



**Karolinska
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Institutionen för Neurobiologi, Vårdvetenskap och Samhälle

Living longer than expected: protective and risk factors related to human longevity

AKADEMISK AVHANDLING

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Debora Rizzuto

Huvudhandledare:

Professor Laura Fratiglioni
Karolinska Institutet
Institutionen för Neurobiologi, Vårdvetenskap
och Samhälle
Aging Research Center

Bihandledare:

Associate Professor Rino Bellocco
Karolinska Institutet
Institutionen för medicinsk epidemiologi och
biostatistik
University of Milano-Bicocca
Department of Statistics and Quantitative
Methods

Professor Miia Kivipelto
Karolinska Institutet
Institutionen för Neurobiologi, Vårdvetenskap
och Samhälle
Aging Research Center

Fakultetsopponent:

Professor Kaare Christensen
University of Southern Denmark
Institute of Public Health

Betygsnämnd:

Professor Maria Feychting
Karolinska Institutet
Institutet för miljömedicin

Associate professor Fredrik Granath
Karolinska Institutet
Centrum för läkemedelsepidemiologi

Professor Gösta Bucht
Umeå Institutet
Institutionen för samhällsmedicin och
rehabilitering

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ABSTRACT

The scientific community has become increasingly interested in understanding what lies behind the continuing extension of the human lifespan. The main aim of this thesis was to better understand the association between health status, lifestyle, genetic factors and survival in advanced age. Data used in the 4 studies are gathered from the Kungsholmen Project, a longitudinal population-based study on 75 year and older participants living in Stockholm, Sweden.

Study I. Dementia, cardiovascular disease (CVD), and cancer were associated with a 2- to 3-fold increased rate of all-cause mortality. The mean survival times after incident diagnosis were 4.1 years for dementia, 4.2 years for CVD, and 2.2 years for cancer. A total of 3.4 potential years of life were lost because of dementia, 3.6 of CVD, and 4.4 because of cancer. Women aged 75 to 84 years lived longer than coetaneous men after incident diagnosis of dementia because they spent 1.6 years longer than men in the severe stage of the disease.

Study II. Findings suggest that *APOE* alleles play different roles in the survival of elderly women and men. The mortality rate was 40% lower among women, but not men, who carried the $\epsilon 2$ allele, compared with the $\epsilon 3\epsilon 3$ carriers. The $\epsilon 4$ allele was associated with a 50% higher rate of death only among men. Dementia, not ischemic heart and cerebrovascular diseases, accounted for the majority of the increased mortality rate in those with the $\epsilon 4$ allele.

Study III. Maintaining a healthy lifestyle and a rich social network was positively associated with survival even among people aged 75 years and older. People who reported being physically active a minimum of once a month lived about 2 years longer than those who did not. Non-smokers 75 years and older who participated in at least 1 leisure activity a month and had good social support lived about 5 years longer than inactive smokers with poor social support. These association, although attenuated, were also found in individuals aged 85 years and older and those with chronic diseases.

Study IV. Genetic risk factors were relevant for survival after age 75. Variations in 4 different genes (*APOC1*, *APOE*, *IDE*, and *PI3K*) were associated with 12–20% increased rate of mortality. However, participants with at least 1 risk allele and a healthy lifestyle had about 70% lower rate of death than those with no risk allele and an unhealthy lifestyle. Those with no risk alleles and a healthy lifestyle had 80% lower mortality rate and 6 years longer median lifespan than people with at least 1 risk allele and unhealthy lifestyle.

In **conclusion**, survival after 75 years of age was associated with health status, lifestyle, genetic factors, and a combination of those factors. These findings may help prognostic evaluation of the duration of specific diseases. They underscore the malignant nature of dementia as a result of the long period individuals lived with the severe disease stages, especially for women. These findings also suggest that the benefit of a healthy lifestyle, healthy behavior, and social support probably last a lifetime. Moreover, allelic variations in genes were associated with higher mortality rate, but the combined effect of genetic-environmental joint exposures may lead to the attenuation of the mortality rate, indicating that people with genetic susceptibility may reduce their initial mortality rate by modifying their lifestyle. Therefore, efforts to encourage smoking cessation, physical activity, and social engagement should be continued long into late life.

Key words: Mortality, age-related chronic diseases, lifestyle factors, genetic factors.

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