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GESUNDHEITS-
STUDIE

Gefördert vom Bund,
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Projecting healthy volunteer bias and effects of eventual improvements in health care access and quality for amenable causes-of-death in the German National Cohort 2014-2111

"Similarities and peculiarities on the way to longer life in human populations"
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In the German National Cohort (GNC), one of the largest population- based Health Studies ever, recruitment of targeted n=200.000, aged 20-69 sampled in 18 recruitment areas started in 2013 and will be completed by October 31, 2019.

2018-2023 will be a second examination wave.

Of the sample target, 50% from each sex, 10% are aged 20-29, and 30-39, respectively, 26.7% 40-49, 50-59, 60-69, respectively.

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Legend:
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First, we will project death counts in the German National Cohort population.

For

- each sex,
- each single birth year and
- each single recruitment year,

survival of subjects is estimated from the generation life tables V2 version of the Federal Statistical Office of Germany.

In these generation life tables, life expectancies at birth for 1944, the oldest cohort, are 68,5 for males and 75,9 for females, for 1999, the youngest cohort, are 85,1 for males and 89,6 for females.

In the year of recruitment, subjects will be considered being exposed only for 6 months. Subjects recruited in 2019 will be considered being exposed for 7 months in that year, since recruitment will be completed by 31.10.2019.

Life table functions in ages 101-112 had to be estimated, assuming a linear increase from observed mortality risk at 100 to level 0.5 at age 111 and of 1.0 at age 112, the maximum life table age.

In this approach, we assume the German National Cohort population to be a random sample of the total population, stratified as in the targeted age and sex composition.

Second, we will project death counts in the German National Cohort study population, simulating

- healthy volunteer effects

- the proportion amenable deaths by comparing projected deaths with deaths at zero-risk factor exposure

- the proportion amenable deaths by comparing projected deaths with deaths at best practice

First:

There were 90.803 recruitments until 31.12.2016 (at this moment this number stands at >110.000).

The total numbers of participants in 2017 (52.764), 2018 (44.982) and 2019 (10.570) will be assumed as planned by the 18 recruiting study centres.

Age and Sex composition of these remaining subjects to be recruited during the Interval 01.01.2017 – 31.10.2019 – with an according adjustment of birth years - will be assumed as observed up to 31.12.2016.

The slight over-target recruitments of altogether 200.048 recruited subjects assumed here are caused by a slight over-plan recruitment in 2013-2015. For 01/2017-10/2019 the overall plan numbers of recruitments are used as estimates.

Females were more likely to be recruited and are projected to make up 54% of the completed sample. For a age- and sex-adjusted population random sample, the following distribution of deaths is predicted until 2111, when the youngest birth cohort in the study (1999) will turn 112.
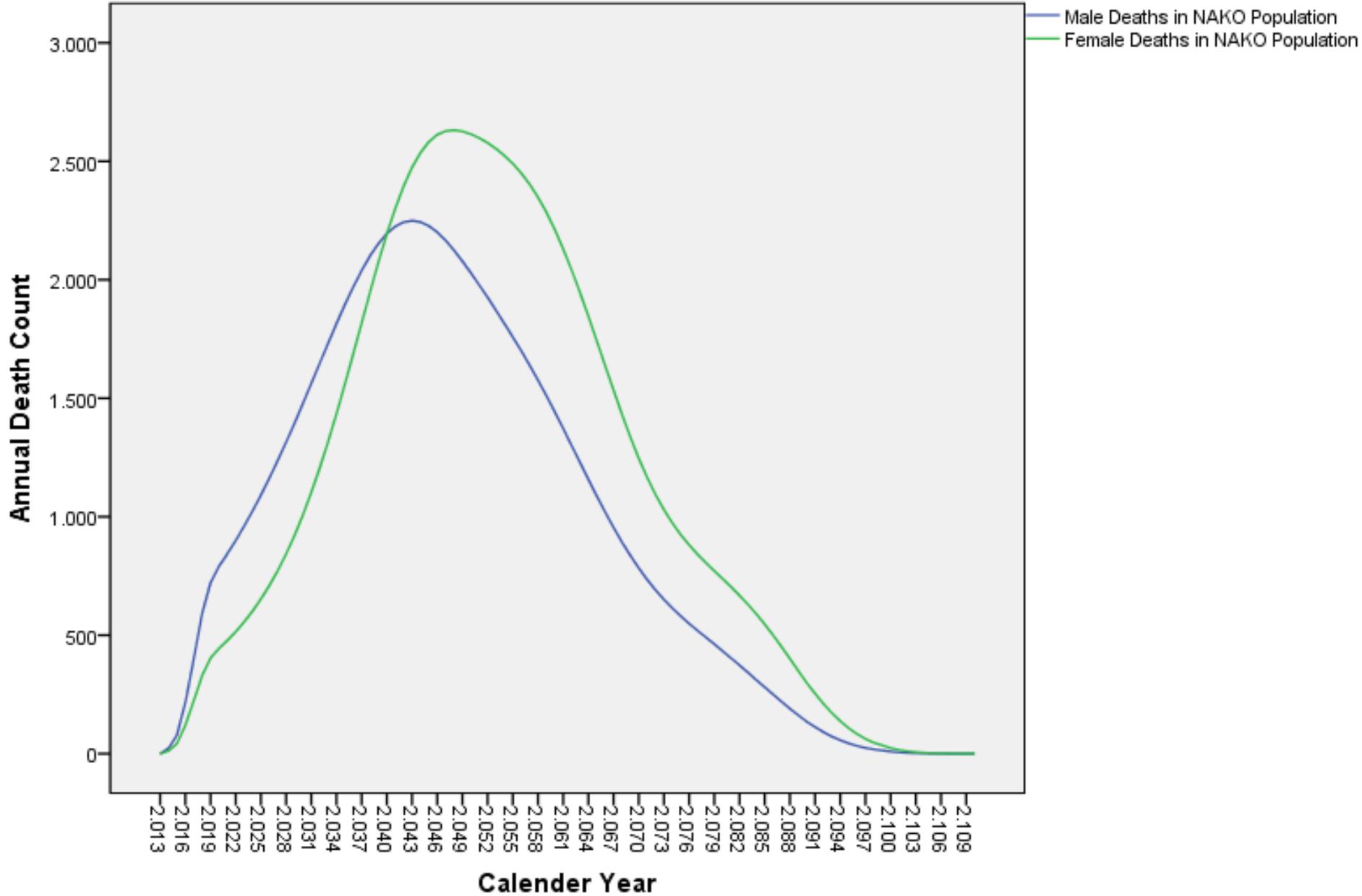
Annual Death Count

Calender Year

Male Deaths in NAKO Population
Female Deaths in NAKO Population

The maximal number of 2.256 male deaths is projected for 2042.
The maximal number of 2.631 female deaths is projected for 2047.

33 study participants (9 males, 24 females) can expect to survive into the 22nd century starting January 1, 2101.

There are no alternatives to the German Federal Statistical Office's cohort life tables. Some authors have set up cohort life tables from micro census data from 1978-1995 (Dinkel 1999) for obtaining a 17 year lifespan, or from German Socio-Economic Panel data 1984-1999 (Unger 2003) for obtaining a 15-year lifespan.

Systematic projections into the future, in particular far into the second half of this century by single-year birth cohorts seem not to exist elsewhere.
In a review of 10 national and international general mortality forecasts for the Netherlands, Stoeldraijer et al. (2013) end up with a rather favourable judgement of Statistics Netherlands' forecasts.

A similarly positive evaluation of the German Federal Statistical Office's forecasts may not be unlikely.

Now, we can extrapolate death counts for subgroups of the GNC population:

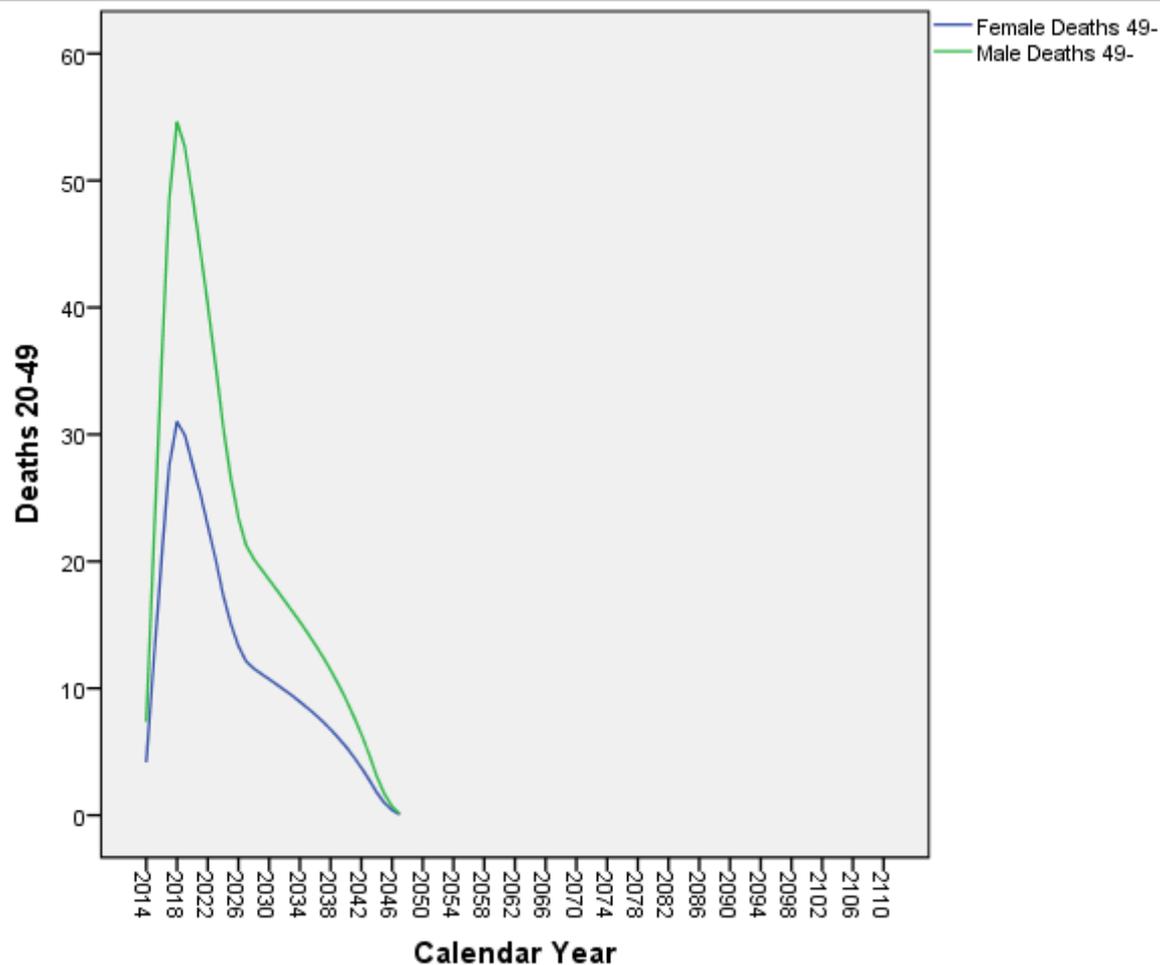for example by birth cohort or by age at death

Extrapolated death counts by cohort – with year of maximal numbers of death per cohort group:
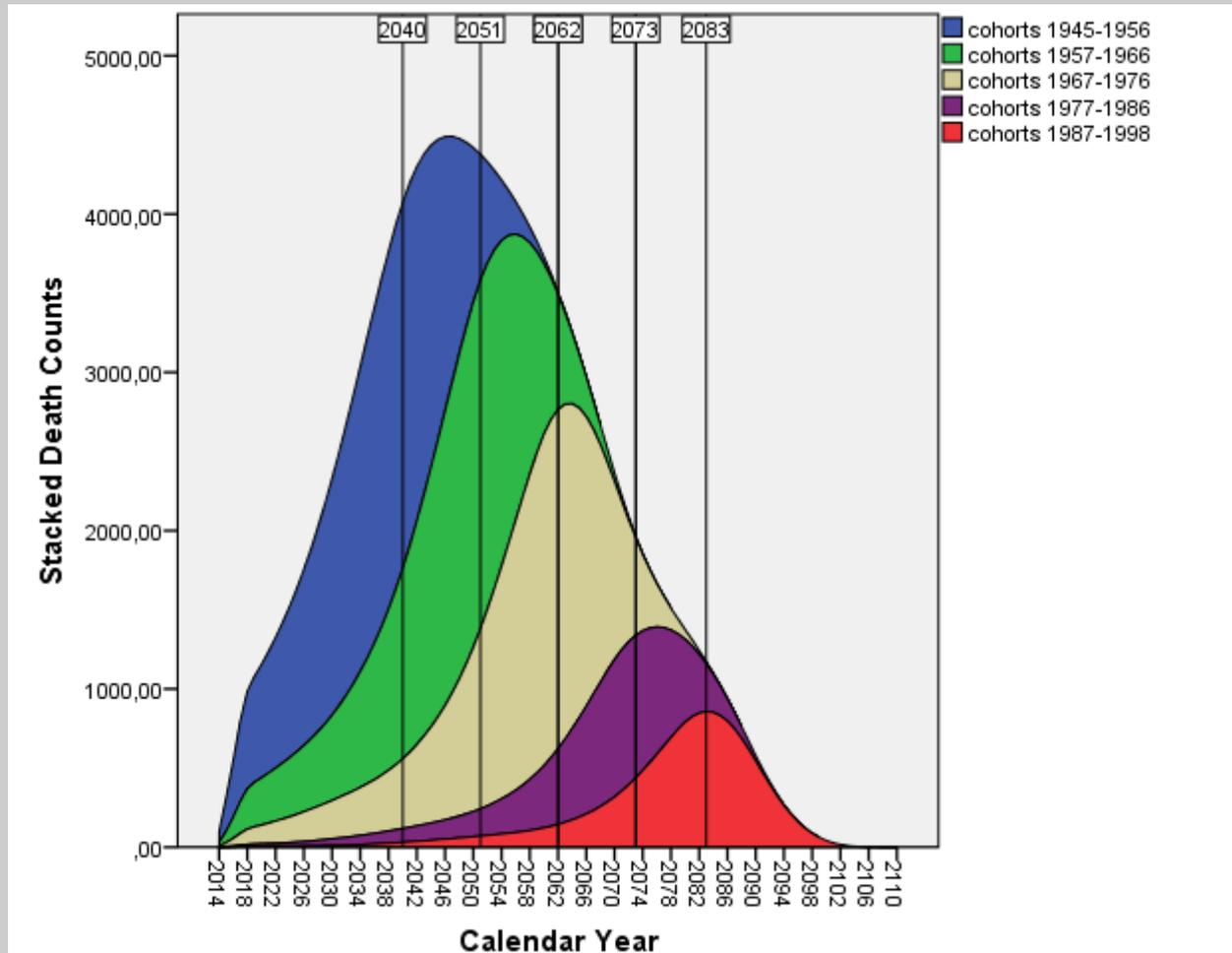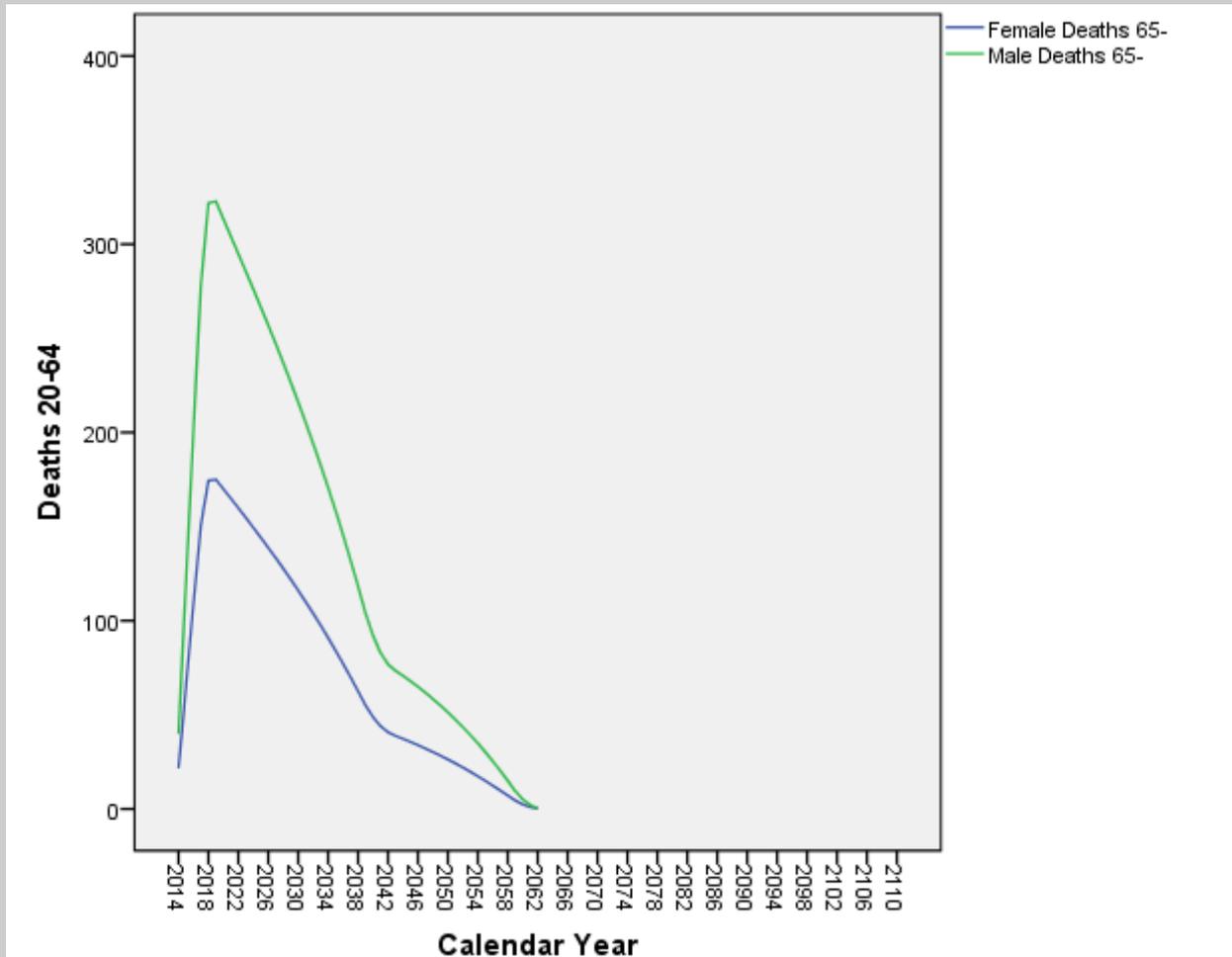
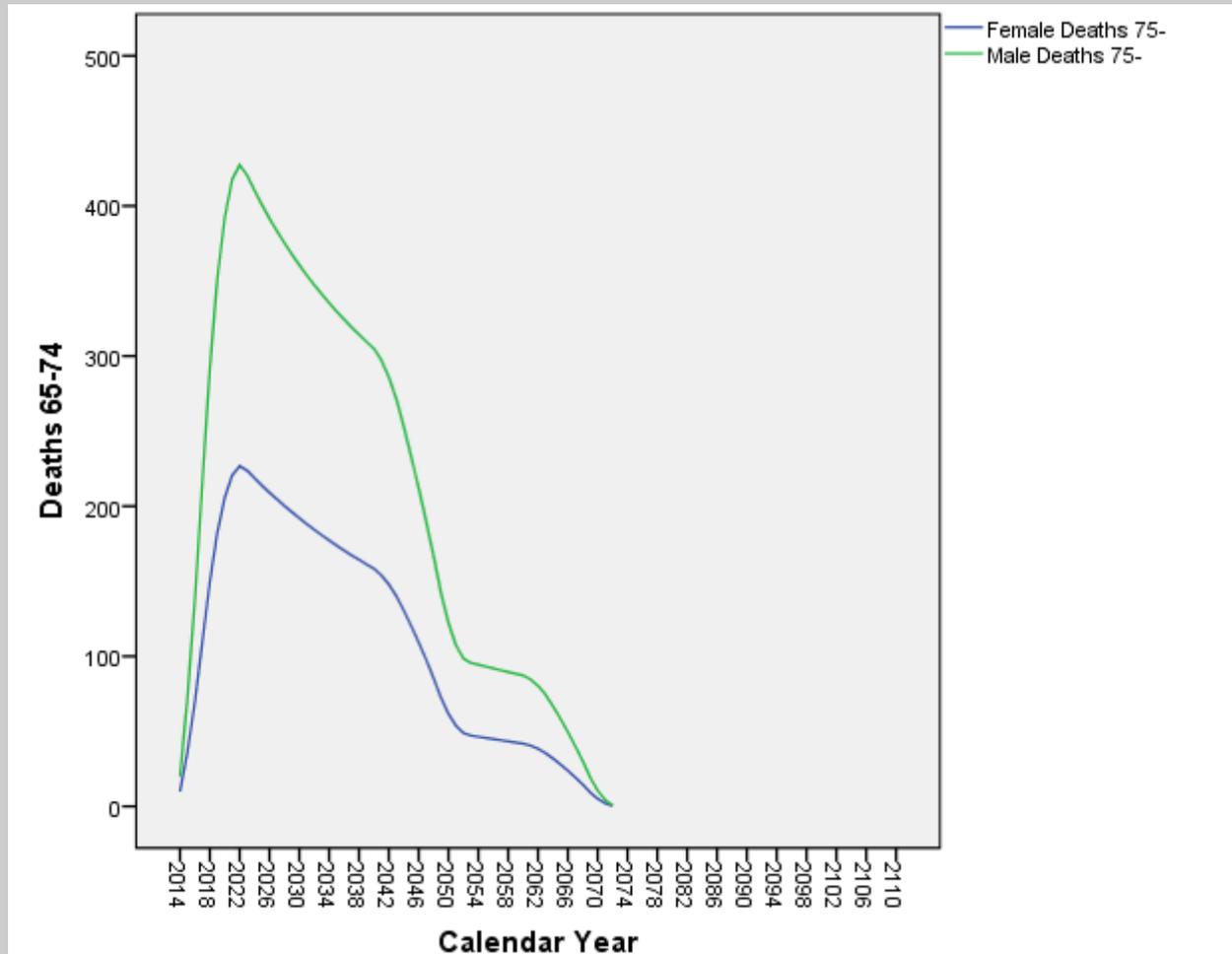## Extrapolated death counts by age at death:
ages 20-49

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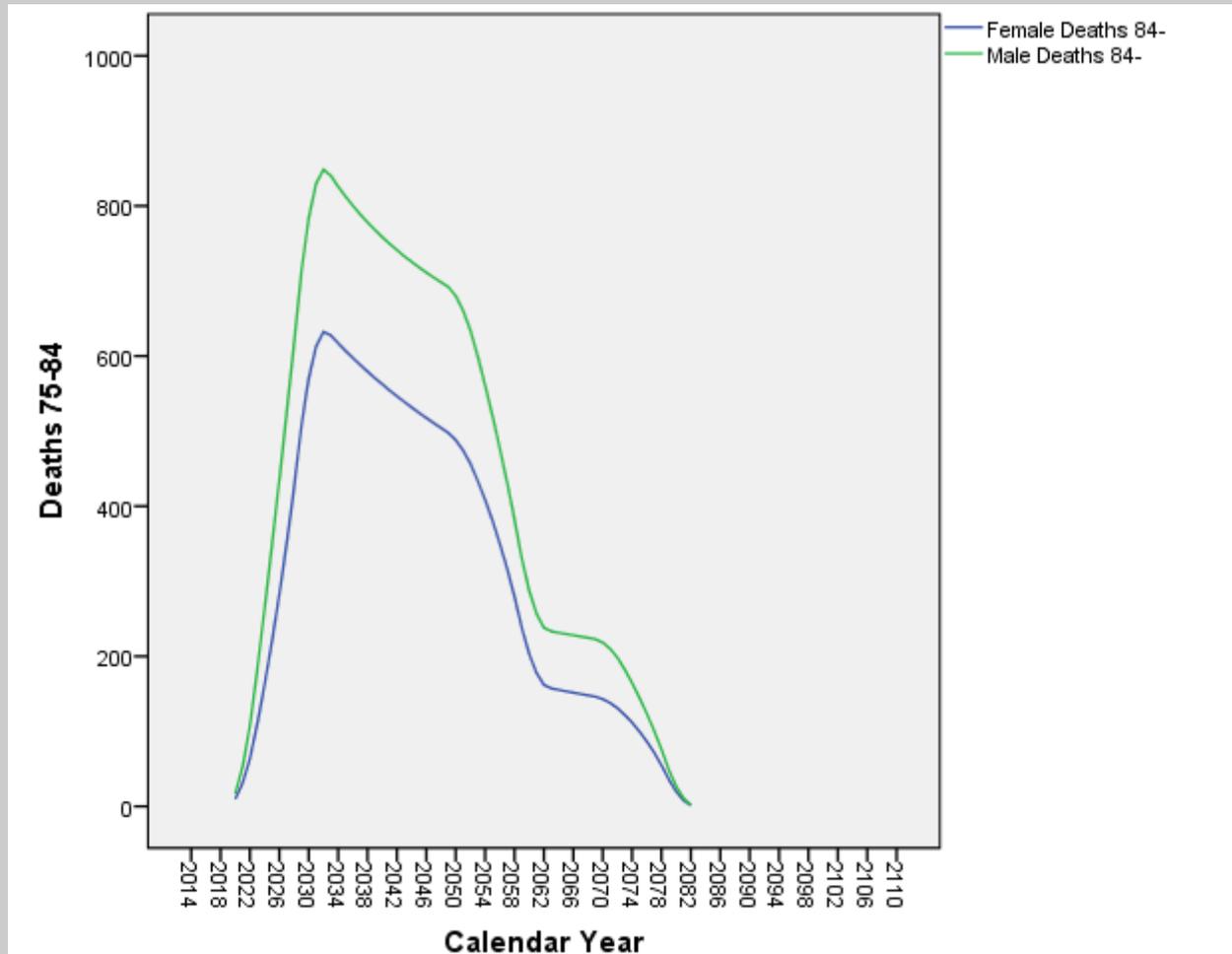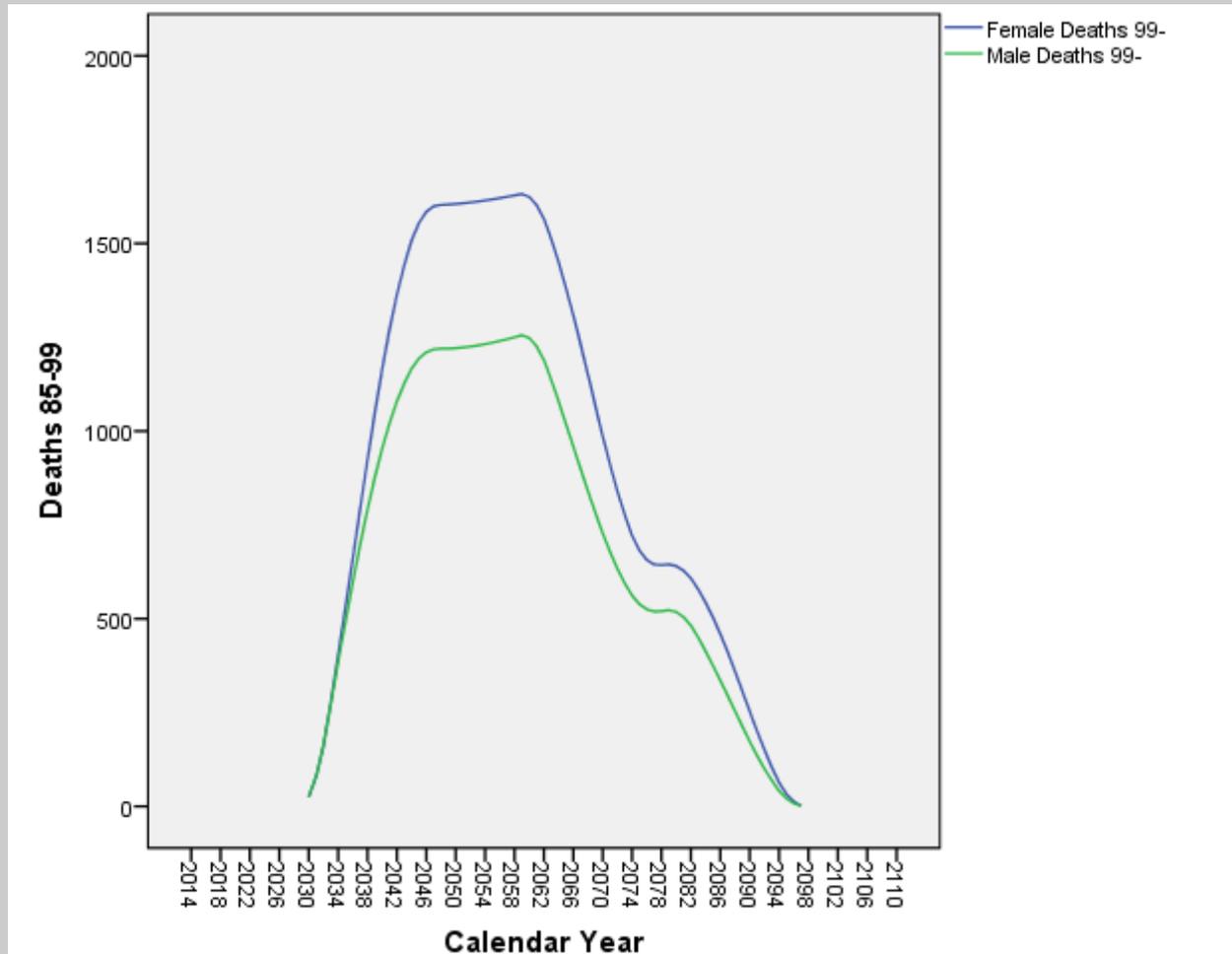Extrapolated death counts by age at death:
ages 20-65

Extrapolated death counts by age at death:
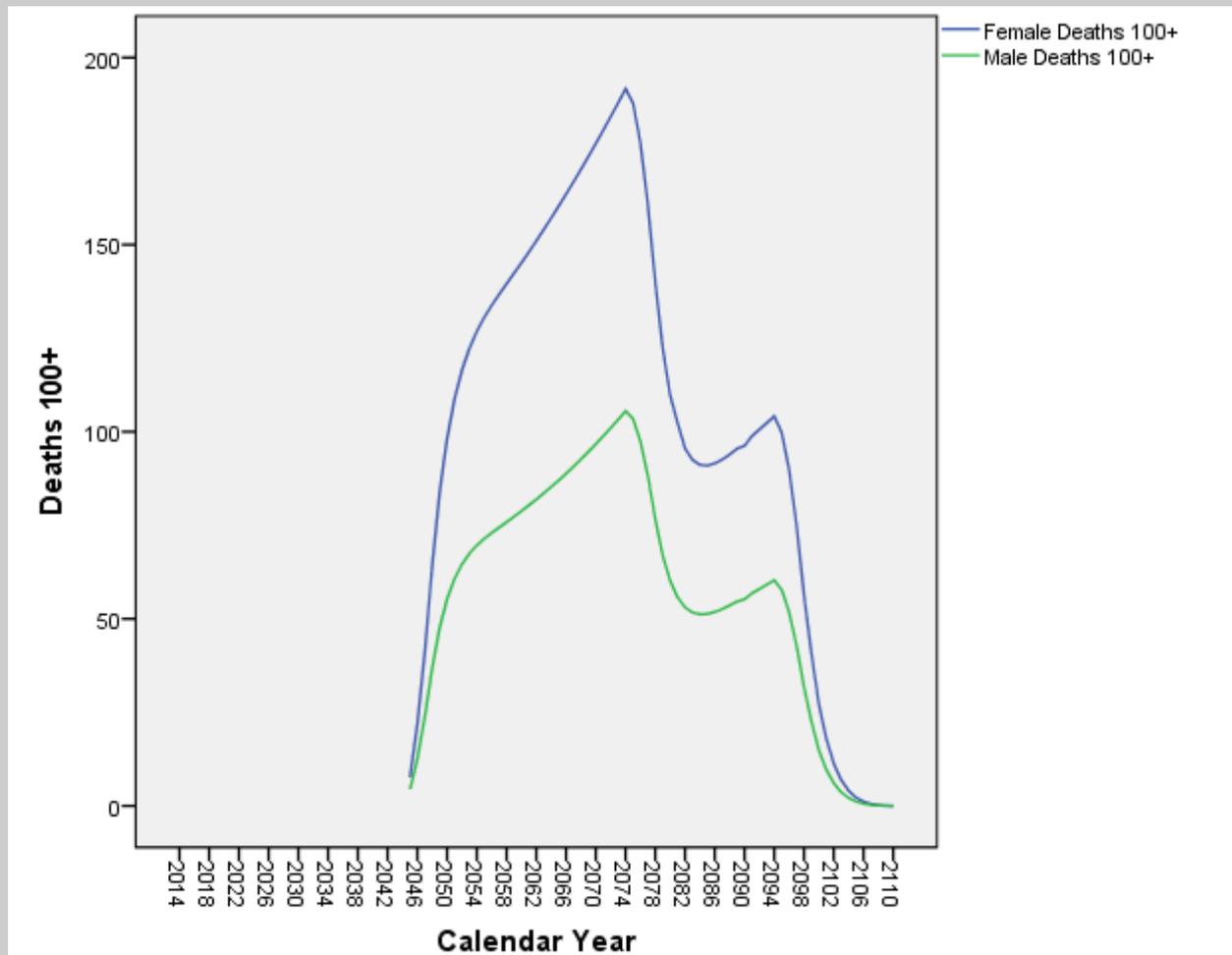## ages 65-75

Extrapolated death counts by age at death:
ages 75-85

Extrapolated death counts by age at death: :
ages 85-99

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Extrapolated death counts by age at death:
ages 100+

These extrapolated death counts over time may serve as reference for actual death counts in these and other subgroups of the GNC population, for identifying and quantifying risk as well as protective factors.

Once recruitment of all n=200.000 subjects is completed by October 31, 2019, adjustments will only be necessary to the generation life tables as their projections become facts.

Second, let us simulate a healthy volunteer bias: people in poor health are less likely to participate in voluntary health surveys. This may limit the generalisability of any findings from such surveys to the general population.

Most what we know about this bias is from all-cause mortality differences between participants and non participants in observational cohort studies, screening programs (mostly screening for frequent cancers – breast, prostate, colon) and in industry sponsored Randomized Clinical Trials.

For general mortality in observational cohorts in Switzerland (three waves of the MONICA study between 1983-1992) and in a very large cohort in Austria up to 40% Relative Risk Reduction has been reported - meaning that the survey participants population had a Standardized Mortality Ratio (SMR) of about 60% of the age and sex adjusted general population.

Bopp M, Braun J, Faeh D, Gutzwiller F; Swiss National Cohort Study Group.(2010): Establishing a follow-up of the Swiss MONICA participants (1984-1993): record linkage with census and mortality data. BMC Public Health. 2010 Sep 21;10:562.

Klenk J, Nagel G, Ulmer H, Strasak A, Concin H, Diem G, Rapp K; VHM&PP Study Group (2009): Body mass index and mortality: results of a cohort of 184,697 adults in Austria. Eur J Epidemiol. 2009;24(2):83-91.

In a large middle-aged observational cohort in Japan Hara et al. (2002) found SMRs of about 50% for all causes of death, of 70% for all cancers, of even 37% for cerebrovascular and other circulatory causes in males, and 63% / 82% / 65% for females, in participants as compared to nonparticipants, but no such effect for ischemic heart disease.

Also, the healthy volunteer effect disappeared for cancer mortality already 2 years after the baseline survey, but remained stable over the full 8 years observation period for cerebrovascular causes.

Hara M, Sasaki S, Sobue T, Yamamoto S, Tsugane S. (2002): Comparison of cause-specific mortality between respondents and nonrespondents in a population-based prospective study: ten-year follow-up of JPHC Study Cohort I. Japan Public Health Center. J Clin Epidemiol. 2002 Feb;55(2):150-6.

In an Israeli cohort of industrial workers initially screened for cardiovascular disease in 1985 with 72% participants, the SMR over 8 years follow-up for all cause mortality was 71% for participants and 99% for non-participants as compared to the age-adjusted general population – indicating a healthy volunteer effect on top of a healthy worker effect.

Froom P, Melamed S, Kristal-Boneh E, Benbassat J, Ribak J. (1999): Healthy volunteer effect in industrial workers. J Clin Epidemiol. 52:731-5.

In a screening trial on prostate, lung, colorectal, and ovarian (PLCO) cancer, that had randomized 155.000 men and women 1993-2001, Pinsky et al. (2007) found even after the exclusion of PLCO mortality an all cause SMR of 46% for men and 38% for women. SMRs increased from 31% at year 1 to 48% at year 7 of the study.

For prostate cancer alone, Pinsky et al. (2012) found 5 years later a prostate cancer specific SMR of 60% for the intervention and 55% of the control arm of the PLCO Cancer Screening Trial as compared to the general US population.

SMR avoid biases of lead time and over diagnosis, but are interpreted by the authors as the result of a healthy volunteer bias.

Pinsky PF, Miller A, Kramer BS, Church T, Reding D, Prorok P, Gelmann E, Schoen RE, Buys S, Hayes RB, Berg CD (2007): Evidence of a healthy volunteer effect in the prostate, lung, colorectal, and ovarian cancer screening trial. Am J Epidemiol. 165(8):874-81.
Pinsky PF, Black A, Parnes HL, Grubb R, David Crawford E, Miller A, Reding D, Andriole G. (2012): Prostate cancer specific survival in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. Cancer Epidemiol. 36(6):e401-6

Masters et al. (2013) demonstrated in large datasets from the US National Health Interview Survey 1986-2004 linked to the National Death Index, that the weakening of the association between obesity and mortality with advancing age, that several studies had found, is caused by confounding by disparate cohort mortality and age-related survey selection bias.

In the obese population the healthy volunteer bias is stronger than in the normal-weight population, and this effect grows with age. After statistical controlling for this, the association between obesity and mortality in fact grows with advancing age.

Masters RK, Powers DA, Link BG (2013): Obesity and US mortality risk over the adult life course. Am J Epidemiol. 2013 Mar 1;177(5):431-42.

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The Healthy volunteer bias exists, is strong up to a Standard 40%-50% Relative Risk Reduction initially - meaning that the voluntary survey participants population initially had a Standardized Mortality Ratio (SMR) of about 50%-60% of the age and sex adjusted general population.

The sustainability of that bias is an open question:

- in general, it starts to wash out very soon,

- It may have disappeared for some diseases already 1-2 years after the survey,

- but it may be present for some other diseases up to a decade and beyond.

Here, we simulate a healthy volunteer bias much stronger in the long run than any real healthy volunteer bias has been described in the literature, by shifting every subject to a birth cohort 10 years younger than the original one.

The oldest cohorts recruited – 1944 – instead of having a life expectancies at birth 68,5 for males and 75,9 for females, now would have the life expectancies of the cohort 1954: 74,3 for males, 80,4 for females.

Likewise, the youngest cohort 1999, instead of 85,1 for males and 89,6 for females, now would have the life expectancies of the cohort 2009: 86,4 for males, 90, 7 for females.

In our original projection,

the maximal number of 2.256 male deaths is projected for 2042.
the maximal number of 2.631 female deaths is projected for 2047.

33 study participants (9 males, 24 females) can expect to survive into the 22nd century starting January 1, 2101.

Under our Healthy Volunteer Bias Assumption:

the maximal number of 2.268 male deaths is projected for 2043.
the maximal number of 2.652 female deaths is projected for 2048.

38 study participants (10 males, 28 females) can expect to survive into the 22nd century starting January 1, 2101.
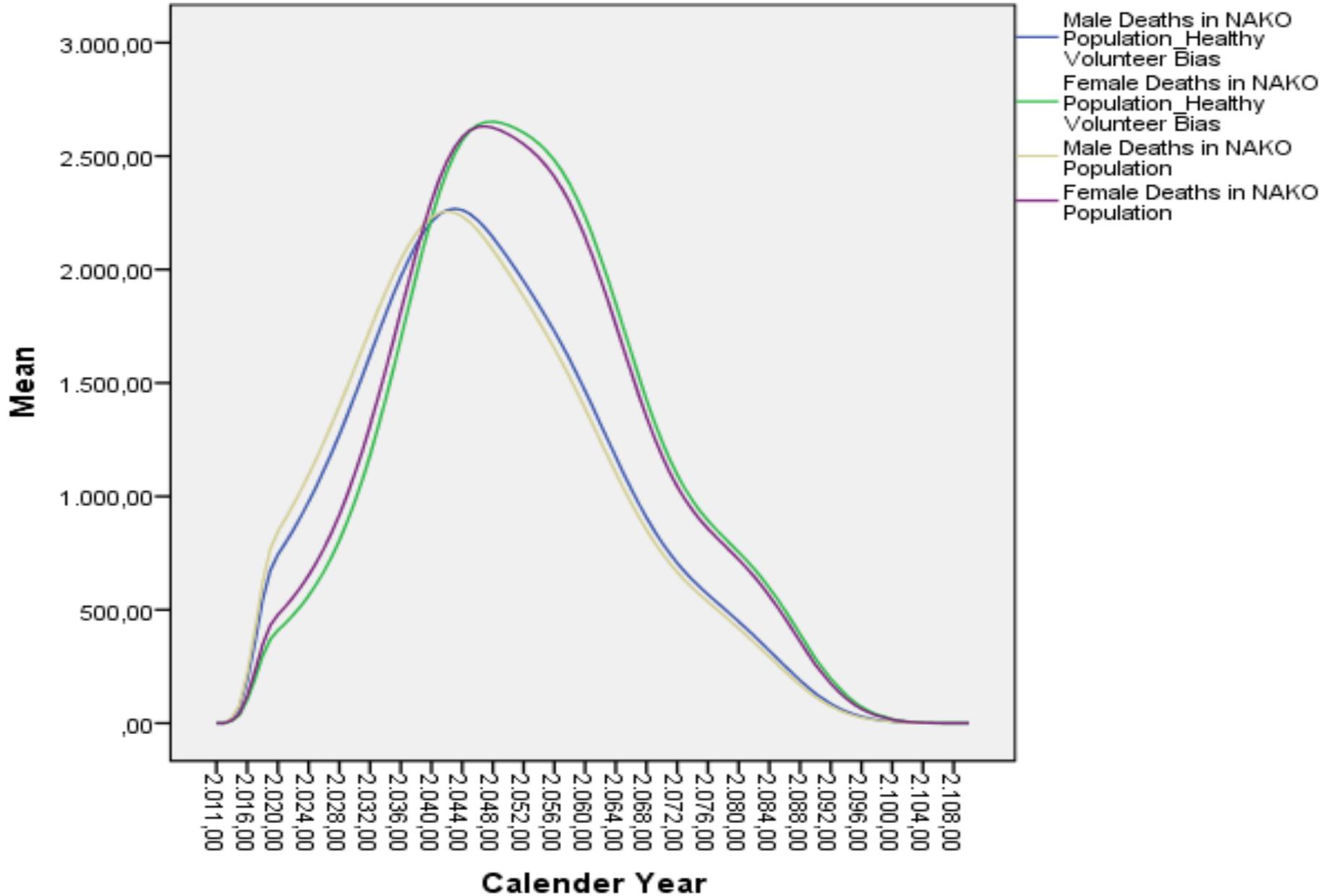
Long term effects of the Healthy Volunteer Bias in the recruited study population may be measured by the Years of Life Lost (YLL) avoided by participating in the study.

The GBD methodology for measuring Years of Life Lost may be used for a novel way to measure amenable deaths.

The core tool of the methodology is the normative standard life table, a period life table containing for every age the lowest age-specific mortality risk presently observed in any nation with a population of at least 5 million.

We may extend this idea to a family of normative standard cohort life tables, for each birth cohort containing the lowest age-specific mortality risks observable worldwide.

This would not be a mission impossible. We just would have to check the usual suspects: Australia, Japan, South Korea, Sweden and some few more.

Using this normative standard cohort life tables for calculating the ideal death count as reference for finding the number of deaths avoidable in real populations would be a an application to cohort studies of the GBD approach which was used

in

"*Healthcare Access and Quality Index based on mortality from causes amenable to personal health care in 195 countries and territories, 1990–2015: a novel analysis from the Global Burden of Disease Study 2015*"

published in The Lancet last week and received with much applause worldwide.

Thanks for your attention

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