THE EFFECTS OF GENETIC HEALTH RISKS ON PERSONAL EXPECTED LONGEVITY, INSURANCE COVERAGE, AND RETIREMENT DECISIONS*

* THIS POWERPOINT IS A SHORTENED ONLINE VERSION

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NETSPAR – BIG DATA EN DATA SCIENCE IN HET PENSIOENDOMEIN
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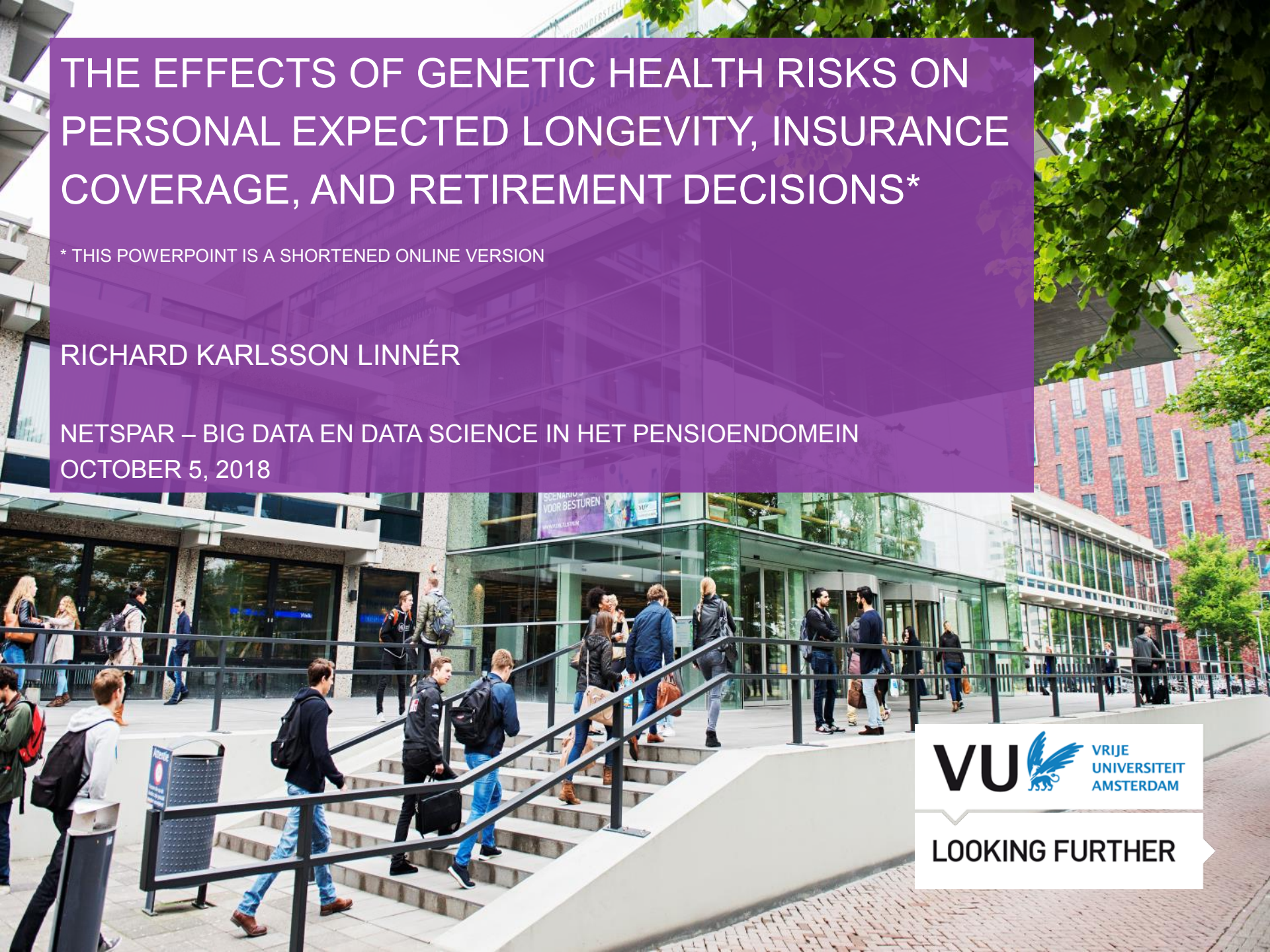

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LOOKING FURTHER

ABOUT ME

- BSc & MSc in Economics – Linköping University, Sweden
- PhD candidate – Vrije Universiteit
  - Supervisor: Prof. Dr. Philipp Koellinger
  - Expect to defend thesis early 2019
- Postdoctoral researcher – Vrije Universiteit

- My research interests include the genetic and environmental basis of human behavior and (economic) decision-making

- Junior researcher in the Social Science Genetic Association Consortium (SSGAC)
  - PIs: Dan Benjamin (USC), David Cesarini (NYU), and Philipp Koellinger (VU)

AGENDA

1. Introduction to expected longevity
2. Health information and retirement decisions
3. The ongoing revolution in the molecular-genetic study of common medical conditions
4. Overview of our Netspar project

INTRODUCTION

- Life-cycle decisions are partly based on how long people expect to live—their personal *expected longevity (EL)*[1]
- Importantly, EL has been shown to be a good predictor of actualized longevity
  - > People *do* have an understanding of their lifestyle and health status
  - > Not entirely driven by optimism/pessimism/irrationality

- Overall, genetic factors explain 25–30% of the population variation in longevity, and increasingly so with age[2]
- Thus, information about genetic health risks should be important for the formation of EL, and in turn life-cycle decisions

1 Benítez-Silva & Huan. (2008). *Journal of Health Economics*.
2 Brooks-Wilson. (2013). *Human Genetics*; Ganna et al. (2013). *Human Genetics*; Pilling et al. (2016). *Ageing*.

ACCESS TO GENETIC HEALTH INFORMATION

- Genomic medicine and direct-to-consumer genetic testing will drastically increase the amount of genetic health information available to patients and consumers

https://www.sciencenews.org/article/review-genetic-tests-23andme-veritas-genos-health-comparison
https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm551185.htm
https://blog.23andme.com/health-traits/major-milestone-consumer-health-empowerment/
https://geneticoncept.com/
https://ghr.nlm.nih.gov/primer/dtcgenetictesting/directtoconsumer

INTEGRATION OF HEALTH INFORMATION

- Individuals have been shown to integrate newly acquired health information, accurate or not, in the formation of their expectations[1]
- Thus, it is likely that the increased access to genetic health information will lead to changes in economic and financial behavior with respect to old age and retirement
- Examples include:
  - Insurance coverage and annuities
  - Preferred risk in portfolio and investment horizon
  - Labor supply, (pension) savings rate, and age at retirement
  - Allocation of consumption and withdrawal of pension funds

1 Smith et al. (2001). *American Economic Review*; Nielsen et al. (2001). *Journal of Consumer Policy*; Francke et al. (2013). *PeerJ*.

GENETIC HEALTH RISKS

- Today, genetic health risks are typically latent and unobserved by most asymptomatic individuals
  - Can be inferred from family history, however with considerable noise
  - Currently, the predictive accuracy of direct-to-consumer testing is questionable
    - Varies strongly across conditions
- In the future, the *true* individual genetic risk will be known if:
  - *All* health and longevity related genetic risk factors have been discovered
  - Individuals undergo "comprehensive" genotyping/sequencing
- Thousands of rare monogenic disorders already mapped to genes[1]
  - Although such disorders have detrimental consequences for the affected individuals, because of their low prevalence in the population they jointly explain little of the overall variation in health and longevity

1 Duncan et al. (2014). Genes;

COMMON DISORDERS AND POLYGENIC RISK

- Instead, common non-communicable medical conditions account for more than 60% of total deaths worldwide[1]
  - The largest contributors are cardiovascular diseases and cancer, which account for 30% and 13% of total deaths, respectively
  - Common mental and neuropsychiatric disorders, and SUDs are associated with drastically decreased longevity[2]; some conditions reduce life expectancy with 10–20 years

- Additive genetic factors account for roughly 30–60% of the variation in such common medical conditions[3]
  - Common traits are typically *polygenic*—influenced by many genetic variants
  - However, risky lifestyle factors are important, such as smoking, BMI, physical inactivity, and alcohol consumption; which are also heritable
    - Such observable factors can already be taken into account in the formation of EL

1 Bloom. (2011). *World Economic Forum and the Harvard School of Public Health*
2 Chesny & Goodwin. (2014). *World Psychiatry.;* WHO (2014).
3 Price et al. (2015). *Proceedings of the Royal Society B: Biological Sciences*

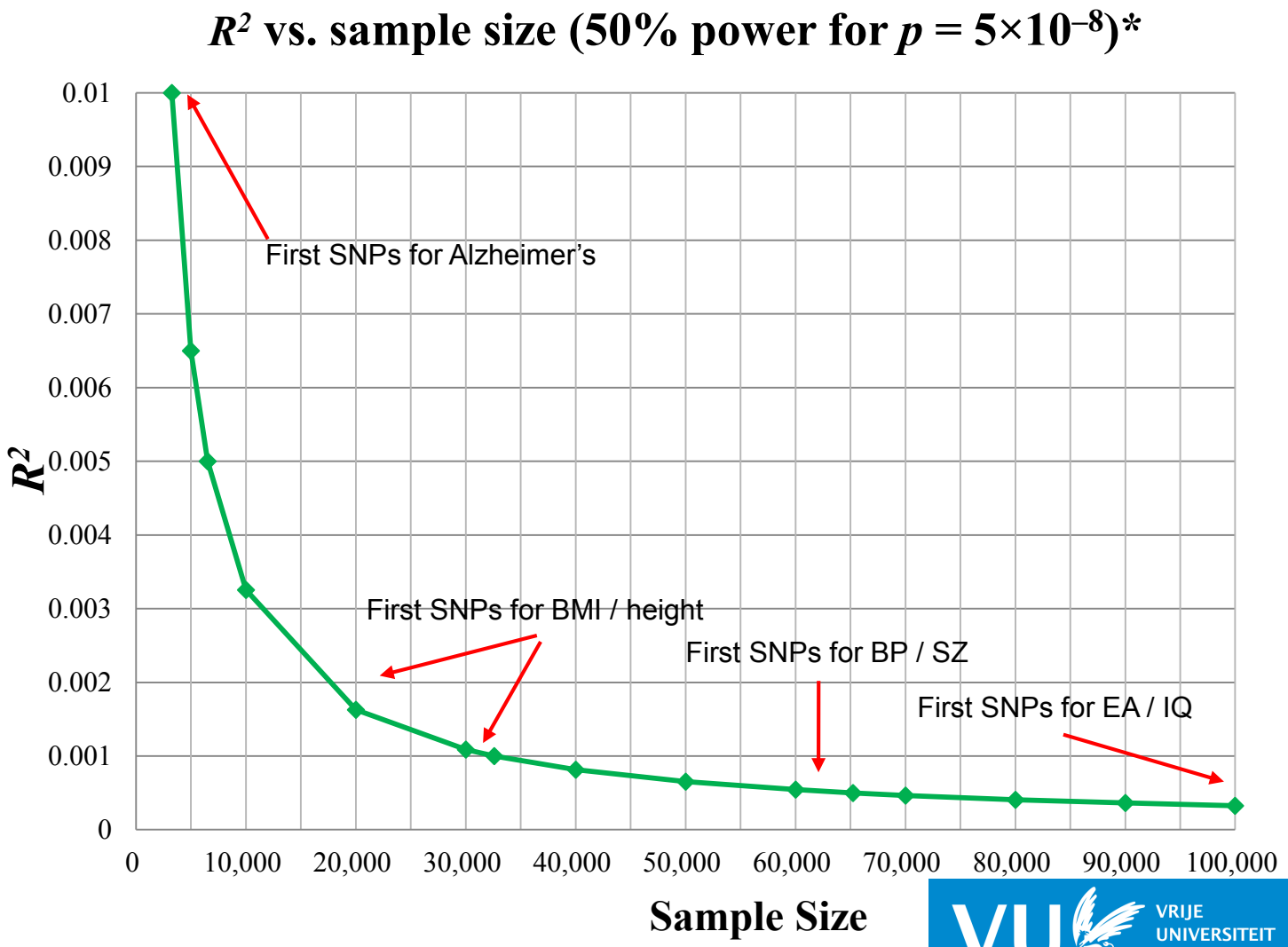
GENETIC EFFECTS VERSUS ALLELE FREQUENCY

- Today, there is a rapid, ongoing scientific revolution in the molecular-genetic study of common medical conditions
  - > Aim is to discover the particular genetic variants responsible for the heritability

- The genetic effects on most common behaviors and medical conditions have been found to be smaller, and distributed across a much larger set of variants than previously thought[1]

1 Gibson. (2015). *Nature Reviews Genetics*; Manolio et al. (2009). *Nature Reviews Genetics*; Chabris. (2015). *Psychological Science.*

THE BIG PROBLEM OF SMALL EFFECTS



* Bonferroni-corrected "genome-wide" significance threshold

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MODERN GENETIC DISCOVERY

- Genome-wide association studies (GWAS) are the modern workhorse to identify genetic associations
- The most common form of genetic variation is the single-nucleotide polymorphism (SNP; pronounced as "snip)
  - A SNP is a single DNA base pair that differs across individuals in a population
- GWAS "naïvely scan" the genome, variant by variant (g_j), for association with an outcome, modeled similar to:

$$\text{(Eq 1)} \qquad \boldsymbol{y} = \alpha + \beta_j g_j + \mathbf{X}\boldsymbol{\gamma} + \varepsilon,$$

where $\boldsymbol{y}$ is an outcome of interest, α is an intercept, $\mathbf{X}\boldsymbol{\gamma}$ contains demographic variables and genetic PCs to control for population structure, and ε is an error term. Model estimated separately for each variant *j*.

Visscher et al. (2017). *American Journal of Human Genetics.*

GWAS FINDINGS

- Landmark GWAS of schizophrenia (h^2 ~0.8[1]) in 34,241 cases and 45,604 controls identifies 108 associated genetic regions

Ripke et al. (2014). *Nature*.

1 Sullivan. (2012). *Nature Review Genetics.*

RECENT LARGE-SCALE GWAS

- Recent large-scale GWAS on traits related to health and longevity:
  - Atrial fibrillation[1]
    - Major risk factor for stroke, heart failure, and other CVD-related conditions
    - 142 independent hits, *n* ~ 1 million
  - Insomnia[2]
    - Related to various mental illness and neuropsychiatric disorders
    - 202 independent hits, *n* ~ 1.3 million
  - Educational attainment[3]
    - Strongly related to economic behavior, lifestyle risk, longevity, and overall health
    - 1,271 independent hits, *n ~ 1.1 million*
  - Risk preferences and risky lifestyle behaviors[4]
    - 99 independent hits with general risk tolerance, *n* ~ 940,000
    - 604 hits across six risky behaviors, *n* ~ 315,000–579,000.

- Sample sizes expected to increase further, many new biobank initiatives

1 Nielsen et al. (2018). *Nature Genetics.*
2 Jansen et al. (2018). *Forthcoming Nature Genetics*.
3 Lee et al. (2018) *Nature Genetics.*
4 Karlsson Linnér et al. (2018). *Forthcoming Nature Genetics.*

PREDICTIVE POWER OF POLYGENIC SCORES

- The predictive power (R^2) of a single variant is small (<0.05%)
  - > Yet, the predictive power of many variants (> 500k–1m) can be substantial
  - > Narrow-sense heritability estimates suggest an approximate upper limit
  - > R^2 increases as a function of GWAS sample size; less noise due to estimation error
- Polygenic scores (PGS) are predictors that summarize genetic liability across many variants into an index:

(Eq 2)
$$\hat{S}_i = \sum_{j=1}^{J} \hat{\beta}_j g_{ij}$$

- PGS can be constructed with GWAS summary statistics and individual-level genetic data, with some caveats*
  - > Not only genome-wide significant hits are predictive
    - > Suggests there are thousands or hundreds of thousands left to identify

*** In short, the correlation among variants must be accounted for, among other complicating factors**

EMPIRICAL PREDICTION

- PGS of schizophrenia explains about 7% of the variation in liability
- PGS of educational attainment (EA) explains about 11–13%
  - > EA predicts longevity, risky lifestyle behaviors, and a multitude of health conditions[1]
- Preferences more heritable than specific economic decisions
  - > Decisions are more noisy and biologically distal; many complex pathways and culture
  - > Nonetheless, PGS of risk preferences predict about 1% of the variation in occupational choice, and health and life insurance coverage[2]
- Importantly, a wide range of health conditions may jointly explain a non-negligible proportion of the variation in economic decisions

1 Marioni et al. (2016). *PNAS.*
2 Karlsson Linnér et al. (2018). *Forthcoming Nature Genetics.*

OTHER IMPORTANT ADVANCES

- Costs of genotyping and low-depth sequencing continue to decrease
  - > Soon, less than €20 per study participant
  - > Coverage not perfect, but comprehensive enough for accurate prediction
- Increasing number of large biobank initiatives (*n* > 500k)
  - > Substantial challenges to scale and complexity
- Phenome-wide analysis
  - > Increasing number of explored genetic health risks
- Efficient solutions like Hail[1]
  - > A scalable parallel computing framework for efficient analysis

- Thus, these developments will contribute to the affordability and predictive accuracy of direct-to-consumer genetic testing

1 http://www.nealelab.is/tools-and-software/

OVERVIEW OF NETSPAR PROJECT

- Netspar awarded a topicality grant for a pilot project
- Initiated September 1st, 2018
- Expected timeline about 1 year
- Industry report and scientific publication

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POTENTIAL IMPLICATIONS

- Many big questions without clear answers
  - Multitude of economic and moral aspects
- Consumer protection versus insurability and solvency
  - Family health history, the case of Huntington's disease
  - Question about penetrance/accuracy of genetic testing
  - What risks should be priced?
    - The influences of lifestyle factors that are modified by genes, such as diabetes/cancer?
- Asymmetric information and equality
  - Particular strata may be more prone to genetic testing (and to use such information)
  - Adverse selection, direction unknown
  - Stranger-originated life insurance and annuities could threaten long-term solvency
- Appropriate savings rate, consumption, and pension behavior
  - Poverty at old age
  - Effects of misinterpreted information/speculation

THANK YOU!

QUESTIONS?

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