

Diseases of ageing: beyond epidemiology



“Defining diseases of ageing through epidemiology can be misleading. We must consider the underlying biological mechanisms to estimate the true disease burden of ageing.”

Dr William Letton, Consultant for R&D

Ageing is the biggest risk factor for disease

In the modern world, death is far more likely to be caused by disease than external causes such as accidents or violence.¹ Ageing is the main risk factor for the most prevalent diseases and causes of death in developed countries, including cardiovascular disease, cancer, neurodegeneration, and diabetes.²

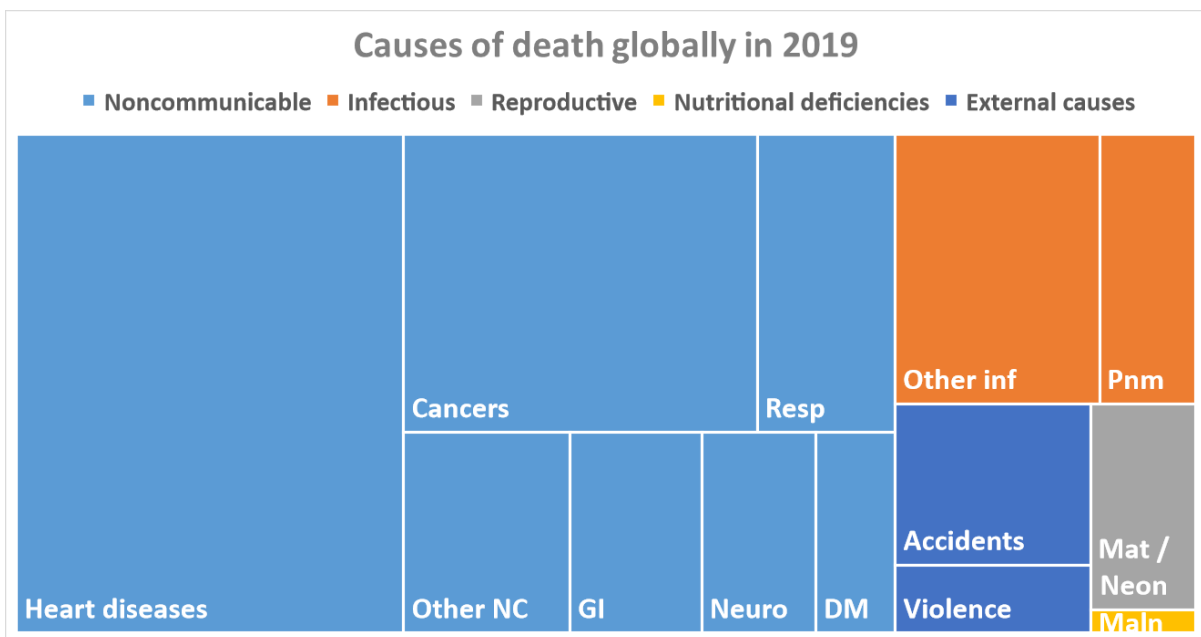


Figure 1 - Cause of death globally in 2019. Adapted from <https://ourworldindata.org/causes-of-death>. GI = gastrointestinal diseases, Neuro = neurological diseases, DM = diabetes mellitus, Mat / Neon = maternal and neonatal, Maln = malnutrition, Other inf = other infectious diseases, Pnm = pneumonia, Resp = chronic respiratory diseases, Other NC = other non-communicable diseases

What is an ageing-related disease?

The distinction can be made between *age*-related diseases and *ageing*-related diseases. The former refers to any disease which has a particular age of incidence, while the latter is specifically associated with the process of biological ageing. For example, the incidence of

diabetes is age-related, but Type I is associated with younger ages and the Type II with older ones.³

Within this epidemiological definition, a disease is said to be ageing-related if it has a rate of onset that increases significantly with age in adults. The ageing-relatedness of a disease may be quantified by how well it fits an exponential⁴, quadratic⁵, or Gompertz function.³

What age-related diseases could be considered ageing-related diseases?

Using an epidemiological definition of ageing-related diseases relies on the assumption that an increase in incidence with age indicates a causal association with the underlying biological mechanisms of ageing. However, incidence alone may be misleading where ageing processes interact with other factors.

One example is in pregnancy-related diseases, such as hypertension and gestational diabetes. Here we see a significant increase in disease incidence and pregnancy-related mortality with increasing maternal age.^{6,7} However, this then falls to zero as the ageing effects on pregnancy-related disease are masked by a decline in fertility.

Fertility itself is strongly age-related, particularly in women^{8,9}, with births to mothers aged 50 or over being extremely rare.¹⁰ Depending on your expectations and definition of health, infertility is either an ageing-related disease state, or is a natural post-reproductive phase of the human lifespan.

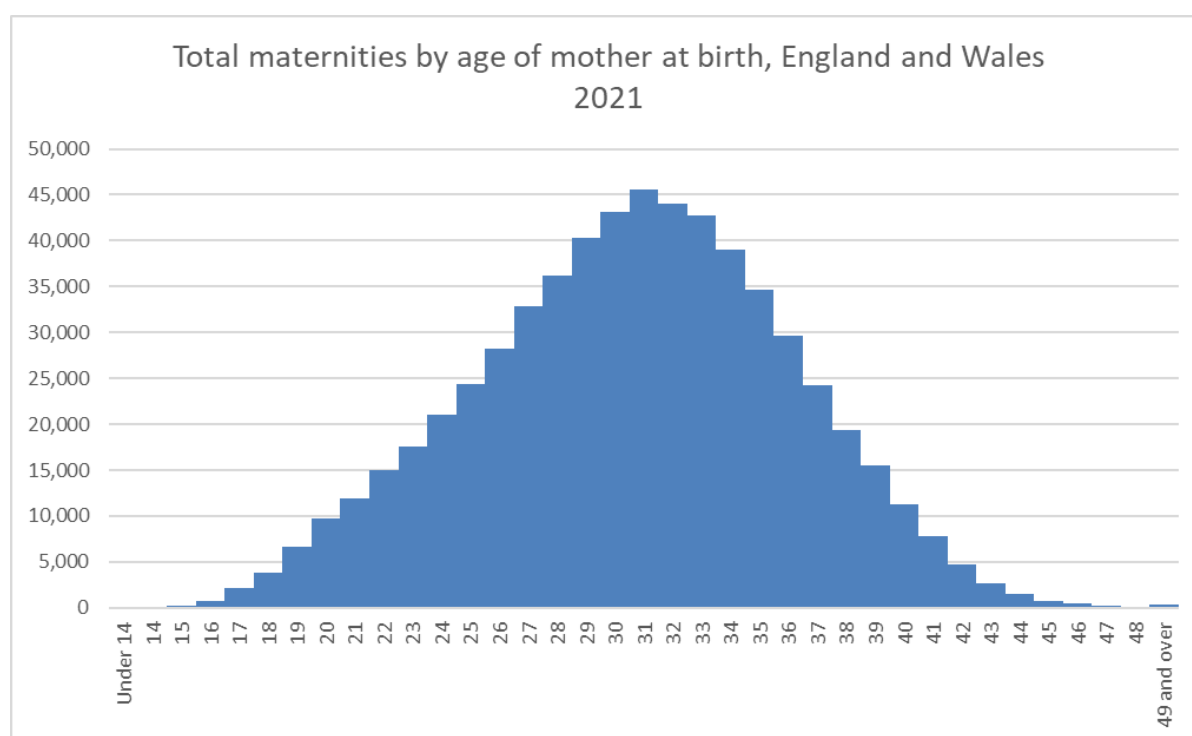


Figure 2 - Total maternities by age of mother at birth, England and Wales 2021. Source - ONS population statistics

Parental ageing can also affect the incidence of diseases in offspring. For example, the probability of Down's syndrome increases particularly with maternal age.¹¹ Should this be considered a disease of ageing, albeit the ageing of the parental generation?

Why do we need a biological perspective?

The epidemiological definition of ageing-related diseases is a first step. However, biological studies are needed to determine whether the process of ageing are the sole or primary cause of a disease.⁴

What is this process? Ageing is commonly defined as an accumulation of damage at the molecular and cellular level that increases the susceptibility to loss of function and disease.¹² Not all definitions centre on the idea of damage, and may instead focus on the inappropriate activation of genetic programs and cellular pathways.¹³

The so-called 'hallmarks of ageing' are a collection of twelve biological processes that have been linked the ageing phenotype across species.¹⁴ These include genomic instability, chronic inflammation, and deregulated nutrient sensing. By linking ageing to specific measurable processes, we should be better able to identify which diseases are caused by ageing. This in turn should help us to prevent and treat these diseases by targeting the ageing hallmark processes that cause them.

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