

The disease burden of peanut allergy in Denmark measured by disability-adjusted life years (DALYs)

To the Editor,

Peanut allergy (PA) can result in life-threatening reactions and has negative impact on the quality of life (QoL). The prevalence of PA has increased, especially in Western countries. To monitor public health and identify ways to improve it, it is relevant to provide evidence on the burden of various diseases. Traditional indicators of public health impact are prevalence, incidence, and mortality. However, they do not comprehensively reflect the burden of disease, including living with PA, as they do not account for the years living with disability due to a disease. Several metrics convey disease burden, including disability-adjusted life years (DALYs) developed in the 1990s and applied by the World Health Organization for the Global Burden of Disease (GBD) study.¹ DALYs are a composite measure of population health that combines mortality and morbidity of diseases, the latter computed by weighting the duration of a disease with a disability weight (DW) that accounts for the health-related QoL (HRQoL) (Figure 1). Allergy has not been included in the GBD study, and only one study has estimated the disease burden of PA in Western countries in terms of DALYs.² An estimate of the disease burden of PA is not published for Denmark, nor for any other country.

We estimated the disease burden of PA in Denmark, a Nordic European country with a publically financed healthcare system, by applying Danish PA prevalence data in a model based on the natural history of PA. PA caused a disease burden of 906.2 DALYs in 2016 (95% UI: 512.8–1429.6) (Figure 2). Persistent PA contributed with more than 97% of the total disease burden whereas fatal PA represented less than 0.5%. This estimate may be considered conservative, as the prevalence was based on clinically confirmed PA in individuals in two Danish cohorts and did not include the prevalence of individuals with suspected allergy, who may experience the same level of psychosocial impairments. The mean DALYs per case of PA was estimated to be 3.4 DALYs (95% UI 2.7–4.2), indicating that any individual living with PA loses on average 3.4 years of healthy life (See supplementary material for details on methods).

DWs indicate the relative severity of a given disease and are available for a range of diseases from the GBD study but have not been derived for PA. We assumed a proxy DW based on existing DWs of other diseases³ and on reported HRQoL of food allergy in comparison with other diseases.⁴ Scenario analyses showed that the disease burden of PA was up to 1,055 DALYs if the DW is assumed to lie somewhere between the DW of uncomplicated diabetes mellitus

type 1 (DM1) and asthma, and up to 5,115 DALYs if it is assumed that the DW lies somewhere between DM1 and rheumatoid arthritis (RA) (Figure 2). For comparison, the disease burden reported for 2016 in Denmark was 6874 for DM1, 13,285 for asthma, and 5210 DALYs for RA. Data on the BoD of some food-associated diseases are available for Denmark, and the disease burden of *Salmonella* spp. and *Campylobacter* spp., foodborne pathogens receiving much public attention, was estimated to 492 and 1709 DALYs, respectively.⁵

In conclusion, we advocate for national specific estimates of disease burden of PA in terms of DALYs, as such estimates are the most comprehensive to reflect the public health burden and allow for tracking changes in the epidemiology of the disease over time, both within or between countries or regions. They are useful for comparison of the health impact of similar diseases, for example, if our model was extended to other food allergies like tree nut, wheat, and milk

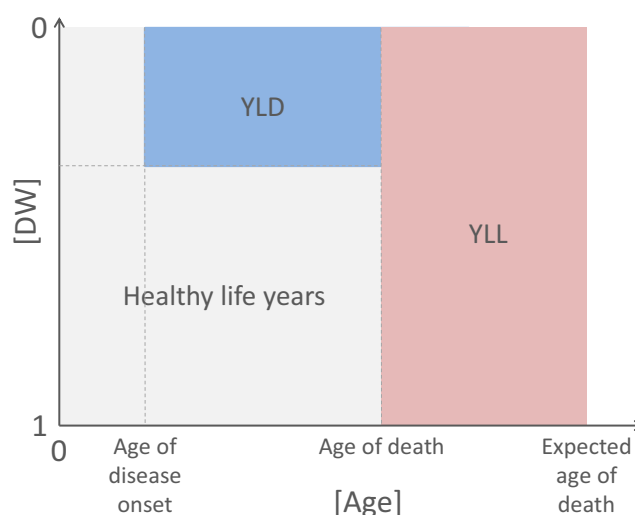


FIGURE 1 Disability-adjusted life years (DALYs) are conceptualized by that any person is expected to live a full life (x-axis) in perfect health (y-axis). If a person falls ill, time lived with disease is adjusted by a disability weight (DW), indicating disease severity. The DW ranges from perfect health (0) to death (1). Blue-shaded area represents years lived with disability (YLD). Red-shaded area represents years of life lost (YLL) due to premature death compared with expected age of death. DALYs are the sum of YLL and YLD. DALYs caused by a disease in a population are the sum of DALYs attributed to each diseased person. The figure is not a specific representation for peanut allergy

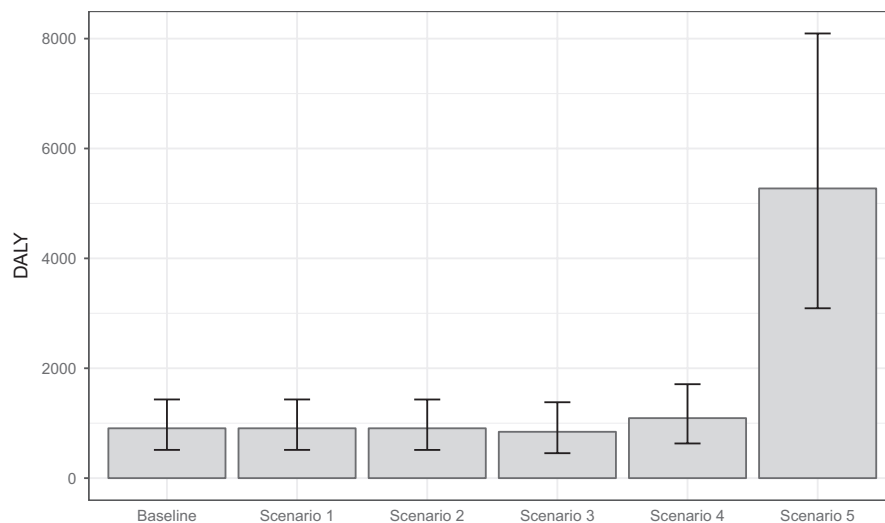


FIGURE 2 Mean disability-adjusted life years (DALYs) estimated in the baseline model and scenario analyses. Error bars represent the 95% uncertainty interval. Scenario 1 and 2 estimated the impact of changing mean age of death from 32 to 15 years and a zero risk of peanut allergy-induced fatal anaphylaxis, respectively. Scenario 3–5 investigated the impact of the disability weight being equal to uncomplicated diabetes mellitus type 1, asthma, and the mean of rheumatoid arthritis and Crohn's disease, respectively

but also for comparison of the impact of otherwise non-comparable diseases, for example, foodborne or non-communicable diseases. Lastly, DALYs may be used for evaluation of the public health impact of management strategies both pro- and retrospectively.

CONFLICT OF INTEREST

Dr Jakobsen, Dr Pilegaard, Dr Pires, and Dr Bøgh have nothing to disclose.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Confirmed case of PA

Living with PA:

- Reactions upon exposure
- Anxiety related to accidental exposure
- Psychosocial aspects of PA

P1

Persistent PA

P2

Resolving PA

P3

PA-induced fatal anaphylaxis

Supplementary material

Data, methods and assumptions applied to estimate the disease burden of peanut allergy in Denmark measured in Disability Adjusted Life-Years (DALYs)

The code behind the methods are provided at https://github.com/leaja/BoD_PA_DK2016

Overall approach An incidence-based approach was applied to estimate Disability Adjusted Life-Years (DALYs) attributed to peanut allergy (PA) in Denmark for the reference year 2016, i.e. the incidence of PA in Denmark in 2016 was estimated and future DALYs were assigned to those incident cases. DALYs are made of the sum of two components; 1) the Years of Life lived with Disability (YLD) and 2) the Years of Life Lost due to premature death (YLL). One DALY equals one year of healthy life lost. Statistical uncertainty was propagated in incidence and DALYs estimations using Monte Carlo simulations. Models and simulations were developed and performed in the statistical software R version 3.5.2.¹

Computational disease model The computational disease model described living with PA and included the probability of a clinical confirmed PA to either: i) be persistent, ii) to resolve, or iii) be fatal (Figure S1). DALYs attributed specific events of allergic reaction following accidental exposure to peanuts were not estimated due to lack of data on the incidence of accidental exposure to peanut leading to allergic reactions, the duration of the symptoms, and the probability of type and combination of reactions upon exposure.

Incidence Point prevalence of primary (i.e. non-pollen mediated) PA in different age groups was extracted from five Danish cohorts (Table S1). To calculate incidence from point prevalence, it was assumed, that PA is diagnosed in the first five years of life, and that point prevalence therefore represents the prevalence of children $\leq$ the age of five. The point prevalence was multiplied by the mean of the Danish population of the age groups 0, 1, 2, 3, 4 and 5 years from the first quarter of 2016 (Table S2).

Probability of resolving PA Begin et al² studied the resolution of PA in a 12 year follow up study of 202 Canadian children with PA clinically confirmed at age one. By age 4, 6, 8, 10 and 12 PA had resolved in 10%, 18%, 22%, 26% and 27% of children, respectively. In the Australian HealthNuts study, PA had resolved in 22% of children by age four.³ Data on the resolution of PA in Danish children were not available but based on the Canadian and Australian data, a mean resolution of 22% at age eight was assumed (Table S2).

Probability of PA-induced mortality Data on the mortality rate of peanut-induced allergy was collected from a meta-analysis⁴. Data on mortality due to PA specifically for Denmark were not available.

Disability weight (DW) DWs are derived systematically for the GBD study^{5,6} but not for any food allergies (FA) including PA. A DW for PA was derived by taking into account a distribution of severity of symptoms and DWs for disorders considered of similar characteristics in terms of health related quality of life (HRQoL) as described in the following. The severity of reactions may impair HRQoL as a result of anxiety, interference with daily life etc.⁷ Deschildre et al⁸ reported that 30% of 669 peanut allergic individuals in France, Belgium and Luxembourg experienced severe symptoms including anaphylactic shock, laryngeal angioedema, acute asthma or severe systemic reactions involving two or more organ systems. Non-severe reactions including rash/dermatitis, urticaria, subcutaneous angioedema, oral allergy syndrome, or isolated mild gastro-intestinal symptoms were experienced by 70% of individuals.⁸ It was assumed

that this severity distribution applies to Danish peanut allergic individuals and that a higher DW applies to individuals experiencing severe symptoms than individuals experiencing less severe symptoms. Flokstra-de Blok⁹ compared HRQoL of individuals with FA with HRQoL of patients with diabetes mellitus type 1 (DM1), asthma, irritable bowel syndrome (IBS) and rheumatoid arthritis (RA). The authors found that HRQoL of individuals with FA was lower than for individuals with DM1 but higher than for individuals suffering from asthma, IBS and RA. The DW for uncomplicated DM1 is 0.049 and a mean DW of controlled, partially controlled and uncontrolled asthma is 0.062.⁶ We assumed DWs of 0.049 and 0.062 were representable for individuals with PA experiencing non-severe and severe symptoms, respectively. An average of the two DWs was weighted by the respective proportions (i.e. severe: 30% and non-severe: 70%) to derive a DW representing the disability of living with PA (Table S2).

Age of PA-induced death A mean age of death due to PA-induced fatal anaphylaxis was assumed to be 32 years of age as reported by Turner et al¹⁰ (Table S2).

Scenario analyses Scenario analyses (SA) were performed to estimate the impact of different model assumptions on the disease burden of PA. SA1 assessed the impact of assuming an earlier mean age of death to accommodate the possibility of higher risk in children and teenagers.^{8,11} SA2 assessed a zero risk of dying from PA induced anaphylaxis. The impact of the DW was assessed by applying: the DW for uncomplicated DM1, i.e. 0.049 (SA3); the mean DW of mild, moderate and severe asthma, i.e. 0.062 (SA4); and the mean of DWs for Crohn's disease and mild, moderate and severe RA, i.e. 0.310 (SA5).^{5,6}

Table S1. Point prevalence of peanut allergy reported in Danish cohorts.

Age group	Number participants	Confirmed cases	Prevalence (%)	Cohort (Reference)
< 3 years	111	0	0.00	DARC Birth cohort†, Osterballe et al. ¹²
3 years	486	1	0.21	
> 3 years	301	0	0.00	
> 20 years	936	4	0.43	
6 years	404	2	0.50	DARC Birth cohort, Kjaer et al. ¹³
18 months	137	1	0.73	DARC Birth cohort, Eller et al. ¹⁴
Adolescents	979	4.5‡	0.46	TOACS‡, Mortz et al. ¹⁵
22 years	843	5	0.59	TOACS, Osterballe et al. ¹⁶

†Danish Allergy Research Centre Birth cohort

‡ The Odense Adolescent Cohort Study. This number is derived by extrapolation of the prevalence of clinical relevant peanut allergy in individuals examined by Double Blind-Placebo Controlled oral Food Challenge to all individuals in the cohort with a positive skin prick test, as described in Mortz et al. (2005).

Table S2. Parameters to estimate incidence of peanut allergy in Denmark, related health outcomes and disability-adjusted life years (DALYs).

Model parameter	Notation	Value/distributional assumption	Reference
Mean Danish population size per year < 6 in 2016	pop	60012	Statistics Denmark ¹⁷

Proportion of peanut allergics in Denmark	Pr_{PA}	$rbeta(18.5; 4189.5)$	see supplementary table 1
Incidence of peanut allergy, 2016	Inc_{PA}	$Pr_{PA} * pop$	-
Probability of peanut allergy being persistent	$P1$	$1-(P2+P3)$	-
Probability of peanut allergy resolving	$P2$	$rpert(10, 22, 27)$	Begin et al. ²
Probability of peanut allergy induced death	$P3$	$rpert(1.09*10^{-6}, 2.31*10^{-6}, 4.6*10^{-6})$	Umasunthar et al. ⁴
Proportion with severe reactions	Pr_{severe}	0.30	Dechindre et al. ⁸
Proportion with non-severe reactions	$Pr_{non-severe}$	0.70	Dechindre et al. ⁸
Age of onset of peanut allergy	aoo	0	Sicherer et al. ¹⁸
Age of which peanut allergy resolves	aor	8	Begin et al. ²
Disability weight for living with peanut allergy - severe	DW_{severe}	$rpert(0.031, 0.049, 0.072)$	Global Burden of Disease Collaborative network ⁶
Disability weight for living with peanut allergy - non-severe	$DW_{non-severe}$	$rpert(0.053, 0.062, 0.081)$	Global Burden of Disease Collaborative network ⁶
Disability weight for living with peanut allergy	DW	$(Pr_{severe} * DW_{severe}) + (Pr_{non-severe} * DW_{non-severe})$	-
Age of peanut allergy-induced fatal anaphylaxis	aod	32	Turner et al. ¹⁰
Life expectancy at birth	LE_{0-5}	78.7	Statistics Denmark ¹⁹
Standard expected years of life lost	$SEYLL$	Dependent on age of death	World Health Organization ²⁰
DALY caused by persistent peanut allergy	$DALY_{persistent}$	$Inc_{PA} * P1 * DW * LE_{0-5}$	-
DALY caused by resolving peanut allergy	$DALY_{resolving}$	$Inc_{PA} * P2 * DW * (aor - aoo)$	-
DALY caused by peanut allergy-induced anaphylaxis	$DALY_{fatal}$	$Inc_{PA} * P3 * (aod - aoo) * DW + SEYLL$	-

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Figure S1. Computational disease model for peanut allergy (PA). P1 is the probability that an incident case of PA is a life-long (persistent) disorder, P2 is the probability that an incident case of PA resolves, P3 is the probability that an incident case of PA has a fatal outcome.