Parental lifespan; age attained by parents | Yes | No | Multiple |
| **USP42**<sup>141</sup> | Age ≥ 99th percentile | None | Yes | No | None |
| **TMTC2**<sup>141</sup> | Age ≥ 99th percentile | None | Yes | No | None |
| **ILG**<sup>145</sup> | Age ≥ 100 years | None | No | No | Inflammatory |
| **ANKRD20A9P**<sup>145</sup> | Age ≥ 90 years | None | No | No | None |
| **LINCO2227**<sup>142</sup> | Age ≥ 90 years | None | Yes | No | Cardiovascular |
| **FOX03A**<sup>146</sup> | Age ≥ 90 years | None | Yes | No | None |
| **RAD50 and IL13**<sup>147</sup> | Age ≥ 90 years | None | No | No | None |
| **MC2R**<sup>143</sup> | Parental age ≥ 90th percentile | None | Yes | No | None |
| **USP2-AS1**<sup>143</sup> | Parental age ≥ 90th percentile | None | Yes | No | None |
| **HLA-DQA1 and HLA-DRB1**<sup>143,144</sup> | None | Parental lifespan; age attained by parents | Yes | No | Inflammatory |
| **ATXN2**<sup>143</sup> | None | Age attained by parents | No | No | Multiple |
| **FURIN**<sup>143</sup> | None | Age attained by parents | No | No | Cardiovascular |
| **EPHX2**<sup>143</sup> | None | Age attained by parents | No | No | Cancer |
| **PROX**<sup>143</sup> | None | Age attained by parents | No | No | None |
| **CELSR2 and PSRC1**<sup>143</sup> | None | Age attained by parents | No | No | Cardiovascular |

We included only studies that showed one or more genome-wide significant associations with lifespan-related phenotypes (P < 5 × 10⁻⁸), with the exception of the RAD50 and IL13 locus (P = 5.42 × 10⁻⁸), which was based on the number of linkage disequilibrium-independent markers on the genotyping array (Immunochip) used in the study<sup>142</sup>. We excluded studies that were based on results from cohorts that were also included in more recent and larger studies. ‘Within publication’ refers to replication of a locus in different cohorts within the same publication. ‘Between publications’ refers to replication of a locus in different cohorts from different publications.
Age-related frailty and its association with biological markers of ageing

Arnold Mitnitski, Joanna Collerton, Carmen Martin-Ruiz, Carol Jagger, Thomas von Zglinicki, Kenneth Rockwood, and Thomas B. L. Kirkwood

analyzed baseline data and up to 7-year mortality in the Newcastle 85+ Study (n = 845; mean age 85.5).

The Frailty Index by Biomarkers (FI-B) combined 40 biomarkers of cellular ageing, inflammation, haematology, and immunosenescence.

The Kaplan-Meier estimator was used to stratify participants into FI-B risk strata.

Inflammation biomarkers from set of 40 covering inflammation, haematology and immunosenescence

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Cut Point</th>
<th>N</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>High sensitivity C-reactive protein (mg/L)</td>
<td>&gt;25 High</td>
<td>737</td>
<td>37</td>
</tr>
<tr>
<td>Leptin (ng/mL)</td>
<td>&lt;40 Low</td>
<td>214</td>
<td>495</td>
</tr>
<tr>
<td>Adiponectin (μg/mL)</td>
<td>&gt;20 High</td>
<td>657</td>
<td>83</td>
</tr>
<tr>
<td>Homocysteine (μmol/L)</td>
<td>&gt;30 High</td>
<td>422</td>
<td>35</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>&lt;40 Low</td>
<td>365</td>
<td>397</td>
</tr>
</tbody>
</table>

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4499935/

Example? Biomarker profiles might identify at risk individuals for intervention and map progression?
National Innovation Centre for Ageing

Home / Environment monitoring

Clinical Insights & Evidence
Behaviour change
Service re-design

Automated coaching

Real time feedback

Devices screening, monitoring & feedback

Cloud/Internet

Visualisation
Data analytics & AI

https://www.eithealth.eu/vitality

www.ncl.ac.uk/nica
National Innovation Centre for Ageing

- NICA for Business
- NICA Insights for Ageing
- NICA Teaching and Learning Hub
- NICA as a catalyst for economic growth

www.ncl.ac.uk/nica
Thank You
How broad a view to take of ‘diagnostics’?

Dahl gren and White head model of the determinants of health
Low physical activity, high television viewing and poor sleep duration cluster in overweight and obese adults; a cross-sectional study of 398,984 participants from the UK Biobank
Sophie Cassidy, Josephine Y. Chau, Michael Catt, Adrian Bauman and Michael I. Trenell

Those who are obese are two to five times more likely to display an ‘unhealthy phenotype’ compared to normal weight adults. Current guidelines for obesity recommend pharmacological intervention to begin only once lifestyle have been implemented. Despite this emphasis on lifestyle, the results from the UK Biobank suggest that physical activity, sedentary behaviour and sleep remain significant unaddressed risk factors for obesity. This highlights the need for more effective strategies, which target multiple lifestyle behaviours, to prevent the rising tide of obesity.
In 2040, Japan, Singapore, Spain, and Switzerland had a forecasted life expectancy exceeding 85 years for both sexes, and 59 countries including China were projected to surpass a life expectancy of 80 years by 2040.
Factors across life associated with remaining free from functional limitations despite lifelong exposure to socioeconomic adversity.

Kok AAL1,2, Stafford M3, Cosco TD4,5, Huisman M6,2, Deeg D6, Kuh D7, Cooper R7.

Author information

Abstract

BACKGROUND: There are substantial socioeconomic inequalities in functional limitations in old age. Resilience may offer new insights into these inequalities by identifying constellations of factors that protect some individuals from developing functional limitations despite socioeconomic adversity.

METHODS: Data from 1973 participants in the Medical Research Council National Survey of Health and Development (Great Britain), followed from birth until age 60-64, were used. Functional limitations were defined as reporting difficulty with at least 1 of 16 activities at age 60-64. Lifetime socioeconomic adversity was based on socioeconomic trajectories, categorised into three adversity levels. Analysis of covariance and regression models were used to compare psychosocial factors and health-related behaviours between a 'Resilient' group (high adversity but no functional limitations) and five groups with other combinations of adversity and limitations.

RESULTS: Prevalence of functional limitations in high, intermediate and low adversity groups was 44%, 30% and 23% in men, and 61%, 55% and 49% in women, respectively. Compared with the other high adversity group, the resilient group had a lower prevalence of childhood illness (12% vs 19%) and obesity throughout ages 43-64 (70% vs 55%). Partially adjusted models also showed higher adolescent self-management, lower neuroticism, higher prevalence of volunteer work and physical activity (age 60-64) and lower prevalence of smoking (age 43) in the resilient. Marital status and contact frequency were not associated with resilience.

CONCLUSION: Results suggest protection against childhood illness, health-behavioural factors and self-regulation as targets for interventions across life that may particularly benefit those with long-term exposure to socioeconomic adversity.

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Trends in gene expression with age: inflammation

Pathways Altered In Ageing:
- TNF-α
- IGF
- MAPK
- IL-6
- P53
- TGF-β
- IFN-γ

Complex patterns of gene expression in human T cells during *in vivo* aging

Daniel Remondini, Stefano Salvioli, Mirko Francesconi, Michela Pierini, Dawn J. Mazzotti, Jonathan R. Powell, Isabella Zironi, Ferdinando Bersani, Gastone Castellani and Claudio Franceschi

https://pubs.rsc.org/en/Content/ArticleLanding/2010/MB/c004635c#divAbstract
National Innovation Centre for Ageing

Home / Environment monitoring

Clinical Insights & Evidence
- Behaviour change
- Service re-design

Automated coaching

Real time feedback

Devices screening, monitoring & feedback

Cloud/Internet

Visualisation
- Data analytics & AI

https://www.eithealth.eu/vitality

www.ncl.ac.uk/nica