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The Blue Zones: areas of exceptional longevity around the world

Michel Poulain, Anne Herm and Gianni Pes*

Abstract

The aim of this study was to compare the level of population longevity and the characteristics of four geographic areas where unusually high proportions of long-lived individuals have been observed. For these areas (Ogliastra in Sardinia, Okinawa in Japan, the Nicoya peninsula in Costa Rica and the island of Ikaria in Greece). The term of 'blue zone' (BZ) given to these areas is defined as a limited region where the population shares a common lifestyle and environment and whose exceptional longevity has been accurately verified. This paper discusses the use of different indexes to measure the longevity of a population. As a preliminary result of our investigations we confirm the exceptional level of male longevity in the Sardinian BZ and both male and female longevity in Okinawa. Considering possible explanations, we observed that BZ populations are geographically and/or historically isolated (islands and mountainous regions). These populations succeeded in maintaining a traditional lifestyle implying an intense physical activity that extends beyond the age of 80, a reduced level of stress and intensive family and community support for their oldest olds as well as the consumption of locally produced food. This is likely to have facilitated the accumulation of ideal conditions capable of limiting the factors that negatively impact on health in most Western populations. These people experienced the epidemiological transition—and its implications—in relative recent times, and their remarkably good health status during ageing could be the result of a delicate balance between the benefits of the traditional lifestyle and those of modernity (increased wealth, better medical care). All these factors could have promoted an ideal milieu for the emergence of long-lived phenotypes at the population level.

* Michel Poulain (correspondance author), Estonian Institute for Population Studies, Tallinn University, Estonia; IACCHOS, Université catholique de Louvain, Belgium.
Email: michel.poulain@uclouvain.be

Anne Herm, Estonian Institute for Population Studies, Tallinn University, Estonia.

Gianni Pes, Department of Clinical and Experimental Medicine, Università degli Studi di Sassari, Italy.

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1 Individual longevity versus population longevity

Longevity is a phenomenon related to individuals (individual longevity) as well as to populations as a whole (population longevity). While an exceptional age at death or the extreme survival of the oldest old individuals generally allows identifying the first phenomenon, the second can only be characterised through various indexes that are mostly associated with life tables computed for that population as a whole. When searching for the determinants of population longevity, the relevant characteristics or behaviours are those shared by a large part of the population. By considering these common characteristics, the chance to find more powerful explanatory variables is increased as most persons concerned are born and live in the same place and thus are more likely to share the same genetic make-up, early life conditions as well as traditional behaviours and habits, including the same locally produced food. So, by identifying areas where people live the longest, the search for longevity determinants could be improved.

Practically speaking, gerontologists use the term longevity to refer to any individual who is beyond the age 90 and actively functional. Living to 100 is an attractive threshold in the lifespan for the media as well as for research although it does not have any demographic significance in itself. Other age thresholds could be used to define the gates of longevity[1] but the majority of research dealing with longevity considers usually centenarians. Based on the proportion of centenarians enumerated in censuses or mortality rates, the first potential longevity areas were identified at the beginning of the 20th century. The US Census Bureau compared the proportion of centenarians in different countries and pointed out the exceptional cases of Bolivia with 75 centenarians per 100,000 in 1900, Bulgaria with 60 in 1905 and the Philippines with 51 in 1903 (Bowerman 1939).

In the January 1973 issue of *National Geographic* magazine, the physician Alexander Leaf gave a detailed account of his journeys to countries of purported long-living people: the Hunzas from Pakistan, the Abkhazians from the Soviet Union, and Ecuadorians from Vilcabamba. According to Leaf, there were ten times more centenarians in these countries than in most Western countries and he pointed out that each of them was characterised by *poor sanitation, infectious diseases, high infant mortality, illiteracy, and a lack of modern medical care making the inhabitants' extreme longevity even more extraordinary* (Leaf 1973). However, some years later Mazess and Forman showed that age exaggeration was predominant in Vilcabamba with a large number of the men and women who tended to increase their age in order to improve their social status or to promote local tourism (Mazess and Forman 1979). Later Leaf acknowledged this conclusion and made a final statement agreeing

[1] As an example, in Okinawa, every year on the third Monday of September, during the 'Respect for the Aged Day', those persons who reached the age of 97 are celebrated by the local municipality following a special ritual called 'Kajimaya' symbolising one's return to youth (The Secret of Longevity the Okinawan Way! (http://www.dietriffic.com/2009/02/06/longevity/)

that no evidence proves the unusual ages in the village of Vilcabamba (Leaf 1981). More recently, demographers have become increasingly concerned with the accuracy of longevity claims given the unprecedented rise in very old people in developed countries (Jeune and Vaupel 1999; Young et al. 2010). As a consequence, more careful checks have been conducted resulting in a systematic invalidation of all allegedly long-living populations on earth as most claims of extreme age appeared to be undocumented or exaggerated. In 1999, following the publication of data showing extreme male longevity in Sardinia (Deiana et al. 1999), this scepticism pushed demographers to assess the validity of the alleged ages of the oldest olds in Sardinia (Koenig 2001). Based on a strict validation method, the ages of Sardinian centenarians were thoroughly proven to be correct (Poulain et al. 2006). This validation was based on investigations in the civil register of births from the two last decades of the XIX century and the register of deaths from the last two decades of the XX century. Considering the marginal annotation on death found in the birth register, all centenarians were identified by place of birth. Surprisingly, the spatial distribution of Sardinian centenarians according to their place of birth was far from random. Figure 1 helps to clarify the difference in the spatial distribution of centenarians in terms of low or high prevalence, as well as presence or absence of concentration of centenarians.

The number of centenarians born in a given place was reported to the number of newborns in the same place a century earlier. The spatial distribution of centenarians by place of birth smoothed by a Gaussian method was fully different from the original one that considered the distribution of centenarians by place of residence without considering the variation in the size of the population (Figures 1a and 1b).

As a result of the validation process, an area has been identified in the mountainous part of Sardinia with a significantly higher proportion of centenarians out of population born in the same place. This area was called the 'blue zone'[2] (Poulain et al. 2004) and the concept of *longevity blue zones* has since been elaborated as areas where the population is characterised by a significantly higher level of longevity compared with neighbouring regions, provided that the exceptional longevity of people in this population has been fully validated. **In practice, a *blue zone* (BZ) is defined as a rather limited and homogenous geographical area where the population shares the same lifestyle and environment and its longevity has been proved to be exceptionally high**. Other validated BZs have been found so far in Okinawa (Japan), on the Nicoya peninsula (Costa Rica) and on the island of Ikaria (Greece).

The advantages of the BZ concept are evident as potential longevity determinants may be found among common traits of the concerned population and characteristics of the shared lifestyle and environment. Moreover some of longevity determinants, identified for one BZ, could apply to populations of other BZs as well. Accordingly,

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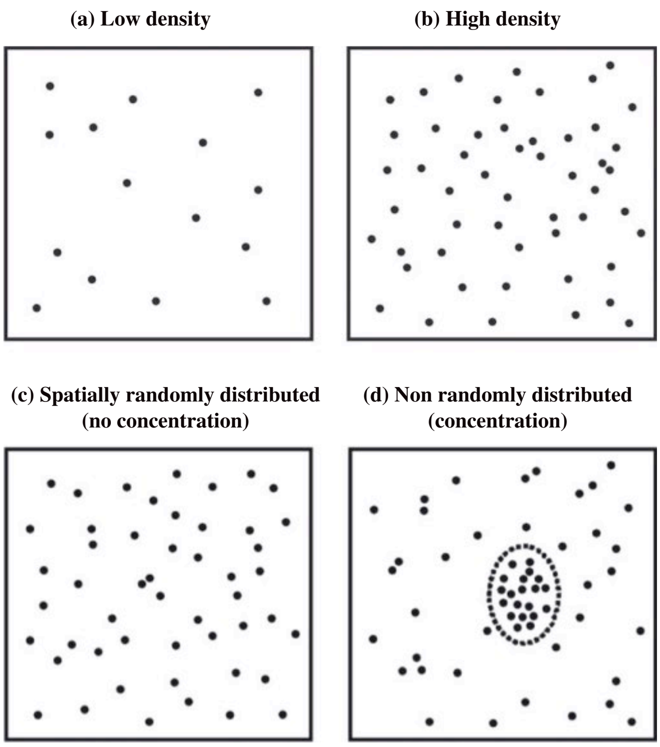
[2] The term was chosen simply because at the time the authors used a blue pen on a map to mark the villages with long-lived population.

Figures 1a, b, c and d:
Spatial distribution of long-lived subjects in a given area



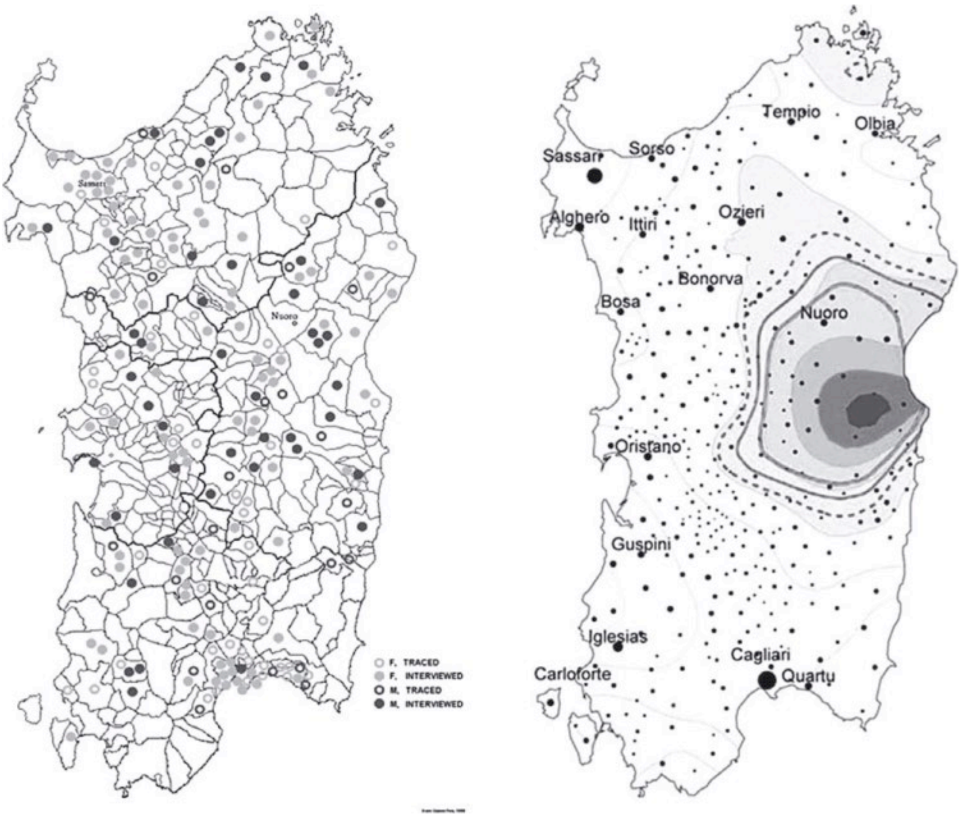
developing research investigations on several BZ populations and comparing their characteristics and behaviour is a potential step forwards when searching for longevity determinants. In this perspective, the present contribution proposes a first comparison of the longevity level as observed in the four BZs identified so far.

2 Data and method

To identify a BZ and to prove the exceptional longevity of its population it is necessary first to validate the individual longevity of people living in this area and more precisely to assess the exact age at death or the extreme survival of oldest olds in the concerned population. Age misreporting and, more specifically, age exaggeration must be ruled out. Perls explained that "*there are several geographical areas that have claimed inhabitants with extreme longevity",* and would be therefore considered as longevity areas, *"but after closer examination these claims have been found to be false"* (Perls et al. 2002). He concluded that such cases of extreme longevity

Figures 2a and 2b:
Spatial distribution of centenarians in Sardinia

(a) Crude distribution by place of residence **(b) Smoothed distribution by place of birth after adjusting for birth cohort size.**



required detailed scrutiny because they are so incredibly rare. Young et al. (2010) listed various cases of invalidation of extreme ages while Poulain (2010) applied validation rules on a selection of supposedly long-living persons. In addition to the validation rules for individual centenarians, the validation of an extreme population longevity demands several specific investigation steps that could vary depending on the current availability of data sources for every specific population. In order to assess the level of population longevity that is estimated through the average individual longevity within a given population, data on all births and deaths occurring within this population must be collected. The key objective is to ensure exhaustive data on births a century ago, data on currently surviving centenarians and data on deaths of centenarians during the last decades.

More precisely, the methodology used for identifying the first BZ in central Sardinia was the following one:

- a target area was selected covering all municipalities located in the Nuoro and Sassari provinces—two areas that emerged as potential places for exceptional longevity according to AKEA research results (Deiana et al. 1999);
- birth registers of municipalities in this area from 1880 to 1901 were scrutinised and the numbers of births were counted;
- based on marginal annotations of the date of death on the birth record, persons who died at age 100 and over were exhaustively identified;
- additional centenarians still alive were identified, whether they were surviving at their place of birth or elsewhere;[3]
- the age of each centenarian was validated according to accepted criteria for individual age validation;
- an Extreme Longevity Index (ELI) was computed as the ratio between the number of centenarians born between 1880 and 1901 and the total number of births recorded during the same time interval. This index, expressed as the number of centenarians per 10,000 newborns, is equivalent to the probability for any person born in that municipality to reach 100 years of age, there or anywhere else;
- thereafter a Gaussian spatial smoothing method was used to outline the area where ELI reached the maximum value.

The extreme longevity area identified in Sardinia and named as *Blue Zone* (BZ) includes a group of 14 villages in Barbagia and Ogliastra, covering the highest mountain area of Sardinia.[4] The total population of this BZ is currently about 40,000 inhabitants who are mainly engaged in pastoral and agricultural activities and follow a relatively traditional lifestyle.

During the period 1880–1900, covered by the centenarians validation project (AKEA II) 17,965 people were born within the BZ area, 91 persons (47 men and 44 women) among whom reached the age of 100. The resulting ELI values per 100,000 births are 512 and 506, for men and women respectively. For the rest of Sardinia, ELI values are significantly lower, with 103 for men and 264 for women (Poulain et al. 2004).

Starting from 2005, in cooperation with D. Buettner, a journalist writing for National Geographic, the BZ concept was extended to other relevant regions of the earth (Buettner 2012). Exceptional longevity at population level has been identified and validated so far in three other settings: the island of Okinawa in Japan, the peninsula of Nicoya in Costa Rica and the island of Ikaria in Greece (Figures 3). Compared to the situation in the first BZ in Sardinia, we faced more difficulties to

[3] The survival of centenarians born in the municipality and surviving outside was checked by contacting the family or the administration of the current municipality of residence.

[4] The highest mountain of Sardinia is *Punta La Marmora*, 1856 m above sea level.

validate the population longevity in these three BZs because of limited availability of appropriate data sources. Indeed the situation is quite different between the three settings.

In Okinawa, as elsewhere in Japan, the individual validation of age is based on the *koseki*, a family register containing records of all members of a family, including gender, dates and places of birth, names of parents, dates of marriage and divorce if any, date and place of death (Saito 2010). Unfortunately, for privacy reasons, data extracted from the *koseki* such as birth and death records are only accessible by directly asking the relatives of the concerned persons or for official legal proceedings (Willcox et al. 2008). Accordingly, individual age validation can only be performed by a direct interview of centenarians alive and comparing self-reported information during the interview with data found on their personal *koseki* documents. In 2005 Willcox et al. (2008) recruited 52 centenarians alive in Okinawa and reached the conclusion that 49 of them were actually older than 100 years of age while the other three were 2, 3 and 6 years younger than alleged. Censuses, statistics on age at death and regional life tables are available for Okinawa ensuring an exhaustive coverage of centenarians. Still, one must keep in mind that age in these data is often based on *koseki* records. Various additional investigations developed by Willcox et al. (2008) on aggregate statistics confirmed the overall reliability of the data. Even if some doubt still exists on the large number of centenarians found in Okinawa as demonstrated by the first author (Poulain 2011), the exceptional longevity in Okinawa could not be put into question and Okinawa should be considered as a BZ.

In the Nicoya Peninsula, the identification and validation of age of the oldest olds and the assessment of the population longevity were performed based on public voting lists (*padrón electoral*) disseminated by the Supreme Electoral Tribunal (*Tribunal Supremo de Elecciones*) and produced from the birth registry. The later includes data on births, naturalisations and deaths of all ever-living Costa Ricans who contacted the civil registration system since its computerisation in 1970 (Rosero-Bixby 2008). Each of them was given a unique identification number, either at birth or at naturalisation, appearing on their identification card or *cédula*. The age of the oldest olds appearing on their *cédula* was successfully confronted with self-reported information given during the interview. The data quality and the higher level of longevity in Nicoya in comparison to the rest of Costa Rica are confirmed by the results presented by Rosero-Bixby in this yearbook (2013). These support the BZ status of the Nicoya Peninsula.

In Ikaria, census data and age-at-death statistics obtained from Statistics Greece were considered and confronted with individual data extracted from the *dimotologio*, an administrative registry that includes demographic information on all Greek citizens of a given municipality. Unfortunately, for the oldest olds on the island no birth records could be found and therefore the extinct-cohort method based on an exhaustive identification of those surviving above 90 as well as of persons being part of the same birth cohorts who died during the two last decades was used to estimate the level of population longevity. Individual age validation was successfully achieved during an exhaustive base of interviews with all those aged 90 and above in the northern part of the island by using a battery of questions on the occurrence of demographic events and the age of close relatives (Poulain and Pes 2009).

3 First attempt to compare the BZs

Conventionally, the apparent exceptional longevity of a population is inferred from the existence of an unusually large proportion of centenarians/nonagenarians. The *centenarian prevalence* (CP), i.e. the ratio between the number of living centenarians in a given population and the total resident population, is largely used in the literature as well by the media. However, the reliability of this indicator for measuring and comparing longevity between different populations deserves critical evaluation as it is sensitive to a number of biases owing to migration and changes in fertility. For example, in case of a population that experienced large-scale immigration flows in the younger generations or a baby boom the CP will fail to identify remarkable survival of persons in old ages as the proportion of elders is artificially lowered. On the contrary, where the younger population has decreased due to emigration the proportion of elderly may result artificially increased. In such cases the prevalence or proportion of oldest olds is no longer reliable to measure longevity and to compare it between populations. Nevertheless, CP is still the most frequently used indicator by gerontologists as well as by national and regional authorities eager to claim a longevity status for the area of the concerned population.

Compared to CP, life tables provide a better measurement of longevity and allow comparing different populations more safely. The *cohort life table* is computed from mortality rates of a given birth cohort observed during one century or longer while the *period life table* is calculated on a fictive cohort by considering mortality rates for each age group at a given time. In most populations longevity is rising so fast that only the same cohorts of different populations should be compared and accordingly *cohort life tables* are preferred. Nevertheless computing a *cohort life table* is not a straightforward exercise as different methodologies and assumptions should be used while ad-hoc data are not always available. As a result, very few countries produce *cohort life tables* and no cohort life table exist up to now for any of the BZs.

A closely related indicator, the *Centenarian Rate* (CR), has been proposed by demographers to compare longevity levels. It has been introduced by Robine and Caselli (2005) as the ratio of the number of persons aged 100 years who were forty years earlier 60 years old in the same population or, more precisely, living within the same territory. This index is easy to calculate by using census data and is said to "*eliminate the impact of the size of the cohort, the role of migration, naturalization, fertility and infant mortality*" (Robine and Caselli 2005). However, there may still be

Figures 3:
Geographical location of the Ogliastra, Ikaria, Costa Rica and Okinawa BZs

some bias when migration flows between age 60 and 100 are not negligible.[5] The CR, as it was initially proposed, measures the average longevity of the members of a specific cohort by counting how many individuals who were 60 years old in the census forty years before the time of measurement and later reached age

5 This is a situation existing in some areas regarded as highly favourable for retirement, such as Florida in the US. In countries where retirement age coincides with a higher level of migration, it may be better to compare the survival between 75 and 100.

Table 1:
Centenarian Rate (CR) for the 1900 birth cohort (number of persons surviving to 100 years for 10,000 persons alive at 60 years)

Country	Females aged 60 in 1960	Females aged 100 in 2000	Female CR	Males aged 60 in 1960	Males aged 100 in 2000	Male CR
Italy	248 571	1 941	**78.1**	212 849	412	**19.4**
of which Sardinia	*5 889*	*64*	**108.7**	*5 594*	*25*	**44.7**
Japan	310 764	3 948	**127.1**	305 703	900	**29.5**
of which Okinawa	*2 925*	*145*	**495.7**	*2 069*	*17*	**82.2**
France	270 842	2 965	**109.5**	239 348	450	**18.8**
The Netherlands	52 213	388	**74.4**	47 247	83	**17.6**
Norway	19 652	146	**74.3**	17 798	27	**15.2**
Sweden	41 928	315	**75.1**	39 262	72	**18.3**
Switzerland	30 877	271	**87.8**	25 808	59	**22.9**
Australia	42 812	524	**122.5**	40 212	84	**21.0**
Belgium	57 847	300	**51.8**	50 438	51	**10.1**
Canada	60 070	1 080	**179.8**	61 456	244	**39.7**
Denmark	24 465	160	**65.4**	22 076	31	**14.0**
Finland	21 965	90	**41.0**	16 671	28	**16.8**
Poland	122 695	336	**27.4**	97 732	76	**7.8**
Russia	470 626	1 605	**34.1**	235 003	201	**8.5**
UK	318 869	2 438	**76.5**	270 280	288	**10.6**
USA	780 115	12 706	**162.9**	728 821	2 253	**30.9**

Source: Human Mortality Database (stock data) and national census data available through national statistical institutes for Sardinia and Okinawa.

100. Even if the specificity of the selected cohort may limit the comparative power of the CR, its advantage is that the data required for its computation are easily available from population censuses as well as in the Human Mortality database. Still, the interpretation of CR values relies on the assumption that the net international migration between ages 60 and 100 years can be neglected for the considered cohort.

Using the data from the *Human Mortality database* for observed countries, and data provided by the national data sources for Sardinia and Okinawa, we calculated the CR for the cohort born in 1900. For that specific cohort the observed number of persons aged 100 on 31 December 2000 was compared with the observed number of persons aged 60 in the same population on 31 December 1960, that is forty years earlier. The figures presented in Table 1 support the idea that males in Okinawa and Sardinia have a higher longevity compared to their peers in other countries. Extremely high values were observed for women in Okinawa, being three times higher than for women in all of Japan.

Although the CR can be used with some limitations to compare longevity at national level, it is less appropriate for smaller populations because of the limited number of persons reaching age 100 within a cohort corresponding to a single year of birth (among the BZs, only Okinawa has a sufficient number of centenarians to compute the CR). Accordingly, it is preferable to consider the between-census survival of broader population groups by comparing, for example, the number of persons aged 60–69 years in a 1970 census with those recorded thirty years later in a 2000 census and aged 90–99 or, alternatively, comparing the number of 60–79 years olds in 1970 and the aged 90+ thirty years later. In Table 2 these alternative CR are presented for the four longevity BZs as well as a few other countries. When interpreting these figures the possible bias resulting from migration should be kept in mind. In cases where the net migration cannot be neglected, these figures are automatically over-estimated if the population experienced a positive net migration during the 30 years' period before observation, or under-estimated in case of negative net migration. The figures in Table 2 display the superiority of Okinawa for women and of Sardinia for men. As for Ikaria, owing to high rates of emigration of old persons to the Athens Metropolitan Area, their figures are under-estimated. By contrast, for Costa Rica and Nicoya, important immigration from abroad and age exaggeration among nonagenarians in the 2000 census (Roxero-Bixby 2008) cause an inflation of CR.

The table in Appendix 1 shows summary ecological and socio-economic variables, selected from the existing literature, for the four BZs known so far, taking into account their possible role as longevity determinants. Most geographical features, though somewhat variable across the four sites, point predominantly to a condition of insularity and remoteness. The site altitude ranges from sea level to mid-mountain, with the highest value being found in the Sardinia BZ and the lowest in the Okinawa BZ. Average steepness of land, which correlates with altitude, reaches a maximum in the two Mediterranean islands and a minimum in Okinawa. The climate varies greatly across the four sites with a prevalence of relatively warm temperatures. A noteworthy observation, even when taking into account the large geographic heterogeneity of the four sites, is that high levels of sunlight, wind speed and humidity seem to be prevalent. Some socio-economic factors observed in the BZs, especially the lower degree of industrialisation and income per capita, seem to indicate the presence of populations emerging from a long-standing state of economic vulnerability although they may have experienced a constant improvement of their well-being level during the last few decades. Besides, some lifestyle and health indicators such as the moderate average calorie intake and the low prevalence of overweight/obesity in the adult population indicate a strong persistence of traditional habits, along with a low susceptibility to adopt a more Western lifestyle.

4 Discussion

The concept of BZ aims at characterising an area where a population sharing a common lifestyle and environment displays exceptionally high longevity. The first question to discuss is the very existence of such areas and whether the methods used to demonstrate their high level of longevity and compare longevity between

Table 2:
Probability to survive between 1970 and 2000 for the 1890–1919 birth cohorts

	Persons in 1970		**Persons in 2000**		**Survival rates (%) 1970–2000[1]**	
	Age 60–69	**Age 60–79**	**Age 90–99**	**Age 90+**	**90–99/60–69**	**90+/60–79**
Males						
Italy	2 311 202	3 384 724	84 276	85 131	3.1	2.0
Sardinia	58 178	87 965	3369	3 422	5.8	3.9
Villagrande	172	259	23	23	13.4***	8.9**
Japan	3 098 290	4 544 841	159 302	161 297	5.1	3.5
Okinawa	19 685	30 592	1978	2 031	10.0***	6.6***
Costa Rica	27 605	39 590	3 050	3 154	11.0	8.0
Nicoya	1700	2 347	211	221	12.4	9.4*
Greece	379 960	561 124	8 846	9 386	2.3	1.7
Ikaria	604	800	20	20	3.3	2.5
France	2 259 802	3 352 607	90 236	91 159	4.0	2.7
USA	7 117 859	11 011 845	312 843	318 473	4.4	2.9
Females						
Italy	2 697 844	4 292 653	257 827	262 360	9.6	6.1
Sardinia	61 377	98 411	6 446	6 580	10.5	6.7
Villagrande	166	269	22	23	13.3	8.6
Japan	3 467 619	4 514 236	464 402	473 879	13.4	10.5
Okinawa	28 258	46 237	7 226	7 544	25.6***	16.3***
Costa Rica	27 456	39 930	4 150	4 282	15.1	10.7
Nicoya	1 518	2 179	225	245	14.8	11.2
Greece	417 664	657 288	26 203	27 379	6.3	4.2
Ikaria	532	856	47	49	8.8*	5.7*
France	2 720 096	4 599 804	318 095	325 260	11.7	7.1
USA	8 407 784	13 815 593	1 025 834	1 060 367	12.2	7.7

Source: Data source: Human Mortality Database (stock data) and national census data available through national statistical institutes for Sardinia and Okinawa.
[1] The survival rates for Villagrande, Okinawa, Nicoya and Ikaria have been compared with the corresponding ones for Sardinia, Japan, Costa Rica and Greece, respectively. The statistical Z-test for two proportions shows significant differences at 5% (*), 1% (**) or 0.1% (***).

different populations are adequate. The second question is whether some ecological characteristics of the four BZs could be considered as potential determinants of the exceptional longevity of such populations. However, before discussing these two questions it is worth reminding that the age of a person is measured by the number of chronological years from birth. Therefore, validating accurately the age of every centenarian and ensuring the exhaustiveness of collected data is an absolute prerequisite for assessing and comparing the levels of population longevity. Inaccuracy in extreme ages has been often reported in the past and is still commonly found today in populations lacking civil registration (Kannisto 1988; Wilmoth and Lundstrom 1996; Poulain 2010). By the available evidence, data sources differ considerably between the four BZs, with the most favourable situation in Sardinia and the weakest one in Ikaria. Nevertheless, based on research done by other scientists as well as on our own investigations we are confident that the high level of longevity of these populations is real even if more in-depth validation could still be helpful to confirm our findings.

Among several indicators, which one should be considered ideal to compare longevity between different populations? We would briefly like to summarise the pros and cons of two indicators, i.e. CR and ELI.

- CR estimates the survival of cohort(s) between two different censuses. It can be computed by using census data or the Human Mortality Database under the hypothesis of the net international migration being negligible. Unfortunately, CR cannot be used to compare longevity at local level as cohorts may be too small and in a large number of cases no centenarians are found at the second census in many municipalities. Moreover, the assumption of negligible net migration, while possibly acceptable at national level, is no longer valid at local level where a significant number of old people may move away to another municipality, either to a nursing home or the residence of one of their children. Thus, CR cannot be used to compare the longevity between sizable long-living populations.
- ELI was used at local level in Sardinia because it was possible to match every birth with the corresponding death by using the marginal annotations in the birth register. This information allows identifying every death at age 100 and over, regardless of where it has occurred. Moreover, to overcome the problem of small number of newborns the data of all Sardinian cohorts from 1881 to 1901 included have been pooled. Unfortunately ELI cannot be computed in the three other BZs as birth registers are either lacking (Ikaria) or inaccessible (Okinawa) or no marginal annotations on death exist for every newborn (Nicoya).

Having in mind these limitations the data gathered in Table 2 confirm the exceptional longevity in Okinawa for both men and women compared to all of Japan while similar levels of longevity are also found in the Sardinian BZ compared to Sardinia as a whole, but for men only. Also women in Ikaria are shown to live longer than Greek women in general, which cannot be confirmed for men. Due to migration biases it has not been possible to prove any exceptional level of longevity in the Nicoya BZ and more details on the longevity registered in that population are proposed by Roxero-Bixby (2013) in this volume.

As far as the second point of the discussion is concerned, the comparison of the four BZs relies on the underlying assumption that, despite the large number of potential causes involved in the increased survival at individual level, a more limited subset of 'shared longevity determinants' may exist at population level. The utility of the BZ concept can be easily appreciated as these populations exhibit an unusual level of homogeneity in both environment and lifestyle. Moreover the comparison of the four BZs favours replication studies as well as testing of hypotheses across various ethnic and cultural settings. The comparison proposed here for the first time is rather limited, qualitative in essence, and takes into consideration only a few ecological and socio-cultural variables as potential predictors of longevity, selected on the basis of the available evidence and sparse literature data. Nevertheless some interesting features could emerge that will be the starting point for additional investigations.

Among the ecological variables, geographical features such as altitude and terrain steepness are particularly intriguing. Most populations who enjoy high life expectancy have been reported to live in mountains. Although many of them turned out to be myths (Leaf 1981) it has been suggested that living at high altitude could reduce the risk of mortality especially from cardiovascular disease. While this could be true for truly high elevations (above 1500 meters), it is rather questionable for lower altitudes. Besides, a recent study across US counties reported that after adjustment for confounding variables the association between altitude and life expectancy is no longer significant (Ezzati et al. 2012). Nevertheless, it is possible that people living even at modest elevation might benefit from positive effects on their health that could be partly explained by the relative isolation of these areas. As matter of fact, life in the mountains or on a remote island is associated with a set of tightly linked variables affecting both individual behaviour (diet, physical activity) and, more generally, the social context (habitat, economic activity, community support) and the environment (degree of pollution, quality of drinking water). All these factors are regarded as having a positive influence on health. Mountain environment is associated with increased land steepness which entails a constant stimulus for outdoor physical activity even by subjects in advanced age. Recently we have suggested that the elevated average slope of the terrain, fairly common in mountainous areas, may imply greater energy expenditure during active life, thus resulting in improved cardiorespiratory fitness, and ultimately in better survival (Pes et al. 2011).

In the past, populations living in mountains were likely to suffer from a degree of isolation that led to delayed economic growth compared to the whole country. During the early stages of industrialisation in Western countries, mountain areas were often regarded as backward pockets where traditional agro-pastoral activities persisted despite the rise of industrialism. However, this had important individual and social consequences, including a better preservation of the traditional habitat and a lower probability of coming into contact with health-threatening pollutants, not to mention a more satisfying and less alienated individual and occupational life. This, perhaps unintentionally, allowed a relevant proportion of the population to maintain the traditional way of life centred on tight social relationships, meaningful emotional exchange between generations and a considerable degree of support for weaker individuals by the community as a whole that in the long run could have been beneficial for survival.

The observation that all the BZs identified so far are slightly economically underdeveloped compared to the rest of their respective country, as reflected by their lower per capita income, seems to defy the so-called social gradient theory postulated by Evans (1994) stating that longevity would increase in proportion with the economic prosperity owing to its advantages in reducing anxiety and stress. When looking at the regional level, as highlighted by Cockerham (2000) in the case of Okinawa, areas ranking higher on levels of health are those where the process of modernisation came later and more slowly, as in the case of the three other BZs. This apparent discrepancy linking low income with longevity can be better understood if the economic development of these areas is evaluated in relative rather than absolute terms. When around the middle of the last century areas like Sardinia and Ikaria started their economic development, largely assisted by their governments, this resulted mainly in shifting from extreme poverty and deprivation to a relative material well-being, with limited social stratification. As pointed out by Poland (1998), the absence of a true class gradient and a consequent absence of social competition and individual stress, hallmarks of the Sardinian and Greek BZs, might have created significantly more favourable conditions for individual health than those operating in the more competitive mainland framework, a hypothesis that should be checked also for Okinawa and Nicoya.

Other life-shortening factors listed in Appendix A.1, such as smoking habits, the obesity rate and suicide prevalence, display a wide variation across the various BZs and their value is surprisingly high in some of them. This, however, does not provide evidence of their lack of influence on survival if we take into account two particular aspects: (i) the variable values might refer to the current population and do not necessarily reflect the historical situation of previous generations; (ii) the influence of potentially negative factors might be counteracted by concomitant factors acting in the opposite direction. The latter seems to be the cause of the paradox reported in some long-lived populations whose lifestyle appears to be unhealthy (Rajpathak 2011) yet it is buffered by coexisting protective factors. In this regard some dietary factors also deserve attention. The average caloric intake of the BZ's populations, with the possible exception of Okinawa, is not distinct from the general population of their mainland countries and does not fit the criteria for calorie restriction with optimum nutrition considered up to now the only longevity-promoting diet (Fontana 2010). Of course it is theoretically possible that not the quantity itself but rather the quality of food might have played an important role in maintaining a high standard of health in these populations, an aspect that will deserve further research.

In conclusion, the BZs, representing the extreme manifestation of population ageing operating in many contemporary populations as well, should be potentially regarded as a promising theoretical model, perhaps as important as the model of centenarians in the field of individual longevity. In fact, these rare populations to some extent might have retained significant longevity-related cause–effect links that in other post-industrial populations are masked by the effect of greater heterogeneity in genetic, socio-economic and lifestyle aspects.

5 Future scientific research and policy implications

The search for common longevity determinants in the different BZs is just beginning. Quantitative and qualitative surveys are currently under development in a comparative way for Sardinia and Ikaria, involving biomedical and behavioural aspects. A comprehensive approach is being considered, favouring the analysis of individual life as well as an anthropological viewpoint in order to understand how the various transitions experienced by the local community (fertility, epidemiology, education, communication, nutrition. . .) could have interacted to result in exceptional longevity. Additionally, blood samples are being collected to carry out some genetic and epigenetic investigations. In particular the study of DNA methylation is expected to be more useful in populations historically or geographically isolated such as the BZs, which were exposed to high levels of endogamy and have therefore progressively developed a significant reduction in their genetic diversity.

As far as policy implications are concerned, Appel (2008) expressed the thought that "*Blue Zones, now limited to just a few populations in the world, can become commonplace*". The question is how the lessons obtained from the BZs can be transposed for improving the healthy ageing of our post-industrial societies. This led Dan Buettner to initiate the Blue Zones Community Project, aimed at creating a programme at community level to help communities harness schools, businesses, families and governments into improving their residents' health and well-being.

The Blue Zones Project initiative to become a Blue Zones Community is a systems approach that allows citizens, schools, employers, restaurants, grocery stores and community leaders to work together on policies and programmes that will make the most impact and move the community towards optimal health and well-being. Blue Zones Project initiatives have been launched in several places in the US: Albert Lea in Minnesota, three beach cities near Los Angeles in California and, more recently, ten communities in Iowa. Specific lifestyle and environmental characteristics in each of the BZs are transposed to help American cities joining the project to optimise their own communities for better fitness and longevity.

For all Iowa communities, tools will be available to help them continue their path to improved wellbeing. The Blue Zones Project provides leadership training and guidance to help leaders transform their community, work and home environments. Can good-health practices of the world's longest-lived communities be transplanted into small US Midwestern cities? This is the real challenge. First results show how "*the Blue Zones impact in how people eat and exercise, how they find new ways to build community and get to know each other, how they are cutting back areas for smoking and expanding opportunities for altruism—all key elements in creating a Blue Zones community*" (Wolfe 2012). Nevertheless it is too early to assess the improvement in healthy ageing that could be associated with the implementation of the Blue Zone Community Project. Scientists should be attentive in the forthcoming years to develop accurate indicators that could help assessing the efficiency of such policy support initiatives.

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Appendix

Table A.1:
Ecological and socio-economic variables in the four BZ sites

	Okinawa BZ	Sardinia BZ	Ikaria BZ	Nicoya BZ
Geographic features				
Area (km^2)	1 201[a]	1 559[b]	255[c]	778[d]
Population	1 384 762[a]	42 113[b]	8 312[c]	326 953[d]
Density (inhab./sq km)	1 015	27	31	67
Average latitude	26° N	39° N	37° N	10° N
Site altitude	Sea level	Mid-mountain	Mid-mountain	Hills
Average land steepness	Low	High	High	Medium
Proximity to the sea	Yes	Yes	Yes	Yes
Climate				
Climate	Subtropical	Mediterranean	Mediterranean	Tropical
Average annual temp and range (°C)	22.4 (16–27)[e]	16.9 (16–18)[f]	18.9 (16–22)[g]	26.4 (23–28)[h]
Average annual rainfalls (mm)	~2 000[e]	~ 800 [i]	631[j]	2 178[h]
Relative humidity (%)	71[e]	65[i]	66[g]	81[h]
Land characteristics				
Main geologic features	Coralline limestone, volcanic rocks	Granite and basalt rocks	Granite rocks	Sedimentary rocks (limestone)
Background radioactivity	Low	High	High	Low
Drinking water hardness	High[k]	Low[l]	Low[m]	High[n]
Forest coverage (%)	46[o]	83.1[p]	> 80 [j]	3[q]
Socio-economic indexes				
Local income (LI) per capita	~$21 000[r]	$19 872[s]	$26 235[t]	$8 700[u]
Agriculture (% of LI)	1.9	1.4	12.2	18.2
Manufacturing (% of LI)	4.7	16.8	9.7	7.7
Services (% of LI)	89.5	81.8	78.1	64
Vehicles per 1,000 inhabitants	490[r]	360[b]	200[t]	177[u]
Lifestyle and health indicators				
Daily food intake per capita (kcal)	<2000[k]	2 600[v]	<1500[w]	2 392[x]
Smoking rate (%)	4.6[y]	~20[z]	82 (men)[w]	40.3[x]
Obesity rate (%, BMI above 30)	10–40[y]	8.7[aa]	12.5[w]	23.6[bb]
Suicide rate (cases/100,000)	32.1/33.5 (men)[cc] 9.1/14.6 (women)	15.3[dd]	2.35[ee]	7.3[ff]

Sources of data presented in Appendix 1

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RESEARCH ARTICLE

REVISED Effects of environmental change on agriculture, nutrition and health: A framework with a focus on fruits and vegetables [version 2; referees: 2 approved]

Previously titled: Effects of environmental change on population nutrition and health: A comprehensive framework with a focus on fruits and vegetables

Hanna L. Tuomisto [1], Pauline F.D. Scheelbeek [1], Zaid Chalabi[2], Rosemary Green[1], Richard D. Smith[2], Andy Haines[1,2], Alan D. Dangour [1]

[1]Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London, WC1E 7HT, UK
[2]Faculty of Public Health and Policy, London School of Hygiene & Tropical Medicine, London, WC1H 9SH, UK

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Abstract

Environmental changes are likely to affect agricultural production over the next decades. The interactions between environmental change, agricultural yields and crop quality, and the critical pathways to future diets and health outcomes are largely undefined. There are currently no quantitative models to test the impact of multiple environmental changes on nutrition and health outcomes. Using an interdisciplinary approach, we developed a framework to link the multiple interactions between environmental change, agricultural productivity and crop quality, population-level food availability, dietary intake and health outcomes, with a specific focus on fruits and vegetables. The main components of the framework consist of: i) socio-economic and societal factors, ii) environmental change stressors, iii) interventions and policies, iv) food system activities, v) food and nutrition security, and vi) health and well-being outcomes. The framework, based on currently available evidence, provides an overview of the multidimensional and complex interactions with feedback between environmental change, production of fruits and vegetables, diets and health, and forms the analytical basis for future modelling and scenario testing.

Open Peer Review

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	1	**2**
REVISED **version 2** published 31 Oct 2017	✔ report	✔ report
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1 **John McDermott**, International Food Policy Research Institute (IFPRI), USA

2 **Marco Springmann**, University of Oxford, UK

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Corresponding author: Pauline F.D. Scheelbeek (pauline.scheelbeek@lshtm.ac.uk)

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REVISED **Amendments from Version 1**

With the helpful comments of our reviewers we have improved our manuscript. In this updated version we have further clarified and justifed our focus on fruits and vegetables and changed the title, introduction and discussion to be consistent with this focus. Furthermore, we expanded the climate change, water quality and water availability sections and added a new section on adaptation and mitigation options.

In Figure 3 "heat stroke" was changed to "heat stress" to better reflect the many gradations of heat impact on producers health and labour productivity.

Furthermore, we adapted the conclusions to point out the various possible applications of the framework.

See referee reports

1. Introduction

In the next decades, the world population will continue to be confronted with environmental changes that pose increasing challenges to our food systems, health and well-being. These changes – such as climate change, increased ground-level ozone, changes in water availability, carbon dioxide fertilisation, soil degradation, deforestation and land use change – can directly and substantially influence agricultural production. In addition, variability in abundance and spread of pests, pathogens and pollinators – which are also related to environmental change – could form an additional, indirect impact on agriculture. Without successful and widespread implementation of adaptation and mitigation strategies aiming to overcome and/or reverse these environmental changes and their consequences, global food security, health and well-being could be significantly affected (IPCC, 2014).

The scale of impacts of environmental change on food systems and health will depend on a variety of environmental, behavioural and economic factors. Firstly, the magnitude of environmental change will depend on the current level and trends of different environmental stressors and the *mitigation* actions taken by both individual countries and the global society as a whole. For example, several countries are taking individual action to ban nicotinoid pesticides to protect insect pollinators, and the Paris agreement (UN, 2015) has committed the global community to mitigating future climate change. Secondly, the effects of environmental change will depend on the *adaptation* mechanisms developed and adopted. This could include changing agricultural production methods and altering the types of crop grown in certain areas that are less sensitive to certain environmental stressors. Thirdly, markets play a key role in distributing food between production and consumption locations. Globalised agricultural systems may be better placed to respond to changes in environmental conditions for food production, whereas food systems in areas that are strongly dependent on local markets may be more vulnerable to environmental change. Fourthly, food prices have an influence on consumer behaviour – consumption of some foods is much more sensitive to price changes than other foods. Finally, the effect of changing food availability on nutrition and health is likely to differ between countries and population groups, due to both price responsiveness and differences in pre-existing dietary patterns. Therefore, predicting the impacts of environmental changes on diets and health requires a detailed understanding of the various interactions and feedback loops between numerous actors and processes, as well as information on environmental, social and economic contexts.

Past research has been largely one-directional and limited to single steps in the pathways linking environment, food and health, e.g. concentrating on the impacts of environmental change on crops or the impacts of different diets on health. Research related to the impacts of environmental change on food production has mainly focused on the effects of climate change on staple crops (Challinor *et al.*, 2014; Knox *et al.*, 2012; Porter *et al.*, 2014), whereas the impacts on other foods and impacts from other environmental stressors have been less studied.

A few studies have integrated environmental change, agriculture, markets, nutrition and health (Myers *et al.*, 2017; Smith *et al.*, 2015; Springmann *et al.*, 2016a) focussing mostly on important staple crops and/or meat. These studies have provided better insight into the potential scale of the impact of environmental change on the food system but the nutritionally-important fruit and vegetable food-groups remain largely understudied. With their unique nutritional features, significance for public health and relatively low environmental footprint (Clune *et al.*, 2017), fruits and vegetables have the potential to play a crucial role in healthy population diets of the future.

The association between low consumption of fruits and vegetables and risk of non-communicable diseases (NCDs) including cardiovascular diseases and certain types of cancer (Forouzanfar *et al.*, 2016; Miller *et al.*, 2017) is well established. Furthermore, recent research has shown that even beyond the WHO recommendation of 400 grams a day, higher intake of fruits and vegetables continues to reduce risk of cardiovascular disease, cancer and all-cause mortality (Aune *et al.*, 2017). The consumption of fruits and vegetables per person has been shown to be linked with socioeconomic status: low income countries have lower consumption per capita than high income countries (Miller *et al.*, 2016a), and within countries consumption has been found to be lower in poor neighbourhoods than in wealthier ones (Dubowitz *et al.*, 2008; Pessoa *et al.*, 2015). However, many fruit and vegetable crops prove to be relatively sensitive to environmental changes (Backlund *et al.*, 2008) raising the prospect of reduced fruit and vegetable availability in the future with contingent public health concerns.

We focus in this paper specifically on fruits and vegetables due to their nutritional importance. The aim of this paper is to illustrate a set of pathways that connect environmental changes, production of fruits and vegetables, nutrition and health in a comprehensive framework. The framework provides a basis for the identification and detailed modelling of the key pathways that link environmental change – through agriculture and nutrition – with population health. Even though this paper focuses on fruits and vegetables, we acknowledge the importance of also considering staple crop and livestock production in a comprehensive analysis. Furthermore, the framework considers only pathways that impact health through nutrition, whereas direct health impacts of environmental changes (for example through air pollution, extreme weather events or infectious diseases) are not included in this paper.

2. Methods

The framework was constructed based on an extensive literature search, including both peer-reviewed and grey literature. First, the literature was searched for existing frameworks covering several parts of the environmental change, agriculture, nutrition and health nexus. The identified existing frameworks, such as Ingram (2011) and McMichael (2003), informed the selection of main components for the new framework and facilitated hypothesis formulation around impact pathways. Subsequently, evidence was gathered (preferably in the form of systematic reviews) to establish the main pathways linking environmental change (through agriculture) with nutrition and health. This exercise included consultations with experts working in the fields of environment, agriculture, trade, nutrition and health including those studying the temporal trends and impact of specific environmental stressors.

The framework is graphically presented in three stages: i) a schematic overview of the links between environmental change, food systems, nutrition and health (Section 3, Figure 1); ii) illustration of the interactions between different environmental stressors (Section 4, Figure 2); and iii) the links between environmental stressors and production of fruits and vegetables (Section 4, Figure 3). The following section presents an overview of mechanisms through which the most important interactions between environmental change and production of fruits and vegetables operate (Section 4). The potential consequences of environmental change on food security (through changes in the availability of fruits and vegetables), nutrition and health outcomes are discussed in Section 5. The feedback loops from dietary choices to agricultural production and the impacts of agriculture on environmental change are discussed in Section 6 and the adaptation and mitigation strategies in Section 7. It was outside of the scope of this article to provide a systematic review of each interaction in the framework, neither was it possible to quantify and rank each individual stressor in terms of the strength of the evidence. We intend, however, to contribute to this evidence base through our future work.

3. Overall framework

Within the overall framework (Figure 1), we refer to the boxes and the arrows in the figure with the symbols ■ and ▲, respectively, followed by a corresponding letter or number) six main components are distinguished to map the interactions between environmental change, agriculture, and nutrition: i) socio-economic and societal factors (■ A); ii) environmental changes (■ B); iii) interventions and policies (■ C); iv) food system activities (■ D); v) food and nutrition security (■ E); and vi) nutritional health and well-being (■ F) (Figure 1). The socio-economic factors, such as culture, religion, wealth distribution and population structure provide the context for environmental change, interventions and policies, food system activities, level of food and nutrition security and nutrition related health and well-being. The environmental changes include stressors that directly affect food systems (▲1, *Section 4*). The interventions component includes research and innovation, technological development and government policies that provide the boundaries, opportunities and restrictions to the interactions between environmental changes, food system activities, food and nutrition security, health and well-being (▲2, 3, 12). The food system activities component covers the interlinked food system functions, including production of inputs and infrastructure, agricultural processes, food processing, trade, consumption and waste management (▲4–11). In the framework, food and nutrition security are identified as a fifth component group, which are important determinants of the burden of disease and well-being. The framework presents a static conceptualisation of the interactions, although we recognise that the interactions are dynamic and operate over different time scales. For example, changes in food prices can have an immediate impact on food consumption, whereas the impacts of some environmental changes on health outcomes may be seen only after a few decades.

4. Impacts of environmental change on production of fruits and vegetables

4.1. Climate change

Climate change has been predicted to impact agricultural production through multiple direct and indirect pathways (Porter *et al.*, 2014; Smith *et al.*, 2014). Changes in temperature and water availability combined with increased variation in weather conditions and more frequent episodic weather events will have a direct impact on crop yields (Lobell & Gourdji, 2012). Increased temperature results in faster crop growth, and therefore, shorter cropping seasons and lower yields. Temperature also impacts on photosynthesis rates and respiration. C4 crops (maize, sorghum, sugarcane, etc.) have higher optimum temperature for photosynthesis than C3 crops (cereals and most vegetables and fruits).

Climate change can have also some positive impacts as on crop production as increased carbon dioxide concentrations in the atmosphere can boost photosynthesis of C3 crops and water use efficiency in both C3 and C4 crops, and improve crop growth (Long *et al.*, 2006). At the same time, however, this can lead to a reduction in protein, vitamin and mineral concentrations in the edible part of the crop, possibly due to reduced canopy transpiration or changes in metabolite or enzyme concentration (McGrath & Lobell, 2013). This phenomenon was studied by Myers and colleagues who modelled the impact of CO_2 on staple and legume crops and found that the impact of CO_2 was very different for C3 plants compared to C4 plants (Myers *et al.*, 2014; Myers *et al.*, 2015). Nearly all fruits and vegetables in the human diet are C3 crops and hence are likely to be relatively vulnerable to these climatic changes. While research on drought and heat resistant staple crops has taken off greatly in the last decades, adaptive capacities in fruits and vegetables are less studied.

Besides the direct effects, increased temperatures may indirectly affect fruit and vegetables yields due to decreased labour productivity of farmers, affecting agricultural productivity (Kjellstrom *et al.*, 2016). Many fruit and vegetable crops require high labour inputs, especially for planting and harvesting and hence climate change induced heat stress may disproportionately affect this sector.

Climate change affects many other environmental drivers, both directly and indirectly (Figure 2). For example, rising temperatures increase tropospheric (i.e. ground-level) ozone formation, and increased ozone levels cause oxidative stress for plants, which reduces photosynthesis and plant growth (Ainsworth *et al.*, 2012). Furthermore, climate change has impacts on animal species, and a

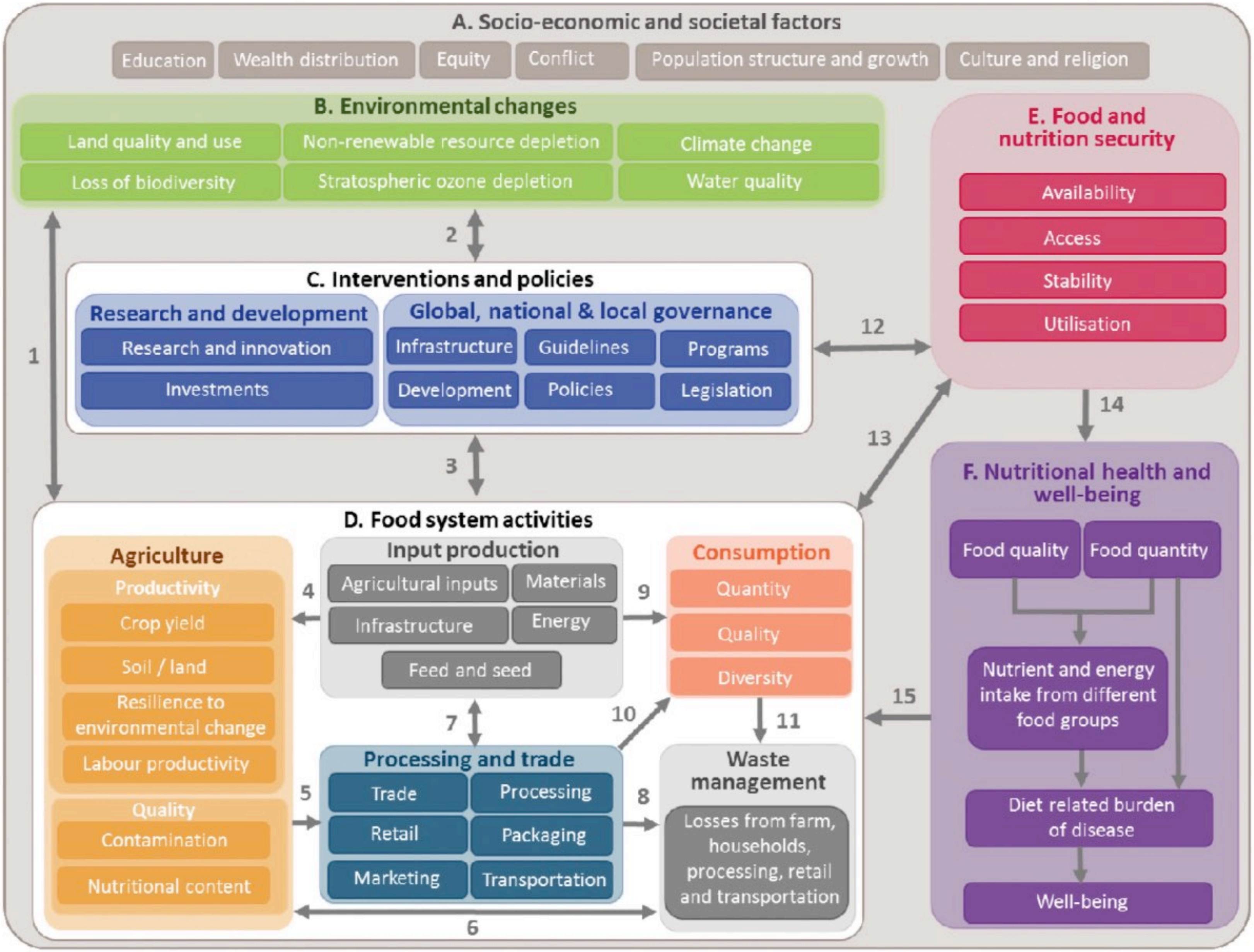

Figure 1. Overall framework connecting environmental change, agriculture, nutrition and health.

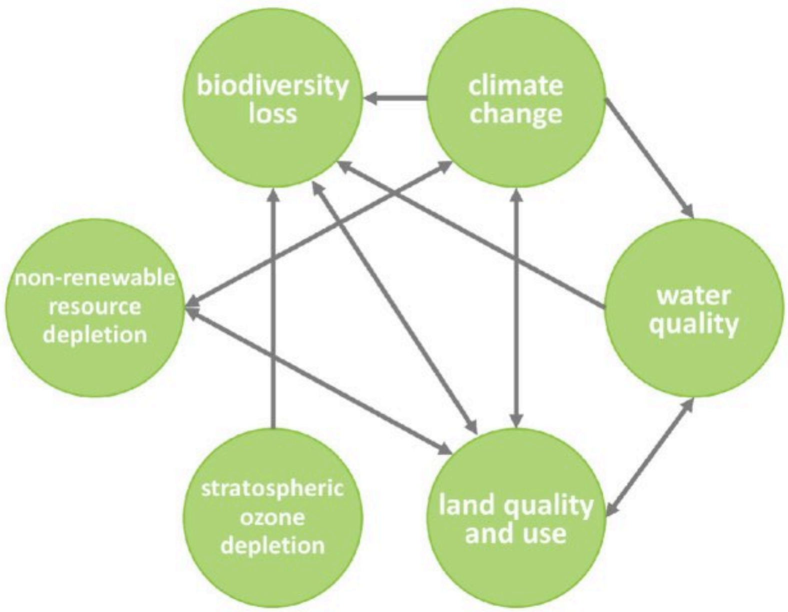

Figure 2. Links between environmental changes.

decrease of plant pollinator populations, for example, could have multiple impacts on agricultural production (Pacifici *et al.*, 2015) (see Section 4.6). Climate change is also likely to increase crop losses and damages due to pests, pathogens, fungi and weeds (Flood, 2010). It has been estimated that hundreds of pests and pathogens have moved towards poles on average by 2.7 km yr^{-1} between 1960 and 2012 (Bebber *et al*., 2013).

4.2. Historical ozone depletion & current ozone layer recovery

The stratospheric ozone layer, protecting the earth from solar ultraviolet (UV) radiation, has been depleting over the past decades due to anthropogenic emissions of chlorofluorocarbon and nitrous oxides, although the recent evidence indicates healing of the ozone layer due to reduced cholofluorocarbon emissions (Solomon *et al*., 2016). However, in Antarctica, ozone depletion continues to occur each year, whereas the Arctic ozone shows high year-to-year variability (Andrady *et al.*, 2015).

Many factors such as cloud cover, altitude, ground reflectance and atmospheric path length, impact on the level of UV-B reaching plants. Due to the natural variations of those factors, the effect of stabilization of the ozone layer is not yet detected in the measurements of UV-B radiation.

UV-B radiation has been found to damage DNA, RNA, proteins and membranes of plants and to impair photosynthesis (Björn *et al.*, 1999; Caldwell *et al.*, 2007). A meta-analysis of the effect of increases in UV-B on yields found that herbaceous plants including most vegetables (e.g. beans, tomatoes, spinach, radish, carrots, cucumber and gourd) and many fruits (such as strawberries and sea-buckthorn) showed a more significant decrease in yield due to the UV-B exposure than woody plants (Li *et al.*, 2010).

4.3. Water quality

The quality of irrigation water has a direct impact on crop quality and quantity. In the past decades, several trends in water quality – with a strong link to environmental change – have put increasing pressure on the agricultural sector, and it is expected that these trends will continue in the future (Turral *et al.*, 2011).

Salinization is major threat to irrigation water quality. Salt tolerance levels vary greatly from crop to crop. Predominantly, salinization decreases yields, but the impact on crop quality is mixed (Hoffman *et al.*, 1989). Many vegetable crops are negatively affected and salinity can substantially reduce their market value. However, in some crops, such as carrots and asparagus, salinity can increase sugar content, whilst in tomato and melon it can increase soluble solids. Generally, however, salinity-induced decreases in yield outweigh any beneficial effects (Hoffman, 2010).

Climate change may exacerbate salinity problems which in turn impact health through drinking water and diet (Khan *et al.*, 2014; Scheelbeek *et al.*, 2017). In several low-lying coastal areas, the increased frequency of tropical cyclones and inundations can have a serious impact on the sodium (and other salts) content of soils as well as ground- and surface-water. In climate-vulnerable coastal areas, such as Bangladesh, an additional problem arises when farmers move away from saline irrigation sources and obtain water from deeper groundwater layers; high arsenic concentrations have been measured in these groundwater sources. Arsenic can remain on the crop's surface after harvesting and could form a serious health threat to its consumers (Das *et al.*, 2004; Su *et al.*, 2014). Further inland, changing precipitation patterns and drought can cause significant increase in sodium concentrations in freshwater bodies, affecting irrigation and drinking water quality (Jeppesen *et al.*, 2015).

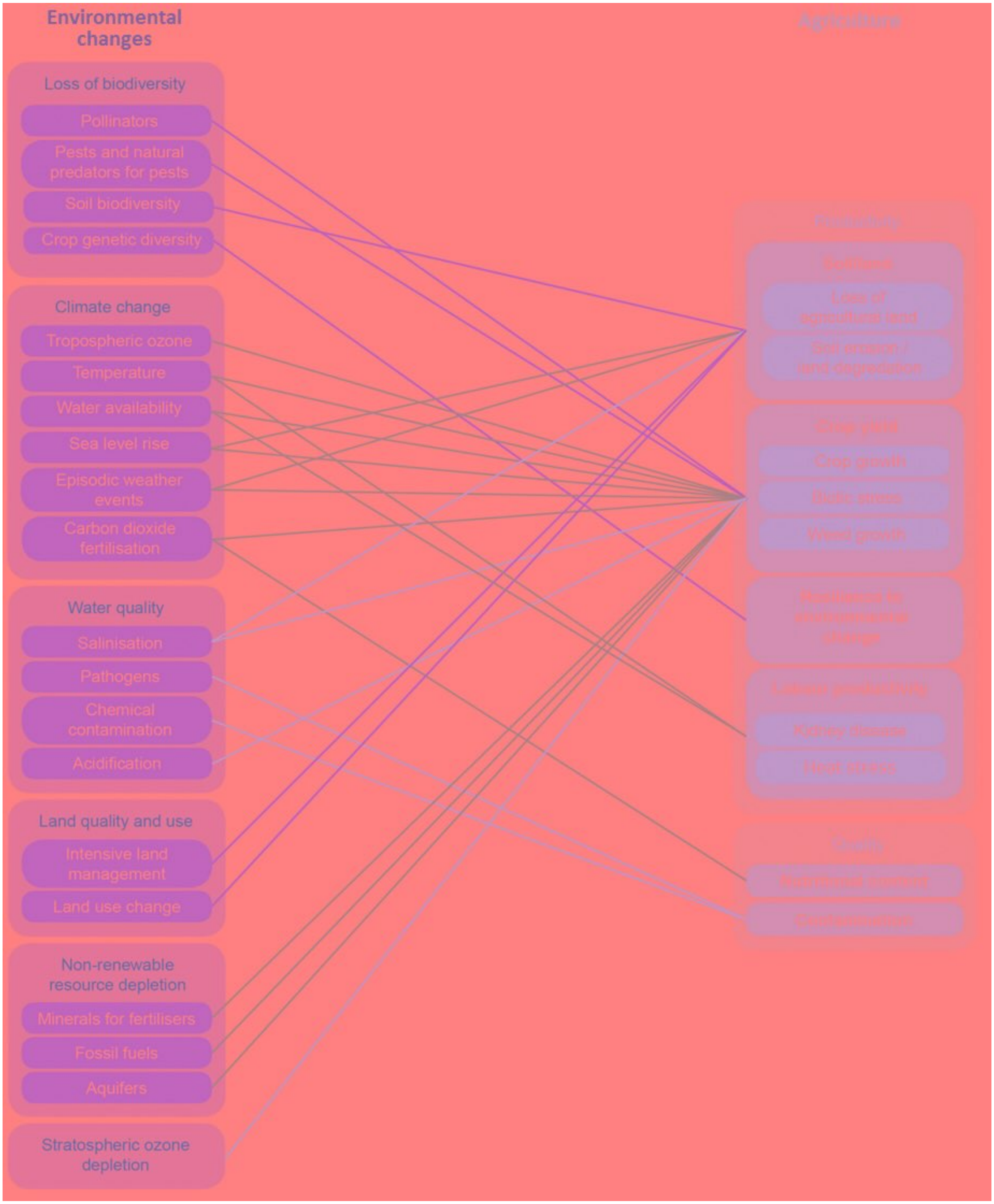

Figure 3. Pathways between environmental changes and agriculture.

Contaminated irrigation water affects crop quantity and quality significantly. More than 10% of the global population consumes foods that are irrigated with untreated wastewater or faecal contaminated surface water, and most of those people live in low-income countries with arid and semi-arid climates (WHO, 2006). Increasing water scarcity, expanding populations and recognition of the fertilisation value of wastewater are the main drivers for the increasing use contaminated water for irrigation. The use of pathogen (e.g. Salmonella spp., norovirus, E. coli, Clostridium perfringens and Cambylobacter spp.) contaminated urban wastewater for irrigation and post-harvest processes has been linked to food-borne disease outbreaks (Antwi-Agyei *et al*., 2015; WHO, 2015). This is particularly a problem with fruits and vegetables that are often eaten without cooking.

Problems also occur if high concentrations of certain toxic ions in irrigation water - such as chloride, sodium and boron - are taken up by the plant and accumulate to concentrations that can cause damage in the crop and reduce yields (Bañón *et al*., 2011). Both agricultural and industrial factors play an important role in toxin concentrations in water, including chemical wastewater being released in watersheds used for agriculture and/or pumping up irrigation water, as well as farm-disposal of agrochemicals. Most irrigation water sources contain concentrations of elements below toxicity thresholds; however, boron tolerance of most vegetable crops is relatively low and even quite low boron concentrations could damage crops (Hoffman, 2010). The magnitude of damage varies per crop; permanent perennial-type crops are believed to be most sensitive to irrigation water toxicity (WHO, 2006).

A third important water quality threat is the occurrence of excessive nutrients in irrigation water, notably nitrogen. This is often the result of (over)fertilisation of agricultural land, whereby excess fertilisers end up in water sources used for irrigation and may damage marine ecosystems. In susceptible crops - such as apricot, citrus and avocado - high nitrogen concentrations trigger excessive vegetative growth and delay of maturing. In leafy vegetables, this causes a decrease in harvestable product and could negatively affect fruit quality parameters, such as sugar content (Ayers & Westcot, 1985). It could also cause crops to grow taller and hence to be more vulnerable to lodging (bending over of stems) in extreme weather events, such as tropical storms.

4.4. Non-renewable resource depletion

Non-renewable resource depletion includes reduced availability of minerals used for fossil fuels, fertilisers or infrastructure, and depletion of aquifers that can be used for irrigation water. The reduced availability of these resources can have an impact on crop production, unless alternative technologies are adopted (e.g. use of renewable energy sources or organic fertilisers).

For example, it has been estimated that the current economically exploitable phosphate reserves will be depleted in approximately 50–100 years (Cordell *et al*., 2009). Therefore, options to recycle nutrients back to the fields from bio-waste and sewage sludge may become more financially attractive. Similarly, industrial agriculture relies heavily on the use of fossil fuels for producing nitrogen fertilisers, running farm machinery and other uses. The depletion of fossil fuel reserves or the inability to exploit them because of climate change imperatives may pose a threat for agricultural production unless renewable energy sources can be significantly scaled up. However, this will be more of a problem in industrial farming systems than in subsistence farming that relies mainly on manual labour.

Finally, the depletion of water resources can have negative impacts on agricultural production, especially in areas where aquifers provide an important source of irrigation water. The depletion of aquifers is linked to changes in precipitation levels, exhaustion of rivers and increased use of water. Climate model simulations project precipitation increases in high latitudes and parts of the tropics, and decreases in some tropical and lower mid-latitude regions (Bates *et al*., 2008). Poor rural farmers in the arid and semi-arid tropics and Asian and African mega-deltas are likely to be the most vulnerable to these changes in water availability. Furthermore, international food trade contributes to the decline of aquifers in the producing countries (Dalin *et al*., 2017). Most of the irrigation water globally is used for staple crops (mainly for wheat) and less than 10% of all irrigation water is used for fruits and vegetables, which is in line with the percentage of land used for fruits and vegetables (FAOSTAT, 2017).

4.5. Land use

Agricultural land is a limited natural resource. It is estimated that nearly a third of global arable land has been lost due to soil erosion and pollution during the past 40 years (Cameron *et al*., 2015). Other reasons for loss of agricultural land include urbanisation, sea level rise, and renewable energy production (e.g. solar panels on agricultural land), as well as land requirements for bio-fuels and other non-food crops. At the same time, forests have been converted to agricultural land, mainly driven by increased consumption of meat and need of land for feed production. Therefore, the percentage of agricultural area of the total global land area has been relatively stable during the past decades. However, deforestation contribute to the acceleration of many environmental changes, such as climate change and loss of biodiversity, and therefore, can have negative indirect impacts on food security, e.g. through loss of wild foods (Section 6).

Soil degradation typically refers to multiple processes, such as erosion, desertification, salinization, compaction and encroachment of invasive species (Gibbs & Salmon, 2015). Soil organic matter plays a vital role in maintaining the long-term productivity of soils. The increased use of industrial farming practices, such as monocropping, minimal use of organic fertilisers and removal of crop residues from fields, is one of the main reasons for decline in soil organic matter contents.

Acidification of soils is caused by acid rains or use of synthetic nitrogen fertilisers in some conditions. Acid rains generally result from the reaction of water molecules and sulphur dioxide or nitrogen oxide in the atmosphere, which mainly originate from anthropogenic sources, such as energy generation and industrial processes (Klimont *et al*., 2013). Soil acidification can alter nutrient availability, and has generally negative impact on plant growth, except in alkaline soils some acidification can be beneficial (Lee *et al.*, 1981). Application of lime and balanced fertilisers help to mitigate crop losses caused by acidification (Mason *et al.*, 1994).

Phytotoxicity means the toxic effect on plants caused by compounds such as trace metals, allelochemicals, pesticides, phytotoxins or salinity. Contamination of soil with toxic metals, such as cadmium and high concentrations of aluminium, has negative impacts both on crop yields and human health (Khan *et al.*, 2015). Metals cause oxidative stress for plants, which reduces biomass accumulation.

4.6. Biodiversity loss

In some cases, losses of biodiversity can have direct impacts on food availability in areas where wild food, including wild fruits and vegetables, comprise a substantial proportion of diets. Field-grown crops and livestock are also heavily dependent on multiple ecosystem services, such as pollination, natural predation of pests and services provided by soil macro- and micro-organisms.

During the past decade, the numbers of pollinators have declined, due to combined stress from parasites, pesticides and habitat loss (Goulson *et al.*, 2015). As many fruit and vegetable species rely on pollinators, a complete loss of pollinators has been predicted to reduce global fruit supply by 23%, vegetables by 16% and nuts and seeds by 22% with major adverse effects on health (Smith *et al.*, 2015).

Ecosystem functions are complex and it is currently not possible to model the required level of biodiversity needed for sustaining agricultural production. Therefore, maintaining a high level of biodiversity is regarded as a precautionary mechanism that increases the resilience of agro-ecosystems to environmental changes (Koohafkan *et al.*, 2012; Lin, 2011). Farming practices that reduce vulnerability to environmental change include diversification of agro-ecosystems, high genetic diversity of crops, integration of livestock and crop production, management of soil organic matter and water conservation. Crop diversification reduces pest, disease and weed outbreaks, and increases resilience towards greater climate variability and extreme events. In low income settings, farms with a high level of biodiversity have been found to be more resilient to climate disasters, such as hurricanes and droughts (Altieri *et al.*, 2015). Smallholder farmers in tropical regions are particularly vulnerable to climate variability, including erratic rainfall, and as a coping mechanism they rely on agricultural biodiversity, such as planting a high diversity of crops each year, including many varieties of the same crop, using drought tolerant crop varieties, changing the locations of crops and planting trees to provide shade and to maintain humidity (Meldrum *et al.*, 2013).

5. Impact of drivers, influencers and activities on food security and health outcomes

5.1. Links between agriculture and food security: From subsistence farming to international trade

The most direct link between agriculture and food security occurs in subsistence farming communities and involves the production and quality of crops and their impact on the availability of nutritious food to producing households. Most people living in the rural areas in low income countries, especially in sub-Saharan Africa, are dependent from subsistence farming, and 72% of all farms in the world are under 1 hectare (FAO, 2014; Herrero *et al.*, 2017).

Considering the predominantly negative influences of environmental stressors on both fruit and vegetable yield and quality (see previous sections), populations heavily reliant on subsistence farming appear likely to have food insecurity in the future (Morton, 2007; Shrestha & Nepal, 2016; Tibesigwa *et al.*, 2015). The extent of these influences on their nutrition and health depends on the farmers' ability to adapt to these environmental changes (Shisanya & Mafongoya, 2016). Many subsistence farmers are particularly vulnerable due to a high dependence on rain-fed agriculture and limited adaptation strategies: rain-fed agriculture accounts for approximately 95% of farmed land in sub-Saharan Africa and 90% in Latin America (Wani *et al.*, 2009). Moreover, in contexts where agricultural surpluses are sold at the local market as critical sources of cash, reduced yields will likely decrease household incomes.

In larger and more complex trade systems – ranging from farmers producing for the local markets to agribusinesses and international trade – a more complex interplay of mechanisms determine the impact of suboptimal yields on food security, including market mechanisms and food choices (Figure 1, ■ D), possible technological or political interventions (Figure 1, ■ C) and the influence of social factors (Figure 1, ■ A).

Compromised production – and therewith reduced availability – of a locally important vegetable could, for example, push up local or regional prices, and make the specific vegetable unaffordable for the less affluent (Brown *et al.*, 2012). Households' purchasing power and preference will determine their substitution strategy, e.g. buying another cheaper vegetable if available, buying more staples, or not substituting the "missing" vegetable. The price elasticities of fruits and vegetables tend to be higher than those for cereals, which means that consumers reduce their demand more in response to an increase in price (Cornelsen *et al.*, 2015). The household substitution strategy used will partly determine the scale of health impacts (UNSCS, 2010).

Forced switches to alternative crops could also have far reaching consequences for farmers, in case the switches become permanent (i.e. consumers start preferring the "new" vegetable above the "conventional" one), as sometimes experienced after temporary food aid programmes (Barrett, 2006). This applies especially to small farmers that might lack the financial resources to shift to another (more commercial) crop as a response to the changed commodity prices, even if this would be much more profitable (García-Germán *et al.*, 2013). Higher prices may push subsistence farmers to sell more and consume less of their own yields, which could also have an impact on their food security (Anríquez *et al.*, 2013; Zezza *et al.*, 2008). Nonetheless, it has been argued that higher food prices will generally affect food security of net consumer countries more than net producer countries (ODI, 2008), and nutritional health, especially among children under 5 years of age (Figure 1, ▲13, 14). In larger markets with more producers integrated across diverse environments, the abundance of competitors offering the same vegetable crop may stabilise the commodity prices, and may therefore directly affect the financial security of farmers that experienced compromised yields of that specific vegetable.

Crop quality, including nutritional content, may affect dietary micronutrient supplies of consumers and subsistence farmers. Especially in areas where nutritional needs are only marginally met or where there is a widespread marginal nutrient deficiency, slight changes in vitamin and mineral concentration in crops – even without any actual change in diet – could be crucial for food and nutrition security. Fruits and vegetables are therefore particularly important as they provide a rich source of essential micronutrients that are present in much lower concentrations in other food groups.

5.2. Links between food security, consumption, health and well-being

There is a substantial evidence base on the impact of food security on population diets. Furthermore, the links between diets, health and well-being are the most well-researched parts of the framework (Figure 1,▲14). Non-optimal diets are estimated to account for ~10% of the global burden of disease (Forouzanfar *et al.*, 2016).

There are two main pathways leading from nutrition to population health: non-optimal *quantity* of food intake (under- and over-nutrition) and non-optimal *quality* of food intake (nutrient deficiencies due to poor dietary composition, toxins, pathogens, etc.). In terms of the former pathway, overweight and obesity increases the risk of various NCDs, including diabetes, certain cancers and cardiovascular disease, whilst undernutrition can lead to several deficiencies, affecting, for example, child growth and development and immune system function (Figure 1, ■ F).

As well as contributing to daily dietary energy requirements, fruits and vegetables play a key role in the second pathway, linking sub-optimal quality of food intake and poor health. For many populations around the world, fruits and vegetables provide several essential vitamins, minerals and amino acids usually found in limited amounts in other components of the diet, particularly where consumption of animal-source foods is low. Low fruit and vegetable intake is associated with increased risk of vitamin deficiencies, all-cause mortality, coronary heart disease, strokes, and several types of cancer (Forouzanfar *et al.*, 2016; Miller *et al.*, 2017; Wang *et al.*, 2014).

To further explore the importance of the pathway between fruit and vegetable consumption and health, full dietary composition (i.e. consumption besides fruits and vegetables) should be considered, as well as the drivers for food choices. Low fruit and vegetable intake can in some situations be the direct results of food insecurity (i.e. limited access, affordability of stability of fruits and vegetables), whilst in other situations it reflects the population's preferences to consume foods high in sugar, salt and saturated fats instead of fruits and vegetables.

Where clinical health outcomes are difficult to measure, anthropometric indicators, such as height-for-age, weight-for-height and biomarkers, including cholesterol level, blood pressure and blood glucose, can be used for modelling the health implications of a diet.

6. Feedback loops from dietary choices and agriculture to environmental change

The framework highlights that – in addition to the described "environment – food system – health" pathway – there are several feedback loops linking dietary choices and nutrition back to agricultural strategies (Figure 1, ▲15) and environmental change (Figure 1, ▲1).

A remarkable example of these feedback loops is based on the rapid global shift towards a more "Western" diet, which is driven by urbanisation, economic growth and changes in technology and culture (Popkin, 2006; Tilman & Clark, 2014). Western diets are characterised by greater consumption of animal source and highly processed foods often in parallel with a reduction of the consumption of vegetables and pulses. To meet the growing demand in animal source products, livestock and dairy farming has increased enormously (FAO, 2015), contributing directly to increased greenhouse gas emissions, eutrophication (the enrichment of an ecosystem with nutrients), and loss of biodiversity due to intensification of agriculture and conversion of forests and natural habitats to agricultural land (Gerber *et al.*, 2013). Currently, livestock production occupies approximately 80% of global agricultural land (including arable and grassland), whereas only a few percent of the land is used for fruits and vegetables (FAO, 2017).

Agriculture is also one of the main contributors to climate change, accounting for ~25% of global anthropogenic emissions (Vermeulen *et al.*, 2012), while livestock production alone has been estimated to account for 14.5% of global greenhouse gas emissions (Gerber *et al.*, 2013). It has been estimated that the consumption of fruits and vegetables accounts for only 7% of all food related GHG emissions globally (Springmann *et al.*, 2016b). Generally, fruits and vegetables have a lower carbon footprint compared to livestock products and grains when measured per unit of product weight, although this is not necessarily the case when measured per unit of energy content, especially if the fruits and vegetables are processed (Drewnowski *et al.*, 2015).

Agriculture is estimated to account for ~70% of global water withdrawals (Mekonnen & Hoekstra, 2010). The water footprint of fruits and vegetables is relatively low compared to cereals and oil crops when measured per unit of product, but higher when measured per unit of energy. However, the variation between different fruits is high - ranging from 235 m^3 water per tonne of watermelon to 3350 m^3 water per tonne of figs (Mekonnen & Hoekstra, 2010).

Particularly in developed countries, agriculture is the main contributor to eutrophication of waterways, due to nitrogen and phosphorus leached from fields (Withers *et al.*, 2014). Eutrophication disturbs the natural balance of the ecosystem by favouring certain species and causing harm to others, e.g. in aquatic ecosystems the nutrient inputs increase the growth of algae and plants, and the decay of the biomass leads to oxygen depletion, causing death of fish and other aquatic animals. The eutrophication potential of fruit and vegetable production is generally higher than that of cereals (Xue & Landis, 2010), due to the relatively high nutrient inputs required for production of fruits and vegetables.

Agricultural emissions, such as ammonia, toxic organic compounds, pesticides and particulates, have an impact on air quality, which has direct implications for human health. Agriculture accounts for ~30% of all acidifying emissions and 90% of ammonia emissions in Western Europe (Erisman *et al.*, 2008). Ammonia emissions are mainly produced from manure management and use of nitrogen fertilisers. The contribution of agriculture to particulate matter emissions in Europe has been estimated to be ~20% (Erisman *et al.*, 2008). Particulate matter emissions from agriculture originate from field operations such as ploughing, tillage and harvesting, and from livestock bedding materials and manure.

Industrialisation of agriculture has also contributed to the losses in biodiversity due to simplification of agroecosystems, reduced number of crops and crop varieties grown, use of chemical fertilisers and pesticides, intensification of agriculture, increase in field size and clearance of natural forests for agricultural land. The increased demand for agricultural products is causing a pressure for converting forests to agricultural land, especially in tropical regions (Laurance *et al.*, 2014). Extensive farming systems, such as organic farming systems, generally have higher on-farm biodiversity compared to intensive farming (Bengtsson *et al.*, 2005; Tuomisto *et al.*, 2012a). However, many studies have questioned whether land sparing, i.e. using intensive farming systems and leaving land out from agriculture for biodiversity conservation would lead to higher total biodiversity benefits compared to land sharing (Phalan *et al.*, 2011; Tscharntke *et al.* (2012); Tuomisto *et al.*, 2012b; points out that there is a clear difference between the type of biodiversity that land sparing and land sharing approaches support. The land sparing concept can under value functional agrobiodiversity that helps to increase the resilience of the farming systems to environmental changes.

7. Adaptation and mitigation options

There are many possibilities for farmers and societies to adapt to and mitigate environmental changes (FAO, 2010; FAO, 2012). These practices can happen at various levels and range from minor changes to major system level changes. The agriculture and food production industries can implement adaptation practices that ensure increased high-quality food production with lower environmental burdens. However, as increasing food production does not guarantee that food would be distributed equally, additional policies will be required to improve the availability and access to healthy and nutritious foods to everybody.

Farmers have possibilities to adapt to environmental changes by altering farm management practices, such as changing crop varieties, planting times, irrigation practices and residue management, or by implementing major systemic changes, such as switches to different crop species and changes in farming systems or even relocation of agriculture to new areas (Challinor *et al.*, 2014). Many farming practices that increase the climate resilience of agriculture also help to mitigate GHG emissions (Altieri & Nicholls, 2017).

Agriculture can also benefit from technological innovations, such as biotechnology and precision farming. Novel plant breeding technologies can provide crop varieties that are more suitable to new environmental conditions, e.g. drought resistant crops (Hu & Xiong, 2014), or have higher concentrations and bioavailability of micronutrients (Bhullar & Gruissem, 2013). Precision farming technologies apply geographical information systems, remote sensing and GPS for identifying variations in fields, and therefore help farmers to target the use of fertilisers and pesticides where they are needed the most. Small unmanned aerial systems are increasingly used for field imaging to find the problem areas at an early stage (Zhang & Kovacs, 2012). The use of robots in agriculture is increasing, especially for activities that are currently often carried out manually, e.g. weed control, fertilisation and harvesting of fruits and vegetables (Bogue & Bogue, 2016). The replacement of human labour by robots can be extremely beneficial as an adaptation to climate change, especially in areas where high daytime temperatures will make working on the fields impossible.

Novel technologies can also provide solutions to more systemic changes. Indoor farming and cellular agriculture enable food production without direct exposure to environmental stressors. Indoor farming in vertical systems (e.g. tall buildings) reduces land requirements and transportation needs, as production can take place closer to cities. The need for artificial lighting in many indoor farming systems is energy consuming (Cheng, 2014), but developments in LED light technology may improve the energy efficiency of those systems in the future (Darko *et al.*, 2014).

Cellular agriculture or the production of agricultural products by using cell culturing technologies, has the potential to revolutionise food production. The products from cellular agriculture include both acellular and cellular products. Acellular products are produced by culturing yeast or bacteria that synthetize a protein (e.g. milk protein or egg albumin) that is used for the final product. Cellular products, such as cultured meat or leather, consist of living or once living cells (Post, 2012). Cellular agriculture is not limited only to replacing animal source foods, but plant cells and algae can also be cultivated in bioreactors for food (Räty, 2017). Most of these technologies are currently at the development stage, but commercial products are expected to appear in the supermarkets during the next few years. Some preliminary studies have estimated that products from cellular agriculture could have potential to reduce environmental impacts substantially compared to conventionally produced livestock products (Mattick *et al.*, 2015; Tuomisto & de Mattos, 2011; Tuomisto *et al.*, 2016). Studies on the environmental impact of plant products produced through cellular agriculture are currently lacking.

Adaptation and mitigation mechanisms are required also in the post-farm/post-primary production stage. Extreme climatic and hydrological events can make transportation of food less reliable due to floods, heavy rains, landslides etc. Therefore, diversification of supply chains and increased local production may increase the resilience and stability of food supply chains (Miller *et al.*, 2016b).

This may require food industries and consumers to adopt purchasing strategies that take into account seasonality based on the local climate. However, relying solely on local production is not a secure strategy due to the risk of extreme climatic and hydrological events affecting the local area.

Consumers have also a key role to play as they have the power to influence in the sustainability of food system by their consumption behaviour and dietary choices. As discussed in section 5&6 the consumption choices regarding quantities of animal source foods have a major impact on the environmental burden of diets. Environmental changes may also require consumers to alter the consumption of fruits and vegetables, as the availability and prices of most popular products may change. Therefore, consumers might need to choose different fruits and vegetables at different seasons and get used to a wider variety of species. Purchasing locally produced commodities could also promote the expansion of local production.

8. Conclusions

The evidence-based framework presented in this paper provides an overview of the multidimensional and complex interactions with feedback between environmental change, the food system, nutrition and health, and forms an analytical basis for detailed investigation of these interactions. The novelty of the framework is in its focus on fruits and vegetables, and in the detailed presentation of the pathways between environmental stressors and plant production (Figure 3). This paper emphasises the importance of considering multiple environmental stressors and their interactions instead of focusing only on a single stressor (e.g. climate change). The focus on fruits and vegetables highlights the need for more research on this nutritionally-important food group as the majority of research efforts to-date have been targeted on staple crops and animal source foods.

The framework can be adapted for other food groups as well as for regional case studies. The inclusion of the livestock sector would require adding livestock specific pathways into the framework, such as changes in livestock diseases and changes in grassland quality and feed production. The current framework can be directly used for staple crops.

This paper has highlighted many environmental issues that can potentially have major nutrition and health consequences unless mitigation and adaptation practices are implemented. However, many of the major risks may be faced by farmers and poor consumers in developing countries whose adaptation possibilities are limited especially in the short term. Therefore, this framework helps to develop further research to estimate the potential nutrition and health consequences of environmental changes on different population groups, and the effectiveness of alternative mitigation and adaptation options with various timeframes.

Some other more specific potential applications of the framework include:

- Guiding our understanding of the complex interactions of environmental, social, political, agricultural, market-related food security, diet and health mechanisms within food systems. It could be used for teaching and training sessions, research priority settings, as well as advocacy purposes.
- Identifying research gaps, determining research directions and guiding proposal writing. Likewise, the information can be used by funders to specify calls for proposals.
- Use as a heuristic tool for future food system and multi-sectoral modelling. This will enable further quantification of the impacts of environmental change – through agriculture and food security – on population health, as well as the assessment of the effectiveness of adaptation mechanisms at different parts of the system. By using an open-source platform, further detail could be added to the framework – and shared with the research community – when more evidence will become available.
- For food system programmes and policy makers, the framework gives an overview of where in the food system there are barriers and opportunities for change. With the available evidence, it would be possible to identify crucial links and mechanisms, which can guide health and sustainability programmes, as well as food system policy formulation.
- Although the framework was written for environment, food system and health interactions, similar frameworks could potentially be constructed in other sectors. The key role and interactions that societal factors, policies and research play within the "core" system mechanisms, is something commonly observed in other sectors (e.g. urban planning). The framework provides an example of how these complex interactions can be captured.

Author contributions

All authors contributed to the development of the framework. HT and PS wrote the first draft of the manuscript. All authors were involved in the revision of the draft manuscript and have agreed to the final content.

Competing interests

No competing interests were disclosed.

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WHO: **WHO estimates of the global burden of foodborne diseases: foodborne disease burden epidemiology reference group 2007–2015.** World Health Organization, 2015.
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Publisher Full Text

Open Peer Review

Current Referee Status: ✔ ✔

Version 2

Referee Report 15 February 2018

doi:10.21956/wellcomeopenres.13915.r30892

✔ **John McDermott**
CGIAR Research Program on Agriculture for Nutrition and Health (A4NH), International Food Policy Research Institute (IFPRI), Washington, DC, USA

In this second review, I will restrict my comments to how the authors have responded to my initial review. As in most work on food systems, the challenge is to investigate complex and dynamic systems and then consider the implications of different actors and actions in the system. Actors and actions may operate at different scales (global, continental, national and sub-national), in different food commodities (plant or animal, cultivated or gathered) and at different stages in the food supply chain (production, logistics, processing, retail and meal preparation). I appreciate the authors efforts in revising this paper to more realistically focus the paper on fruits and vegetables while considering broader system variables. The title and content more accurately reflect that focus.
I am also pleased that the authors have acknowledged and partially addressed the differences between food systems in low- and middle-income countries and rich countries. This is a fundamental issue. In low-income countries 40-80% of people are engaged in agriculture and the agricultural sector accounts for approximately 20-40% of national GDP. With national economic “development” and increasing incomes in countries, the percentage of people engaged in agriculture declines dramatically (<2% in most high-income countries) and most of the value addition in the food systems occurs beyond the farm in logistics, processing, retail and food preparation. Because agriculture is such a major sector in LMICs and has profound environmental implications, I do appreciate the acknowledgement by the authors of the current article’s limitations and the need for further research in the agricultural-environmental implications of food system transformation in LMICS.
With the narrowing of the focus of the article, some of the other environmental concerns I raised are less critical. Relative to habitat change and biodiversity conservation, the expansion of fruit and vegetable production into forests is less important than for more extensive agriculture. The bigger habitat issue for fruits and vegetables will be around the environmental impact on natural wetlands, which are often major sites for fruit and vegetables production. Also, given the perishability of fruits and vegetables, they are often produced close to or in urban areas. In urban and peri-urban settings, more attention to spatial analysis is warranted, particularly relative to important consumer concerns such as microbial and chemical contamination.

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Referee Report 18 December 2017

doi:10.21956/wellcomeopenres.13915.r27449

Marco Springmann
Oxford Martin Programme on the Future of Food, Centre on Population Approaches for Non-Communicable Disease Prevention, Nuffield Department of Population Health, University of Oxford, Oxford, UK

In their revision, Hanna Tuomisto and colleagues have addressed my comments. The manuscript provides a good overview of the various linkages of the food system with environmental change, and I think it will make a useful addition to the literature. I approve the manuscript and recommend it for publication/indexing. There are just three small comments, the authors might want to consider before that.

First, the in their abstract, it is stated that '[t]here are currently no quantitative models to test the impact of multiple environmental changes n nutrition and health outcomes." I find that a rather strong statement, in particular as several research groups are working on such models, and some existing ones could be interpreted as being in that realm. Thus, the statement is or might be out of date soon. In addition, the manuscript does not address this gap, because it focuses on developing a qualitative framework. I would therefore suggest to omit it.

Second, in section 5.2, it is stated that "[n]on-optimal diets are estimated to account for ~10% of the global burden of disease (Forouzanfar et al., 2016)." I find that statement a bit unclear. For example, if one looked at the percentage of attributable deaths that was due to dietary risks, then it was actually 11 million out of 31 million (~35%), and if one looked at attributable DALYs, the reported estimate was 241 million out of 997 million (~24%), both a bit higher than the 10% that was reported in the manuscript. The attributable disease burden that was due specifically to diets low and fruits and vegetables in 2013 were 17% and 11% for deaths and DALYs, respectively. I would suggest to clarify the statement in the manuscript.

Third, would it be possible to supply Figure 1 in a higher resolution? In the current version, it appears to be rather blurry.

Competing Interests: No competing interests were disclosed.

Referee Expertise: Environmental and health implications of dietary change, public health and sustainability research, policy analysis

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Referee Report 30 May 2017

doi:10.21956/wellcomeopenres.12073.r22178

Marco Springmann
Oxford Martin Programme on the Future of Food, Centre on Population Approaches for Non-Communicable Disease Prevention, Nuffield Department of Population Health, University of Oxford, Oxford, UK

In their article ‘Effects of environmental change on population nutrition and health: A comprehensive framework with a focus on fruits and vegetables,’ Hanna Tuomisto and colleagues aim to develop a framework that details the interactions between environmental change, diets, and health, with a particular focus on fruits and vegetables. Their article is a welcome review of the impacts of environmental change on agriculture and health, and I recommend it for indexing subject to addressing a few comments that I am detailing below.

First, I think the motivation of the review could be strengthened. What sets it apart from other reviews, such as the IPCC’s, or maps of the food system? Related to that, the article does not contain any methods and discussion sections. This might be fine for a review/overview article, but if the stated aim is to develop a framework of interactions, then one would expect at least some detail on what the added value of that framework is, how it was constructed, and how it compares to other frameworks. From my reading of the article, it is a review of interactions between environmental change and mostly agriculture, with special emphasis on the implications for fruits and vegetables, and some discussion on health implications. It might therefore be advisable to describe it as such.

That would also address some problems I have with the conclusions, which seem to be a little bit of an overstretch to me. For most of the points raised, what would actually be required is some information on the relative importance of each factor. For advocacy or funding purposes, for example, one would want to know how significant a particular aspect is to gauge whether focussing on it would be worth the investment. The review, I think, nicely catalogues the various interactions between environmental change and agriculture, but it does not contain any interpretation of the information that is presented, or a discussion on what to do with it.

For some of the aspects that are discussed I found myself going back to related IPCC chapters, in particular those on Agriculture, Forestry and Other Land Use (AR5, WG3, Chapter 11), Food Security and Food Production Systems (AR5, WG3, Chapter 7), and Human Health: Impacts, Adaptation, and Co-Benefits (AR5, WG2, Chapter 11). Many of the aspects discussed in the article are reviewed at great length there, and in part using more recent studies. I would at least expect that a review like the present one would mention those reports, so that interested individuals know where they can find more detailed information.

The section on stratospheric ozone depletion is a good case in point. The impacts of changes in ultraviolet radiation on biomass are reviewed, but it is not clear whether it is an important effect or not. For example, what is missing from the discussion is the fact that the ozone hole has started to “heal” (see, e.g., Solomon et al, Science 2016,[1] ; or an earlier IPCC special report on the ozone layer), and where to read on. In addition to the agricultural impacts, changes in ultraviolet radiation also impact human health directly. It might be worth re-emphasizing that the direct health impacts of many of the environmental changes reviewed are not discussed in the article. (That is also the case for tropospheric ozone, which is briefly mentioned in relation to oxidative stress for plants, but which arguably has a bigger direct health impact in its relationship to urban air pollution).

At a couple of instances, it might be worth to add some detail related to attribution. For example, in the discussion on acid rain (3.5), one could get away with the impression that it is a natural phenomenon

("Acid rains generally result from the reaction of water molecules and sulphur dioxide or nitrogen oxide in the atmosphere," p. 6). Whilst natural phenomena, such as volcanic eruptions, surely contribute to acid-rain precursors, the principal causes are anthropogenic emissions of sulphur and nitrogen compounds, especially from coal-fired power plants. Another clarification regarding attribution might be when discussing fruit and vegetable consumption. On page 8, it is mentioned that in some situation, low consumption reflects population preferences. Although one can surely see it that way, another way of explaining consumption behaviour is by pointing to the food environment and its role in shaping preferences. The benefit of this angle is that it allows one to study the influences of actors, such as governments and the food industry, on the food environment and on the preferences shaped by it.

Despite being in the title, health is actually not discussed to a great extent in the review. That's totally fine, but it might be worth being a bit clearer about what is, and what is not discussed in the article. A specific aspect I was missing from the discussion of pathways leading from nutrition to population health (pp. 7-8) is dietary composition. What is mentioned are the quantity and quality of food intake. Although dietary composition is sometimes subsumed under the banner of quality of food intake, that is not obvious from the related paragraph and could be clarified. Of note here is that changes in dietary composition are broader, and more impactful for health than changes in specific nutrient levels – a point illustrated by the ranking of risk factors in the Global Burden of Disease study[2] that is referred to a couple of times in the article.

A final comment is that the literature used could be a bit more general at times. For example, I don't understand why when discussing the greenhouse gas emissions related to agriculture, the only study referred to for quantifying the emissions attributable to fruit and vegetable consumption is a working paper focussed on the UK. There are several more general sources that have quantified the emissions attributable to both global and regional consumption of fruits and vegetables. For example, in one of my own studies[3], I calculated that about 7% of all food-related greenhouse gas emissions in 2005/07 were related to fruit and vegetable consumption. Tilman and Clark's article[4] also includes some global estimates and could be consulted in that regard. Another example is the discussion on changes in water demand (p. 6) where a national case-study on India is cited, without noting more comprehensive, global analyses. Good resources here are again the IPCC, and the Agricultural Model Intercomparison and Improvement Project (AgMIP). In general, I think it is good practice in reviews to indicate whether a reference provides a specific example, or whether it supports a general argument.

Good luck with the revisions. I enjoyed reading the article.

References

1. Solomon S, Ivy DJ, Kinnison D, Mills MJ, Neely RR, Schmidt A: Emergence of healing in the Antarctic ozone layer.*Science*. 2016; **353** (6296): 269-74 PubMed Abstract | Publisher Full Text
2. GBD 2015 Risk Factors Collaborators: Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016; **388** (10053): 1659-1724 Publisher Full Text
3. Springmann M, Godfray HC, Rayner M, Scarborough P: Analysis and valuation of the health and climate change cobenefits of dietary change.*Proc Natl Acad Sci U S A*. 2016; **113** (15): 4146-51 PubMed Abstract | Publisher Full Text
4. Tilman D, Clark M: Global diets link environmental sustainability and human health.*Nature*. 2014; **515** (7528): 518-22 PubMed Abstract | Publisher Full Text

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
No

If applicable, is the statistical analysis and its interpretation appropriate?
Not applicable

Are all the source data underlying the results available to ensure full reproducibility?
No source data required

Are the conclusions drawn adequately supported by the results?
No

Competing Interests: No competing interests were disclosed.

Referee Expertise: Environmental and health implications of dietary change, public health and sustainability research, policy analysis

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 17 Oct 2017

Hanna Tuomisto, London School of Hygiene & Tropical Medicine, UK

Responses to Reviewer 2

Dear Dr Springmann,

Thank you very much for your excellent comments that have helped us to improve our paper. We have revised the paper based on your suggestions as detailed below. In addition, we made revisions based on comments from Dr McDermott and we added a new section discussing adaptation and mitigation options (section 7).

"In their article 'Effects of environmental change on population nutrition and health: A comprehensive framework with a focus on fruits and vegetables,' Hanna Tuomisto and colleagues aim to develop a framework that details the interactions between environmental change, diets, and health, with a particular focus on fruits and vegetables. Their article is a welcome review of the impacts of environmental change on agriculture and health, and I recommend it for indexing subject to addressing a few comments that I am detailing below.

First, I think the motivation of the review could be strengthened. What sets it apart from other reviews, such as the IPCC's, or maps of the food system?"
Authors: We appreciate the motivation/difference was not stipulated clearly: the focus on fruits and vegetables rather than on staple crops. We have strengthened the justification for this in the

introduction section.

“Related to that, the article does not contain any methods and discussion sections. This might be fine for a review/overview article, but if the stated aim is to develop a framework of interactions, then one would expect at least some detail on what the added value of that framework is, how it was constructed, and how it compares to other frameworks.”

Authors: We have expanded the description of the methods, and added a methods heading. We have also strengthened the explanation of the added value and differences compared to the other frameworks. A brief discussion of the potential uses of the framework as well as some limitations can be found in section 8.

“From my reading of the article, it is a review of interactions between environmental change and mostly agriculture, with special emphasis on the implications for fruits and vegetables, and some discussion on health implications. It might therefore be advisable to describe it as such.”

Authors: The title and introduction of the paper have been amended to clarify that it presents a framework with a particular emphasis on fruit and vegetable production. As the paper is designed to be read by a primarily health-focused audience, we have added particular detail on the interactions between environmental change and fruit and vegetable production, as this is the area of the framework the journal’s readership is likely to be least familiar with.

“That would also address some problems I have with the conclusions, which seem to be a little bit of an overstretch to me. For most of the points raised, what would actually be required is some information on the relative importance of each factor. For advocacy or funding purposes, for example, one would want to know how significant a particular aspect is to gauge whether focussing on it would be worth the investment. The review, I think, nicely catalogues the various interactions between environmental change and agriculture, but it does not contain any interpretation of the information that is presented, or a discussion on what to do with it.”

Authors: The aim of the framework is to provide a basis for modelling and quantification of the relative importance of the different factors, and as such the quantification itself is beyond the scope of this piece of work. However, we also identified some uses for the framework itself, which are listed in the conclusions section. We will look into possibilities for other research groups to add to the framework in the future (perhaps using open source software) to further quantify each of the indicated links.

“For some of the aspects that are discussed I found myself going back to related IPCC chapters, in particular those on Agriculture, Forestry and Other Land Use (AR5, WG3, Chapter 11), Food Security and Food Production Systems (AR5, WG3, Chapter 7), and Human Health: Impacts, Adaptation, and Co-Benefits (AR5, WG2, Chapter 11). Many of the aspects discussed in the article are reviewed at great length there, and in part using more recent studies. I would at least expect that a review like the present one would mention those reports, so that interested individuals know where they can find more detailed information.”

Authors: Thank you for the suggestion. We have added citations to the suggested reports in the paper.

“The section on stratospheric ozone depletion is a good case in point. The impacts of changes in ultraviolet radiation on biomass are reviewed, but it is not clear whether it is an important effect or not. For example, what is missing from the discussion is the fact that the ozone hole has started to “heal” (see, e.g., Solomon et al, Science 2016,[1] ; or an earlier IPCC special report on the ozone layer), and where to read on.”

Authors: Thank you for the comment. We have added the point that the ozone layer is healing and added a reference to the Solomon et al 2016 paper. We also removed the following sentence as

the reference is relatively old and is contradicting the fact that the ozone layer is healing: "It has been estimated that the springtime UV doses will increase 14% in the Northern hemisphere and 40% in the Southern hemisphere in 2010–2020 compared to levels in 1979–1992 (Taalas et al., 2000).".
"In addition to the agricultural impacts, changes in ultraviolet radiation also impact human health directly. It might be worth re-emphasizing that the direct health impacts of many of the environmental changes reviewed are not discussed in the article. (That is also the case for tropospheric ozone, which is briefly mentioned in relation to oxidative stress for plants, but which arguably has a bigger direct health impact in its relationship to urban air pollution)."
Authors: We have added a note in the introduction section (end of the fourth paragraph) stating the fact that the paper doesn't cover direct health impacts.

"At a couple of instances, it might be worth to add some detail related to attribution. For example, in the discussion on acid rain (3.5), one could get away with the impression that it is a natural phenomenon ("Acid rains generally result from the reaction of water molecules and sulphur dioxide or nitrogen oxide in the atmosphere," p. 6). Whilst natural phenomena, such as volcanic eruptions, surely contribute to acid-rain precursors, the principal causes are anthropogenic emissions of sulphur and nitrogen compounds, especially from coal-fired power plants."
Authors: We have clarified the point on acid rains and screened the paper for additional paragraphs that would benefit from more detail related to attribution: more detail was added to these sections.
"Another clarification regarding attribution might be when discussing fruit and vegetable consumption. On page 8, it is mentioned that in some situation, low consumption reflects population preferences. Although one can surely see it that way, another way of explaining consumption behaviour is by pointing to the food environment and its role in shaping preferences. The benefit of this angle is that it allows one to study the influences of actors, such as governments and the food industry, on the food environment and on the preferences shaped by it."
Authors: Thank you for this excellent comment. We edited the sentence to: "A remarkable example of these feedback loops is based on the consumer-driven rapid global shift towards a more "Western" diet, which is driven by urbanisation, economic growth and changes in technology and culture (Popkin, 2006)."

"Despite being in the title, health is actually not discussed to a great extent in the review. That's totally fine, but it might be worth being a bit clearer about what is, and what is not discussed in the article."
Authors: we have now clarified the desired focus of the paper, expanded the health section (5.2) and briefly discussed possible implications for health.
"A specific aspect I was missing from the discussion of pathways leading from nutrition to population health (pp. 7-8) is dietary composition. What is mentioned are the quantity and quality of food intake. Although dietary composition is sometimes subsumed under the banner of quality of food intake, that is not obvious from the related paragraph and could be clarified. Of note here is that changes in dietary composition are broader, and more impactful for health than changes in specific nutrient levels – a point illustrated by the ranking of risk factors in the Global Burden of Disease study[2] that is referred to a couple of times in the article."
Authors: we clarified that the term 'food quality' covers also dietary composition, and have altered this section to focus more explicitly on fruits and vegetables and their contribution to quality of dietary intake.

"A final comment is that the literature used could be a bit more general at times. For example, I

don't understand why when discussing the greenhouse gas emissions related to agriculture, the only study referred to for quantifying the emissions attributable to fruit and vegetable consumption is a working paper focussed on the UK. There are several more general sources that have quantified the emissions attributable to both global and regional consumption of fruits and vegetables. For example, in one of my own studies[3], I calculated that about 7% of all food-related greenhouse gas emissions in 2005/07 were related to fruit and vegetable consumption."
Authors: thanks for this information. We have added a reference to your paper.
"Tilman and Clark's article[4] also includes some global estimates and could be consulted in that regard. Another example is the discussion on changes in water demand (p. 6) where a national case-study on India is cited, without noting more comprehensive, global analyses. Good resources here are again the IPCC, and the Agricultural Model Intercomparison and Improvement Project (AgMIP). In general, I think it is good practice in reviews to indicate whether a reference provides a specific example, or whether it supports a general argument."
Authors: We have improved this section and added a reference to the IPCC report.

References

1. Solomon S, Ivy DJ, Kinnison D, Mills MJ, Neely RR, Schmidt A: Emergence of healing in the Antarctic ozone layer.*Science*. 2016; **353** (6296): 269-74 PubMed Abstract | Publisher Full Text
2. GBD 2015 Risk Factors Collaborators: Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016; **388** (10053): 1659-1724 Publisher Full Text
3. Springmann M, Godfray HC, Rayner M, Scarborough P: Analysis and valuation of the health and climate change cobenefits of dietary change.*Proc Natl Acad Sci U S A*. 2016; **113** (15): 4146-51 PubMed Abstract | Publisher Full Text
4. Tilman D, Clark M: Global diets link environmental sustainability and human health.*Nature*. 2014; **515** (7528): 518-22 PubMed Abstract | Publisher Full Text

Competing Interests: We declare that we have no conflict of interest

Referee Report 27 April 2017

doi:10.21956/wellcomeopenres.12073.r22290

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John McDermott
CGIAR Research Program on Agriculture for Nutrition and Health (A4NH), International Food Policy Research Institute (IFPRI), Washington, DC, USA

The objective of this paper is to provide a comprehensive framework for the effects of environmental change on population nutrition and health. The authors correctly, in my opinion, advocate for a more comprehensive approach that considers multiple disciplines and key interactions between the environment, food production and population nutrition and health. The framework is less comprehensive than the title, restricting itself to environmental change and a subset of food production from major crops, and extending that to fruits and vegetables. These could be brought into alignment with revisions by rephrasing the title and narrowing the scope to focus on the subset of issues addressed. If a more comprehensive approach, addressing issues raised below, is desired, the paper would need to be changed much more dramatically.

My comments focus on the utility of the framework for policies and actions for linking the environment, food production, and population nutrition and health in low- and middle-income countries (LMICs). In general, the framework proposed has important elements but seems better suited to the context of high-income countries. Agriculture is the sector with the greatest influence on natural systems globally, and it is changing rapidly in LMICs. Some of the biggest environmental influences of agriculture on the environment in LMICs are:

1. expansion of agricultural lands into natural forests,
2. intensification of livestock and fish systems (that can have beneficial or negative effects, depending on management),
3. depletion of ground water, and
4. land / soil degradation.

All these agricultural changes have important implications for greenhouse gas production and climate change adaptation and mitigation. For all these topics, there are important interactions between agriculture and the environment which have implications for population nutrition and health. As issues 1-3 are not considered in the paper, the comprehensive framework proposed does not adequately address some of the biggest food system issues in LMICs.

In particular, for a paper linking environmental change to population nutrition and health through food, the failure to consider animal production (livestock and fish) is a profound omission. In smallholder systems across Africa and Asia, mixed farming with both animals and plants is very common. The combination of plants and animal production are synergistic – socio-economically and biologically.

The methodology followed has led to a useful initial framework. However, if this framework is to be more generally applicable in LMICs (as is implied) I would suggest that the current framework be revised considering the general points above and some additional, more specific, points below. These points highlight some of the many tradeoffs and challenges that decision makers struggle with in the environment, food, and health nexus that a comprehensive framework needs to consider.

1. Water: water quality is an important issue and is intimately linked with food safety, particularly for vegetables. The landmark WHO Foodborne Disease Burden Epidemiology Reference Group (FERG) report from December 2015 estimates that the main burdens associated with fresh foods are overwhelmingly due to biological pathogens rather than chemicals (http://www.who.int/foodsafety/areas_work/foodborne-diseases/ferg/en/). In general, consumers are more concerned with chemical contamination. Many of the vegetables consumed in urban and peri-urban areas are grown with contaminated wastewater. How this wastewater is managed is a critical issue for vegetable production[1]. The issue of water availability is ignored in the framework, but it is of critical importance. Subsidized water for cereal production is leading to a depletion of groundwater in the western Indo-Gangetic plains. Over-exploitation of ground water is also critical in dryland farming areas in Australia, Central Asia and North America. These systems will be forced to de-intensify or become unproductive. In Africa, there has been relatively little investment in irrigation to date, but it is a very dry continent and sustainable irrigation will be critical to adapting food production systems to increasing climate variability.
2. Biodiversity loss: this is one example of the need to go beyond listing issues to assessing tradeoffs. As noted by the authors, this is complex to model and decide, but people are constantly making decisions between adhering to a precautionary principle of maintaining natural areas, and adopting more intensive and less diverse systems. The framework would need to consider how such tradeoffs can be considered and monitored, and evolve over time.

3. Diet quality in sustainable and healthy food systems: implied in the discussion of fruits and vegetables is the diversification of diets and improving diet quality by promoting consumption of healthy foods (and reducing consumption of unhealthy foods). In LMICs, most agricultural policies provide subsidies and greater investment for cereals with the result that supply chains for cereals are more efficient and the prices lower relative to more nutritious foods such as pulses, fish and vegetables. Thus, rebalancing agricultural policies to make them more commodity-neutral is needed to improve diet quality.
4. Tradeoffs between sustainability and health. Animal-source foods represent the greatest challenge in this regard since they are very nutritious but much more environmentally costly. A strong case can be made that the poor (especially mothers and children) should eat more animal-source foods, but it is desirable, for both sustainability and health reasons, to limit the dramatic increases in consumption of animal-source foods observed as incomes rise in LMICs.

In revising the framework, these are some key issues to consider. It might be useful to get other inputs to adapt or add that a functional comprehensive framework should address.

References

1. Antwi-Agyei P, Cairncross S, Peasey A, Price V, Bruce J, Baker K, Moe C, Ampofo J, Armah G, Ensink J: A Farm to Fork Risk Assessment for the Use of Wastewater in Agriculture in Accra, Ghana.*PLoS One*. 2015; **10** (11): e0142346 PubMed Abstract | Publisher Full Text

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Not applicable

Are all the source data underlying the results available to ensure full reproducibility?
No source data required

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Referee Expertise: Epidemiology, agriculture and livestock production, food systems in low and middle income countries, veterinary medicine, agriculture intensification and infectious disease risk (food safety, emerging diseases)

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 03 Oct 2017

Hanna Tuomisto, London School of Hygiene & Tropical Medicine, UK

Responses to Reviewer 1

Dear Dr McDermott,

Thank you very much for your excellent comments that have helped us to improve our paper. We have revised the paper based on your suggestions as detailed below. In addition, we made revisions based on comments from Dr Springmann and we added a new section discussing adaptation and mitigation options (section 7).

"The objective of this paper is to provide a comprehensive framework for the effects of environmental change on population nutrition and health. The authors correctly, in my opinion, advocate for a more comprehensive approach that considers multiple disciplines and key interactions between the environment, food production and population nutrition and health. The framework is less comprehensive than the title, restricting itself to environmental change and a subset of food production from major crops, and extending that to fruits and vegetables."

Authors: we have changed the title, so that it reflects the focus of the paper better (fruits and vegetables). The new title is: Effects of environmental change on agriculture, population nutrition and health: A framework with a focus on fruits and vegetables

"These could be brought into alignment with revisions by rephrasing the title and narrowing the scope to focus on the subset of issues addressed. If a more comprehensive approach, addressing issues raised below, is desired, the paper would need to be changed much more dramatically."

Authors: we have revised the paper throughout to be clearly focused on fruits and vegetables.

"My comments focus on the utility of the framework for policies and actions for linking the environment, food production, and population nutrition and health in low- and middle-income countries (LMICs). In general, the framework proposed has important elements but seems better suited to the context of high-income countries. Agriculture is the sector with the greatest influence on natural systems globally, and it is changing rapidly in LMICs. Some of the biggest environmental influences of agriculture on the environment in LMICs are:

1. expansion of agricultural lands into natural forests,
2. intensification of livestock and fish systems (that can have beneficial or negative effects, depending on management),
3. depletion of ground water, and
4. land / soil degradation.

All these agricultural changes have important implications for greenhouse gas production and climate change adaptation and mitigation. For all these topics, there are important interactions between agriculture and the environment which have implications for population nutrition and health. As issues 1-3 are not considered in the paper, the comprehensive framework proposed does not adequately address some of the biggest food system issues in LMICs."

Authors: we agree with the reviewer about the many interactions between agriculture and the environment. It would be very useful to further explore all of these in detail, and this is certainly *something we would like to commit to in our future research. For this first paper, we decided to describe the impacts of environmental changes on agriculture and have now further clarified in the text that this was our focus. In a future paper, we could subsequently look at the impacts of agriculture on the environment: for now these are only briefly discussed in section 6. Depletion of groundwater is briefly covered in section 4.4, which we have slightly expanded. We appreciate the reviewer's comments concerning the relevance of the framework to LMICs as well as high income countries: we have now made sure more LMIC examples have been added throughout the revised manuscript.*

"In particular, for a paper linking environmental change to population nutrition and health through food, the failure to consider animal production (livestock and fish) is a profound omission. In smallholder systems across Africa and Asia, mixed farming with both animals and plants is very common. The combination of plants and animal production are synergistic – socio-economically and biologically."

Authors: we agree with this comment and have improved the reasoning why the paper focuses on fruits and vegetables in the introduction section.

"The methodology followed has led to a useful initial framework. However, if this framework is to be more generally applicable in LMICs (as is implied) I would suggest that the current framework be revised considering the general points above and some additional, more specific, points below. These points highlight some of the many tradeoffs and challenges that decision makers struggle with in the environment, food, and health nexus that a comprehensive framework needs to consider.

1. Water: water quality is an important issue and is intimately linked with food safety, particularly for vegetables. The landmark WHO Foodborne Disease Burden Epidemiology Reference Group (FERG) report from December 2015 estimates that the main burdens associated with fresh foods are overwhelmingly due to biological pathogens rather than chemicals (http://www.who.int/foodsafety/areas_work/foodborne-diseases/ferg/en/). In general, consumers are more concerned with chemical contamination. Many of the vegetables consumed in urban and peri-urban areas are grown with contaminated wastewater. How this wastewater is managed is a critical issue for vegetable production (for example, see https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4640866/)."

Authors: thank you for this comment. We have added the issue of pathogen contaminated irrigation water with the above references in section 4.3.

"The issue of water availability is ignored in the framework, but it is of critical importance. Subsidized water for cereal production is leading to a depletion of groundwater in the western Indo-Gangetic plains. Over-exploitation of ground water is also critical in dryland farming areas in Australia, Central Asia and North America. These systems will be forced to de-intensify or become unproductive. In Africa, there has been relatively little investment in irrigation to date, but it is a very dry continent and sustainable irrigation will be critical to adapting food production systems to increasing climate variability."

Authors: We appreciate that the issue of water availability was not appropriately covered and was only partly included in the "non-renewable resource depletion" section of the framework (section 4.4). We have now expanded the text explaining the issue of water availability and referencing the points made by the reviewer above.

1. "Biodiversity loss: this is one example of the need to go beyond listing issues to assessing tradeoffs. As noted by the authors, this is complex to model and decide, but people are constantly making decisions between adhering to a precautionary principle of maintaining natural areas, and adopting more intensive and less diverse systems. The framework would need to consider how such tradeoffs can be considered and monitored, and evolve over time."

Authors: we agree that trade-offs are very important to consider, but feel that exploring them is beyond the scope of a structural framework. Trade-offs between the links and interactions identified here will be addressed in the future modelling work that will be carried out by using the framework.

"Diet quality in sustainable and healthy food systems: implied in the discussion of fruits and vegetables is the diversification of diets and improving diet quality by promoting consumption of healthy foods (and reducing consumption of unhealthy foods). In LMICs, most agricultural policies provide subsidies and greater investment for cereals with the result that supply chains for cereals are more efficient and the prices lower relative to more nutritious foods such as pulses, fish and vegetables. Thus, rebalancing agricultural policies to make them more commodity-neutral is needed to improve diet quality."

Authors: thank you for the helpful comment. This is again an issue that we can explore in our future modelling work, and is mentioned in section 8.

1. "Tradeoffs between sustainability and health. Animal-source foods represent the greatest challenge in this regard since they are very nutritious but much more environmentally costly. A strong case can be made that the poor (especially mothers and children) should eat more animal-source foods, but it is desirable, for both sustainability and health reasons, to limit the dramatic increases in consumption of animal-source foods observed as incomes rise in LMICs."

Authors: as we have now narrowed the focus of the framework following reviewer suggestions to focus more explicitly on fruits and vegetables, animal-source foods are beyond the scope of the paper. We agree that it will be extremely important to explore trade-offs between sustainability and health in our future modelling work, however.

Responses to Reviewer 2

Dear Dr Springmann,

Thank you very much for your excellent comments that have helped us to improve our paper. We have revised the paper based on your suggestions as detailed below. In addition, we made revisions based on comments from Dr McDermott and we added a new section discussing adaptation and mitigation options (section 7).

"In their article 'Effects of environmental change on population nutrition and health: A comprehensive framework with a focus on fruits and vegetables,' Hanna Tuomisto and colleagues aim to develop a framework that details the interactions between environmental change, diets, and health, with a particular focus on fruits and vegetables. Their article is a welcome review of the impacts of environmental change on agriculture and health, and I recommend it for indexing subject to addressing a few comments that I am detailing below.

First, I think the motivation of the review could be strengthened. What sets it apart from other

reviews, such as the IPCC's, or maps of the food system?"
Authors: We appreciate the motivation/difference was not stipulated clearly: the focus on fruits and vegetables rather than on staple crops. We have strengthened the justification for this in the introduction section.
"Related to that, the article does not contain any methods and discussion sections. This might be fine for a review/overview article, but if the stated aim is to develop a framework of interactions, then one would expect at least some detail on what the added value of that framework is, how it was constructed, and how it compares to other frameworks."
Authors: We have expanded the description of the methods, and added a methods heading. We have also strengthened the explanation of the added value and differences compared to the other frameworks. A brief discussion of the potential uses of the framework as well as some limitations can be found in section 8.
"From my reading of the article, it is a review of interactions between environmental change and mostly agriculture, with special emphasis on the implications for fruits and vegetables, and some discussion on health implications. It might therefore be advisable to describe it as such."
Authors: The title and introduction of the paper have been amended to clarify that it presents a framework with a particular emphasis on fruit and vegetable production. As the paper is designed to be read by a primarily health-focused audience, we have added particular detail on the interactions between environmental change and fruit and vegetable production, as this is the area of the framework the journal's readership is likely to be least familiar with.

"That would also address some problems I have with the conclusions, which seem to be a little bit of an overstretch to me. For most of the points raised, what would actually be required is some information on the relative importance of each factor. For advocacy or funding purposes, for example, one would want to know how significant a particular aspect is to gauge whether focussing on it would be worth the investment. The review, I think, nicely catalogues the various interactions between environmental change and agriculture, but it does not contain any interpretation of the information that is presented, or a discussion on what to do with it."
Authors: The aim of the framework is to provide a basis for modelling and quantification of the relative importance of the different factors, and as such the quantification itself is beyond the scope of this piece of work. However, we also identified some uses for the framework itself, which are listed in the conclusions section. We will look into possibilities for other research groups to add to the framework in the future (perhaps using open source software) to further quantify each of the indicated links.

"For some of the aspects that are discussed I found myself going back to related IPCC chapters, in particular those on Agriculture, Forestry and Other Land Use (AR5, WG3, Chapter 11), Food Security and Food Production Systems (AR5, WG3, Chapter 7), and Human Health: Impacts, Adaptation, and Co-Benefits (AR5, WG2, Chapter 11). Many of the aspects discussed in the article are reviewed at great length there, and in part using more recent studies. I would at least expect that a review like the present one would mention those reports, so that interested individuals know where they can find more detailed information."
Authors: Thank you for the suggestion. We have added citations to the suggested reports in the paper.

"The section on stratospheric ozone depletion is a good case in point. The impacts of changes in ultraviolet radiation on biomass are reviewed, but it is not clear whether it is an important effect or not. For example, what is missing from the discussion is the fact that the ozone hole has started to "heal" (see, e.g., Solomon et al, Science 2016,[1] ; or an earlier IPCC special report on the ozone

layer), and where to read on."
Authors: Thank you for the comment. We have added the point that the ozone layer is healing and added a reference to the Solomon et al 2016 paper. We also removed the following sentence as the reference is relatively old and is contradicting the fact that the ozone layer is healing: "It has been estimated that the springtime UV doses will increase 14% in the Northern hemisphere and 40% in the Southern hemisphere in 2010–2020 compared to levels in 1979–1992 (Taalas et al., 2000).".
"In addition to the agricultural impacts, changes in ultraviolet radiation also impact human health directly. It might be worth re-emphasizing that the direct health impacts of many of the environmental changes reviewed are not discussed in the article. (That is also the case for tropospheric ozone, which is briefly mentioned in relation to oxidative stress for plants, but which arguably has a bigger direct health impact in its relationship to urban air pollution)."
Authors: We have added a note in the introduction section (end of the fourth paragraph) stating the fact that the paper doesn't cover direct health impacts.

"At a couple of instances, it might be worth to add some detail related to attribution. For example, in the discussion on acid rain (3.5), one could get away with the impression that it is a natural phenomenon ("Acid rains generally result from the reaction of water molecules and sulphur dioxide or nitrogen oxide in the atmosphere," p. 6). Whilst natural phenomena, such as volcanic eruptions, surely contribute to acid-rain precursors, the principal causes are anthropogenic emissions of sulphur and nitrogen compounds, especially from coal-fired power plants."
Authors: We have clarified the point on acid rains and screened the paper for additional paragraphs that would benefit from more detail related to attribution: more detail was added to these sections.
"Another clarification regarding attribution might be when discussing fruit and vegetable consumption. On page 8, it is mentioned that in some situation, low consumption reflects population preferences. Although one can surely see it that way, another way of explaining consumption behaviour is by pointing to the food environment and its role in shaping preferences. The benefit of this angle is that it allows one to study the influences of actors, such as governments and the food industry, on the food environment and on the preferences shaped by it."
Authors: Thank you for this excellent comment. We edited the sentence to: "A remarkable example of these feedback loops is based on the consumer-driven rapid global shift towards a more "Western" diet, which is driven by urbanisation, economic growth and changes in technology and culture (Popkin, 2006)."

"Despite being in the title, health is actually not discussed to a great extent in the review. That's totally fine, but it might be worth being a bit clearer about what is, and what is not discussed in the article."
Authors: we have now clarified the desired focus of the paper, expanded the health section (5.2) and briefly discussed possible implications for health.
"A specific aspect I was missing from the discussion of pathways leading from nutrition to population health (pp. 7-8) is dietary composition. What is mentioned are the quantity and quality of food intake. Although dietary composition is sometimes subsumed under the banner of quality of food intake, that is not obvious from the related paragraph and could be clarified. Of note here is that changes in dietary composition are broader, and more impactful for health than changes in specific nutrient levels – a point illustrated by the ranking of risk factors in the Global Burden of Disease study[2] that is referred to a couple of times in the article."
Authors: we clarified that the term 'food quality' covers also dietary composition, and have altered this section to focus more explicitly on fruits and vegetables and their contribution to quality of

dietary intake.

“A final comment is that the literature used could be a bit more general at times. For example, I don’t understand why when discussing the greenhouse gas emissions related to agriculture, the only study referred to for quantifying the emissions attributable to fruit and vegetable consumption is a working paper focussed on the UK. There are several more general sources that have quantified the emissions attributable to both global and regional consumption of fruits and vegetables. For example, in one of my own studies[3], I calculated that about 7% of all food-related greenhouse gas emissions in 2005/07 were related to fruit and vegetable consumption.”
Authors: thanks for this information. We have added a reference to your paper.
“Tilman and Clark’s article[4] also includes some global estimates and could be consulted in that regard. Another example is the discussion on changes in water demand (p. 6) where a national case-study on India is cited, without noting more comprehensive, global analyses. Good resources here are again the IPCC, and the Agricultural Model Intercomparison and Improvement Project (AgMIP). In general, I think it is good practice in reviews to indicate whether a reference provides a specific example, or whether it supports a general argument.”
Authors: We have improved this section and added a reference to the IPCC report.

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Relations between the residential fast-food environment and the individual risk of cardiovascular diseases in The Netherlands: A nationwide follow-up study

Maartje Poelman[1], Maciej Strak[2], Oliver Schmitz[3], Gerard Hoek[2], Derek Karssenberg[3], Marco Helbich[1], Anna-Maria Ntarladima[3,4], Michiel Bots[4], Bert Brunekreef[2], Rick Grobbee[4], Martin Dijst[1] and Ilonca Vaartjes[4]

Abstract

Background: The food environment has been hypothesized to influence cardiovascular diseases such as hypertension and coronary heart disease. This study determines the relation between fast-food outlet density (FFD) and the individual risk for cardiovascular disease, among a nationwide Dutch sample.

Methods: After linkage of three national registers, a cohort of 2,472,004 adults (≥35 years), free from cardiovascular disease at January 1st 2009 and living at the same address for ≥15 years was constructed. Participants were followed for one year to determine incidence of cardiovascular disease, including coronary heart disease, stroke and heart failure. Street network-based buffers of 500 m, 1000 m and 3000 m around residential addresses were calculated, while FFD was determined using a retail outlet database. Logistic regression analyses were conducted. Models were stratified by degree of urbanization and adjusted for age, sex, ethnicity, marital status, comorbidity, neighbourhood-level income and population density.

Results: In urban areas, fully adjusted models indicated that the incidence of cardiovascular disease and coronary heart disease was significantly higher within 500 m buffers with one or more fast-food outlets as compared with areas with no fast-food outlets. An elevated FFD within 1000 m was associated with an significantly increased incidence of cardiovascular disease and coronary heart disease. Evidence was less pronounced for 3000 m buffers, or for stroke and heart-failure incidence.

Conclusions: Elevated FFD in the urban residential environment (≤1000 m) was related to an increased incidence of cardiovascular heart disease and coronary heart disease. To better understand how FFD is associated with cardiovascular disease, future studies should account for a wider range of lifestyle and environmental confounders than was achieved in this study.

Keywords
Cardiovascular diseases, population register, environmental exposure, fast food, incidence

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Introduction

Cardiovascular diseases (CVDs) significantly contribute to the global morbidity and mortality.[1] The increased number of people suffering from CVD has paralleled changes in the food environment toward

[1]Department of Human Geography and Spatial Planning, Faculty of Geosciences, Utrecht University, The Netherlands
[2]Institute for Risk Assessment Sciences, Utrecht University, The Netherlands
[3]Department of Physical Geography, Faculty of Geosciences, Utrecht University, The Netherlands
[4]Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, The Netherlands

Corresponding author:
Maartje Poelman, Department of Human Geography and Spatial Planning, Utrecht University, Vening Meinesz Building A, Princetonlaan 8a, 3584 CB Utrecht, The Netherlands.
Email: m.p.poelman@uu.nl
Twitter: @mppoelman

large scale, inexpensive and calorie-dense food production.[2,3] These changes have influenced the population's food consumption, which has been hypothesized to affect the development of CVD.[4–6] The proposed environmental influence that shapes food consumption and, in succession, health aligns with socio-ecological theories.[7,8]

Food that is known as 'fast food' generally consists of processed meat and refined carbohydrates and is high in salt, saturated fat and calories.[9] Worldwide, fast-food availability has expanded rapidly. For example, the number of McDonalds outlets increased by almost 20% globally in the past decade (2005–2016).[10] Fast-food availability has also increased considerably in European countries over the past years.[11,12] Several studies have investigated the link between fast-food availability and the prevalence of CVD or CVD risk factors. The findings are mixed, but that might be caused by different fast-food exposure assessments and CVD outcome measures.[13–19] Most studies determined fast-food outlet density (FFD) for crude predefined areas (e.g. census tract), rather than including measures representing the FFD around people's residential home. In addition, most studies determined CVD *prevalence* within the predefined area, rather than the *incidence* of CVD.[13–18] Additionally, most studies did not account for the time that individuals were exposed to fast-food outlets within the studied area.[13–19]

The aim of this study was to contribute to the literature by determining the relation between FFD and one year incidence of individual-level CVD among a nationwide sample in The Netherlands. This manuscript provides a novel contribution by addressing four key points. First, our study will provide a longitudinal perspective on the fast-food environment and CVD by including CVD incidence rather than prevalence, derived from a large population-wide cohort. Second, only individuals living at the same address for a long period of time were included in order to eliminate influences of prior residential environments for a substantial timeslot. Third, this study was unique in presenting the incidence of individual-level CVD and three subtypes (coronary heart disease (CHD), stroke and heart failure), providing more detail in the studied relations. Finally, instead of geometric buffers we applied more accurate street network buffers of different sizes around the home addresses of participants in both urban and rural areas.[20]

Methods

Study design

A one-year follow-up study among a nationwide sample in The Netherlands was conducted.

Datasets

Several Dutch national registers were linked: population register, hospital discharge register (HDR), national cause of death register (NCDR), regional income survey (RIS), and the Locatus database of business addresses. The population register contains information on all legally residing citizens in The Netherlands, including date of birth, sex, current and previous address, postal code and nationality. The HDR registers medical and administrative data for all admitted and day clinic patients visiting a Dutch hospital. The HDR contains information on patients' demographics, admission data and primary and secondary diagnoses at admission. The primary discharge diagnosis is determined at discharge and coded using the ninth version of the international classification of disease codes (ICD-9 codes).[21] The NCDR contains information on date of death and causes of death. The overall validity of these registers has been proven to be high.[22,23] The RIS is a longitudinal survey primarily based on tax information that started in 1994 with a representative sample of over two million households in The Netherlands. This accounts for roughly one-third of the Dutch population and is corrected each year for migration, deceased residents and new-borns.[24] Locatus maintains a database with independently sourced retail information via annual on-site surveys from which typical outlets selling fast food were extracted over 2009 (fast-food outlets (#59.210.171); delivery/take-away outlets (#59.210.180); grillroom/kebab-outlets (#59.210.215)).

Cohort identification

To construct a cohort we selected everyone in the population register at January 1st 2009 aged 35 years and older, and living at the same address for at least 15 years. Next, we linked these individuals with the HDR using a personal identifier based on linkage variables 'sex', 'date of birth', '4-digits of postal code'. Approximately 85% of the entire Dutch population has a unique combination of date of birth, sex and postal code (i.e. occur only once in the registry and thus identify one person) and these were included.[22] All persons with a hospital admission for CVD since January 1st 1995 were excluded.

Outcome measures

Through linkage with the HDR and NCDR individuals were able to be tracked over time for incident CVD events (ICD-9 codes for CVD admissions and ICD-10 codes for CVD deaths in and outside the hospital provided in Supplementary Material Table 1 online). One-year incident was defined as the number of first individual-level CVD hospital admissions or out of hospital deaths for CVD or CVD subtypes within one year after January 1st 2009.

Determinants

FFD – street-network buffer sizes. FFD was defined as the number of fast-food outlets within network buffers around an individual address. Three different street network buffer sizes around individuals' addresses were calculated using ArcGIS 10.1 (Esri, Redlands, CA, US) and included; 500 meter (m), 1000 m (both easily to walk[25]) and 3000 m buffer sizes.

Neighbourhood-level income. Though the RIS, disposable household income was adjusted for the number of household members in the year before baseline.[24] Standardized disposable household income was divided into tertiles based on the average income per individual in the RIS (the first tertile representing the lowest income group and the third tertile the highest income group).

Comorbidity. Comorbidity was based on discharge diagnoses of previous hospital admissions up to five years prior to the index date of admission or day clinic visit with dementia. Comorbidity was defined using a modified Charlson comorbidity index (CCI), a valid and reliable method to measure comorbidity in clinical research.[26] The updated version of the CCI is based on 12 weighted discharge diagnoses (i.e. chronic pulmonary disease, diabetes mellitus). The CCI ranges from 0 to 24 points, zero points representing no comorbidity. Total scores per individual were subdivided into three groups: 0, 1–2 and $\geq$3.

Population density and degree of urbanization. By means of geospatial data available from Statistics Netherlands (www.cbs.nl), population density of individuals' residential environment was determined by five categories expressing the number of addresses per km^2, ranging from ≤ 500 addresses to > 2500 addresses. Urban areas were classified as ≥ 1000 addresses per km^2 whereas rural areas were classified as < 1000 addresses per km^2.[27]

Ethics and privacy issues

All data linkages and analysis were performed in a secure environment of Statistics Netherlands and in agreement with the privacy legislation in The Netherlands.[28] Only anonymized records and data sets were involved. According to the regulations of the research complying with the Dutch law on Medical Research in Humans, approval by an ethics committee was not required for the present study.

Statistical analyses

Logistic regression analyses using IBM SPSS version 23.0 were conducted. The dependent variable was individual incidence of CVD (1 = yes, 0 = no) as well as incident CHD, stroke and heart failure (1 = yes, 0 = no), respectively. The independent variable was FFD within the three buffers. FFD was entered as a categorical variable with four levels for 500 m, 1000 m and 3000 m buffers. The cut-off values for FFD within each level was set in such way that a sufficient number of individuals remain in each level. The category with the lowest number of fast-food outlets served as reference group in all analyses. Analyses were stratified by the degree of urbanization. In addition to the base (unadjusted) model, subsequent models were adjusted for potential confounders. In the first model, outcomes were adjusted for age, sex, ethnicity, marital status, comorbidity and neighbourhood-level income. In the final complete model, additional adjustments were made for population density.[27] The threshold for significance was set at $p < 0.05$.

Results

Participant characteristics

Baseline characteristics are presented in Table 1. In total, 2,472,004 individuals free of CVD as of January 1st 2009 and living at the same address for $\geq$15 years were included in the cohort. In total, 2.5% had an incident CVD event in 2009. About 87% of the population was native Dutch, 70% of the included population was married, approximately half of the participants were men (46%) and the majority of the population lived in urban areas (61%).

Fast-food density and CVD incidence

The relations between FFD and the incidence of overall CVD, CHD, stroke and heart failure are presented in Table 2 for urban areas and in Table 3 for rural areas. In all analyses there was a large difference between the base model, and especially model 1, in which we adjusted for age, sex, ethnicity, marital status, comorbidity and neighbourhood-level income. Further adjustment for population density (model 2) had limited effect on the outcomes.

Urban areas

500 m residential buffer. Fully adjusted models indicated that the incidence of CVD and CHD was higher in areas with one or more fast-food outlets compared with areas with no fast-food outlets. The incidence

Table 1. Baseline characteristics of study population.

	Total $N = 2,472,004$	Rural areas (<1000 addresses/km^2) $n = 964,485$	Urban areas (≥1000 addresses/km^2) $n = 1,507,519$
Age, mean ± SD	59.3 ± 11.8	58.5 ± 11.7	59.8 ± 11.9
Men, *n* (%)	1,130,308 (46)	457,484 (47)	672,824 (45)
Comorbidity, *n* (%)	129,834 (5.3)	46,722 (4.8)	83,062 (5.5)
Native Dutch, *n* (%)	2,152,848 (87)	897,436 (93)	1,257,412 (83)
Married, *n* (%)	1,729,417 (70)	733,931 (76)	995,486 (66)
Incident CVD, *n* (%)	61,681 (2.5)	21,372 (2.2)	40,309 (2.7)
Incident CHD, *n* (%)	13,987 (0.6)	5021 (0.5)	8966 (0.6)
Incident stroke, *n* (%)	9058 (0.4)	3142 (0.3)	5916 (0.4)
Incident HF, *n* (%)	5077 (0.2)	1635 (0.2)	3443 (0.2)

CVD: cardiovascular disease; CHD: coronary heart disease; HF: heart failure.

Table 2. Relations between fast food density and incidence of CVD, CHD, stroke and HF in urban areas (odds ratios).

		%	Base model OR (95% CI)	Model 1 OR (95% CI)	Complete model OR (95% CI)
500 m					
CVD	D0 (0 FFR within 500 m)	47.9	1	1	1
	D1 (1 FFR within 500 m)	20.0	**1.15 (1.12–1.18)**	**1.05 (1.03–1.08)**	**1.05 (1.02–1.08)**
	D2 (2 FFR within 500 m)	11.0	**1.21 (1.17–1.25)**	**1.08 (1.05–1.12)**	**1.07 (1.04–1.12)**
	D3 (≥3 FFR within 500 m)	21.1	**1.16 (1.13–1.19)**	**1.06 (1.03–1.09)**	**1.04 (1.01–1.07)**
CHD	D0 (0 FFR within 500 m)	47.9	1	1	1
	D1 (1 FFR within 500 m)	20.0	**1.20 (1.13–1.27)**	**1.11 (1.05–1.18)**	**1.11 (1.05–1.17)**
	D2 (2 FFR within 500 m)	11.0	**1.25 (1.17–1.33)**	**1.13 (1.06–1.21)**	**1.13 (1.05–1.21)**
	D3 (≥3 FFR within 500 m)	21.1	**1.18 (1.12–1.24)**	**1.08 (1.03–1.16)**	**1.08 (1.02–1.14)**
Stroke	D0 (0 FFR within 500 m)	47.9	1	1	1
	D1 (1 FFR within 500 m)	20.0	**1.16 (1.09–1.24)**	1.03 (0.96–1.10)	1.03 (0.96–1.10)
	D2 (2 FFR within 500 m)	11.0	**1.23 (1.13–1.34)**	1.05 (0.96–1.15)	1.06 (0.97–1.15)
	D3 (≥3 FFR within 500 m)	21.1	**1.22 (1.14–1.30)**	1.07 (1.00–1.15)	**1.09 (1.02–1.17)**
HF	D0 (0 FFR within 500 m)	47.9	1	1	1
	D1 (1 FFR within 500 m)	20.0	**1.23 (1.12–1.34)**	1.01 (0.92–1.11)	1.01 (0.92–1.10)
	D2 (2 FFR within 500 m)	11.0	**1.49 (1.34–1.65)**	**1.16 (1.04–1.29)**	**1.15 (1.03–1.27)**
	D3 (≥3 FFR within 500 m)	21.1	**1.42 (1.30–1.54)**	**1.11 (1.02–1.21)**	1.09 (0.99–1.19)
1000 m					
CVD	D0 (0 FFR within 1000 m)	15.0	1	1	1
	D1 (1 FFR within 1000 m)	16.9	1.03 (0.99–1.07)	1.01 (0.98–1.05)	1.01 (0.97–1.05)
	D2 (2–4 FFR within 1000 m)	30.2	**1.16 (1.12–1.20)**	**1.05 (1.01–1.08)**	**1.04 (1.00–1.07)**
	D3 (≥5 FFR within 1000 m)	37.8	**1.26 (1.22–1.30)**	**1.08 (1.04–1.11)**	**1.05 (1.02–1.09)**
CHD	D0 (0 FFR within 1000 m)	15.0	1	1	1
	D1 (1 FFR within 1000 m)	16.9	1.08 (0.99–1.16)	1.07 (0.98–1.15)	1.06 (0.98–1.15)
	D2 (2–4 FFR within 1000 m)	30.2	**1.20 (1.12–1.29)**	**1.10 (1.02–1.18)**	**1.09 (1.02–1.17)**
	D3 (≥5 FFR within 1000 m)	37.8	**1.34 (1.25–1.43)**	**1.18 (1.10–1.26)**	**1.17 (1.09–1.25)**
Stroke	D0 (0 FFR within 1000 m)	15.0	1	1	1
	D1 (1 FFR within 1000 m)	16.9	0.91 (0.82–1.00)	**0.89 (0.81–0.98)**	**0.88 (0.81–0.98)**

(continued)

Table 2. Continued.

		%	Base model OR (95% CI)	Model 1 OR (95% CI)	Complete model OR (95% CI)
	D2 (2–4 FFR within 1000 m)	30.2	**1.10 (1.01–1.19)**	0.95 (0.87–1.03)	0.94 (0.87–1.03)
	D3 (≥5 FFR within 1000 m)	37.8	**1.19 (1.10–1.28)**	0.95 (0.87–1.03)	0.96 (0.88–1.04)
HF	D0 (0 FFR within 1000 m)	15.0	1	1	1
	D1 (1 FFR within 1000 m)	16.9	1.03 (0.89–1.18)	1.01 (0.88–1.16)	1.00 (0.87–1.15)
	D2 (2–4 FFR within 1000 m)	30.2	**1.32 (1.18–1.49)**	1.06 (0.94–1.19)	1.05 (0.93–1.18)
	D3 (≥5 FFR within 1000 m)	37.8	**1.74 (1.56–1.95)**	**1.21 (1.08–1.36)**	**1.18 (1.05–1.33)**
3000 m					
CVD	D0 (0–3 FFR within 3000 m)	5.4	1	1	1
	D1 (4–10 FFR within 3000 m)	14.1	1.02 (1.00–1.04)	0.99 (0.97–1.02)	0.97 (0.95–1.02)
	D2 (11–27 FFR within 3000 m)	36.0	1.09 (1.07–1.11)	1.04 (1.01–1.06)	0.96 (0.93–1.01)
	D3 (≥28 FFR within 3000 m)	44.5	1.28 (1.25–1.31)	1.12 (1.10–1.15)	0.99 (0.96–1.04)
CHD	D0 (0–3 FFR within 3000 m)	5.4	1	1	1
	D1 (4–10 FFR within 3000 m)	14.1	0.96 (0.86–1.08)	0.98 (0.88–1.10)	0.99 (0.88–1.11)
	D2 (11–27 FFR within 3000 m)	36.0	**1.11 (1.01–1.23)**	1.07 (0.97–1.19)	1.07 (0.97–1.19)
	D3 (≥28 FFR within 3000 m)	44.5	**1.30 (1.17–1.43)**	**1.17 (1.06–1.29)**	**1.17 (1.05–1.30)**
Stroke	D0 (0–3 FFR within 3000 m)	5.4	1	1	1
	D1 (4–10 FFR within 3000 m)	14.1	**0.86 (0.75–0.98)**	0.89 (0.78–1.02)	0.89 (0.78–1.02)
	D2 (11–27 FFR within 3000 m)	36.0	1.01 (0.90–1.14)	0.96 (0.85–1.08)	0.95 (0.85–1.08)
	D3 (≥28 FFR within 3000 m)	44.5	1.12 (1.00–1.26)	0.94 (0.83–1.06)	0.94 (0.83–1.06)
HF	D0 (0–3 FFR within 3000 m)	5.4	1	1	1
	D1 (4–10 FFR within 3000 m)	14.1	**0.80 (0.66–0.96)**	0.86 (0.71–1.03)	0.85 (0.70–1.02)
	D2 (11–27 FFR within 3000 m)	36.0	0.99 (0.84–1.17)	0.93 (0.79–1.09)	0.91 (0.77–1.07)
	D3 (≥28 FFR within 3000 m)	44.5	**1.31 (1.12–1.53)**	0.98 (0.83–1.14)	0.92 (0.78–1.08)

Bold odds ratios are statistically significantly different against the reference category ($p < 0.05$). Analyses were conducted for areas with ≥ 1000 addresses per km^2. Base model: unadjusted model; Model 1: adjusted for age, sex, ethnicity, marital status, comorbidity and neighbourhood-level income; Model 2: adjusted for covariates of Model 1 plus additional adjustments for population density.
CVD: cardiovascular disease; CHD: coronary heart disease; HF: heart failure; OR: odds ratio; CI: confidence interval; FFR: fast food restaurant (outlet).

of stroke was only higher in areas with three or more fast-food outlets, whereas the incidence of heart failure was only higher in areas with two or more fast-food outlets

1000 m residential buffer. Fully adjusted models indicated that an elevated FFD was associated with a raised incidence of CVD and CHD. The analyses showed marginally higher incidence of CVD in areas with 2–4 fast-food outlets and ≥5 fast-food outlets. Statistically significant relations were found for areas with 2–4 fast-food outlets and areas with ≥5 outlets and CHD. These figures may insinuate a dose–response between FFD within the 1000 m residential buffer and the incident of individual-level CVD and CHD. For the incidence of heart failure, a statistically significant relation was found with ≥5 fast-food outlets. In contrast, an opposed direction was found for stroke. In areas with one fast-food outlet the incidence of stroke was lower than in areas without fast-food outlets within the residential buffer.

3000 m residential buffer. The relations were less pronounced when FFD was calculated for a wider area around the home address. Only a statistically significant higher CHD incidence was found in areas with the presence of 28 or more fast-food outlets.

Rural areas

500 m residential buffer. In comparison with urban areas, fully adjusted models indicated that the incidence of CHD was higher in areas with one or two fast-food outlets. The incidence of individual-level CHD dropped in areas with three or more fast-food outlets and became insignificant. Except that the incident of individual-level heart failure was higher in areas with three or more fast-food outlets, no statistically significant relations were found.

1000 m residential buffer. Fully adjusted models indicated that the incidence of CHD was only higher in areas with 2–4 fast-food outlets

Table 3. Relations between fast-food density and incidence of CVD, CHD, stroke and HF in rural areas.

		%	Base model OR (95% CI)	Model 1 OR (95% CI)	Complete model OR (95% CI)
500 m					
CVD	D0 (0 FFR within 500 m)	68.5	1	1	1
	D1 (1 FFR within 500 m)	18.2	**1.08 (1.04–1.12)**	1.02 (0.98–1.06)	1.02 (0.98–1.05)
	D2 (2 FFR within 500 m)	7.4	**1.12 (1.10–1.22)**	1.02 (0.97–1.08)	1.02 (0.97–1.08)
	D3 (≥3 FFR within 500 m)	5.9	**1.22 (1.16–1.29)**	1.01 (0.96–1.07)	1.02 (0.96–1.07)
CHD	D0 (0 FFR within 500 m)	68.5	1	1	1
	D1 (1 FFR within 500 m)	18.2	**1.15 (1.07–1.23)**	**1.09 (1.01–1.17)**	**1.09 (1.01–1.17)**
	D2 (2 FFR within 500 m)	7.4	**1.34 (1.22–1.48)**	**1.20 (1.09–1.32)**	**1.20 (1.09–1.32)**
	D3 (≥3 FFR within 500 m)	5.9	**1.21 (1.08–1.35)**	1.03 (0.92–1.16)	1.03 (0.92–1.15)
Stroke	D0 (0 FFR within 500 m)	68.5	1	1	1
	D1 (1 FFR within 500 m)	18.2	1.10 (1.00–1.20)	1.00 (0.91–1.10)	1.00 (0.91–1.10)
	D2 (2 FFR within 500 m)	7.4	1.32 (1.17–1.49)	1.10 (0.97–1.24)	1.09 (0.97–1.24)
	D3 (≥3 FFR within 500 m)	5.9	1.48 (1.30–1.69)	1.12 (0.98–1.28)	1.12 (0.98–1.28)
HF	D0 (0 FFR within 500 m)	68.5	1	1	1
	D1 (1 FFR within 500 m)	18.2	**1.21 (1.03–1.43)**	1.06 (0.90–1.25)	1.06 (0.90–1.25)
	D2 (2 FFR within 500 m)	7.4	**1.15 (0.90–1.46)**	0.87 (0.68–1.11)	0.87 (0.68–1.11)
	D3 (≥3 FFR within 500 m)	5.9	**1.97 (1.59–2.44)**	**1.27 (1.02–1.57)**	**1.25 (1.01–1.56)**
1000 m					
CVD	D0 (0 FFR within 1000 m)	37.3	1	1	1
	D1 (1 FFR within 1000 m)	21.4	0.97 (0.94–1.01)	0.98 (0.94–1.02)	0.98 (0.94–1.02)
	D2 (2–4 FFR within 1000 m)	31.2	**1.06 (1.03–1.10)**	1.00 (0.97–1.04)	1.01 (0.97–1.04)
	D3 (≥5 FFR within 1000 m)	10.0	**1.15 (1.10–1.21)**	0.98 (0.93–1.02)	0.98 (0.93–1.03)
CHD	D0 (0 FFR within 1000 m)	15.0	1	1	1
	D1 (1 FFR within 1000 m)	16.9	1.01 (0.93–1.09)	1.02 (0.94–1.10)	1.02 (0.94–1.10)
	D2 (2–4 FFR within 1000 m)	30.2	**1.13 (1.06–1.21)**	1.07 (1.00–1.15)	**1.07 (1.00–1.15)**
	D3 (≥5 FFR within 1000 m)	37.8	**1.25 (1.14–1.37)**	1.08 (0.98–1.19)	1.07 (0.98–1.18)
Stroke	D0 (0 FFR within 1000 m)	37.3	1	1	1
	D1 (1 FFR within 1000 m)	21.4	0.99 (0.89–1.09)	0.98 (0.89–1.09)	0.98 (0.99–1.08)
	D2 (2–4 FFR within 1000 m)	31.2	**1.19 (1.10–1.30)**	1.08 (0.99–1.18)	1.08 (0.99–1.17)
	D3 (≥5 FFR within 1000 m)	10.0	**1.37 (1.22–1.54)**	1.07 (0.95–1.20)	1.06 (0.94–1.19)
HF	D0 (0 FFR within 1000 m)	37.3	1	1	1
	D1 (1 FFR within 1000 m)	21.4	**1.10 (1.02–1.19)**	0.98 (0.89–1.09)	0.98 (0.99–1.08)
	D2 (2–4 FFR within 1000 m)	31.2	**1.21 (1.07–1.35)**	1.08 (0.99–1.18)	1.08 (0.99–1.17)
	D3 (≥5 FFR within 1000 m)	10.0	1.34 (0.98–1.82)	1.07 (0.95–1.20)	1.06 (0.94–1.19)
3000 m					
CVD	D0 (0–3 FFR within 3000 m)	45.5	1	1	1
	D1 (4–10 FFR within 3000 m)	43.1	1.00 (0.97 -1.02)	0.98 (0.95–1.00)	0.97 (0.94–1.01)
	D2 (11–27 FFR within 3000 m)	10.3	0.97 (0.93–1.02)	0.93 (0.88–0.97)	0.93 (0.88–0.97)
	D3 (≥28 FFR within 3000 m)	1.1	**1.26 (1.11–1.41)**	0.98 (0.87–1.10)	0.98 (0.86–1.10)
CHD	D0 (0–3 FFR within 3000 m)	45.5	1	1	1
	D1 (4–10 FFR within 3000 m)	43.1	1.06 (0.998–1.12)	1.04 (0.98–1.10)	1.03 (0.97–1.10)
	D2 (11–27 FFR within 3000 m)	10.3	1.02 (0.93–1.13)	0.98 (0.89–1.07)	0.96 (0.87–1.07)
	D3 (≥28 FFR within 3000 m)	1.1	1.19 (0.92–1.53)	1.01 (0.78–1.31)	1.00 (0.78–1.30)
Stroke	D0 (0–3 FFR within 3000 m)	45.5	1	1	1
	D1 (4–10 FFR within 3000 m)	43.1	**1.10 (1.01–1.19)**	1.05 (0.97–1.14)	1.05 (0.97–1.15)
	D2 (11–27 FFR within 3000 m)	10.3	**1.16 (1.02–1.32)**	1.08 (0.95–1.22)	1.08 (0.94–1.24)

(continued)

Table 3. Continued.

		%	Base model OR (95% CI)	Model 1 OR (95% CI)	Complete model OR (95% CI)
	D3 (≥28 FFR within 3000 m)	1.1	1.24 (0.88–1.75)	0.89 (0.63–1.25)	0.89 (0.63–1.25)
HF	D0 (0–3 FFR within 3000 m)	45.5	1	1	1
	D1 (4–10 FFR within 3000 m)	43.1	**1.10 (1.02–1.19)**	1.06 (0.98–1.14)	1.05 (0.97–1.14)
	D2 (11–27 FFR within 3000 m)	10.3	**1.21 (1.07–1.35)**	1.12 (0.99–1.26)	1.11 (0.98–1.26)
	D3 (≥28 FFR within 3000 m)	1.1	134 (0.98–1.82)	0.91 (0.67–1.24)	0.91 (0.66–1.67)

Bold odds ratios are statistically significantly different against the reference category ($p < 0.05$). Analyses were conducted for areas with < 1000 addresses per km^2. Base model: unadjusted model; Model 1: adjusted for age, sex, ethnicity, marital status, comorbidity and neighbourhood-level income; Model 2: adjusted for covariates of Model 1 plus additional adjustments for population density.
CVD: cardiovascular disease; CHD: coronary heart disease; HF: heart failure; OR: odds ratio; CI: confidence interval; FFR: fast food restaurant (outlet).

3000 m residential buffer. Similar to urban areas, no statistically significant relations were found between the presence of fast-food outlets within the rural 3000 m residential buffers and the incidence of CVD or CVD subtypes in the fully adjusted models.

Discussion

This study showed that the incidence of CVD and CHD was higher among adults living in urban areas with elevated numbers of fast-food outlets within 1000 m of the residential address compared with individuals with no fast-food outlets in this area. In the 500 m buffer, the incidence of CVD and CHD was higher in areas with one or more fast-food outlets compared with areas with no fast-food outlets. Relations between FFD and CVD and subtypes in the 3000 m buffer were largely absent and less consistent. Relations were less pronounced in rural areas or for stroke and heart failure incidence. Effect sizes of the relationships were small to moderate in magnitude, but reflect the nation-wide incidence of a population of more than two million adults. Our findings suggest urban FFD is potentially an important piece of the puzzle when understanding risk factors of CVD.

Relations between the fast-food environment and overall CVD were pronounced in urban areas, but not in rural areas. Speculating on the source of this difference, it is well understood that urbanization is associated with shifts in dietary patterns, expressed by an increase in the consumption of ultra-processed foods, saturated fat and added sugar, and a decrease in fibre intake.[29] Likewise, food intake among urban residents is shaped by the culture of commercial influences (e.g. that of fast-food outlets) or social influences (e.g. purchasing and eating behaviors in public space).[30] However, the difference may also be due to the fact that we were unable to correct for traditional cardiovascular risk behaviors such as smoking or being physical inactive, which are more pronounced among urban than among rural residents.[31]

With respect to CVD subtypes, the outcome of our study, which indicates that FFD is related to the incidence of CHD within <1000 m buffers, is in contrast with previous findings. Although in a prior study similar directions were found of death per 10% increase in FFD (relative risks = 1.39 (95% confidence interval (CI) = 1.19–1.63)), this was not different in magnitude for non-cardiovascular mortality (relative risk = 1.36 (95% CI = 1.18–1.57)). Also the availability of fruit and vegetables was not associated with cardio-vascular mortality. Based on these findings, the authors question the role of the food environment in cardiovascular outcomes.[18] Unlike our study – where we corrected for neighbourhood-level income – the authors of another study corrected for individual-level income, which resulted in the mitigation of any statistically significant relationship between FFD and CHD.[19] Yet, although not the most apparent outcome of this study, the relation between the presence of ≥3 fast-food outlets within the 500 m buffer in urban areas and the incidence of stroke is comparable to the previous studies[15,16] where elevated fast-food availability was associated with stroke risk. We found also an opposite relationship where the incidence of stroke was marginally but significantly lower in areas (1000 m) with one fast-food outlet than in urban areas without fast-food outlets. However, these studies used an area-level approach to determine fast-food exposure and are therefore less comparable to our study.

The present study had a number of strengths, such as the inclusion of a large nation-wide study sample, the use of individual-level health outcomes, the longitudinal perspective by using CVD *incidence* rather than *prevalence* as outcome measure, including CVD subtypes, the use of individual-level fast-food exposure of different sizes of street network buffers, the stratification for urban and rural areas and the inclusion of individuals living at the same address for at least 15 years that were followed for one year. However, some limitations should be considered. The most important limitation is that we could not adjust for all individual-level risk factors such as dietary intake, alcohol consumption or smoking behaviour. Yet, we were able to correct for neighbourhood income level, which is likely an important link between individual dietary and smoking behaviour and neighbourhood FFD. Moreover, we corrected for comorbidity including the diagnosis of diseases associated with dietary and smoking behaviour (e.g. diabetes type 2, chronic pulmonary disease, malignancy). Second, in the construction of the cohort we linked the different datasets (e.g. population register, HDR) by means of the personal identifier base including a unique combination of individual characteristics. Although this is a frequently used technique, we lack exact linkage, which may have resulted into non-differential misclassification of the exposure or outcome. Although this risk is small – approximately 85% of the Dutch population has a unique combination of these characteristics – this should be taken into account when interpreting the results. Finally, we calculated FFD only for one time stamp (2009) and we acknowledge that this exposure may have changed gradually over time. Nevertheless, we expect that FFD changes over time were relatively similar for all participants in the cohort that lived at the same address for a minimum of 15 years.

In the future, studies should explore the relation between FFD and CVD incidence, accounting for a wider range of individual confounders than was achieved in the present study (e.g. smoking behaviour). Additionally, future studies could incorporate area-level proxies for smoking behaviour if available (e.g. area-level chronic obstructive pulmonary disease) or account for individual control endpoints that are unlikely to relate to FFD (e.g. lung cancer). In addition, the relationship between FFD and the hypothesized underlying mechanism of fast-food exposure and CVD, fast-food consumption or overall dietary intake should be investigated.

Public policy makers should be aware of the likely impact of urban FFD on health, especially since the number of fast-food outlets is still increasing. The 2016 European Guidelines on cardiovascular disease of the Sixth Joint Task Force of the European Society of Cardiology recommend population-based approaches to diet in managing CVD prevention. These guidelines also include the recommendation to consider the regulation and density of fast-food outlets in community settings.[32] Already efforts banning fast-food facilities in residential or school environments have been proposed to improve public health.[33]

Conclusion

The study indicated that elevated FFD in the urban residential environment ($\leq$1000 m) was associated with an increased incidence of CVD and CHD. To better understand how FFD is associated with CVD, future studies should account for a wider range of lifestyle and environmental confounders than was achieved in the present study.

Author contribution

MP and IV drafted the manuscript and contributed to acquisition, analysis and interpretation. MS and BB contributed to acquisition and analyses. OS contributed to the analyses. GH, AN and MB contributed to the interpretation. DK contributed to the acquisition and interpretation. MH and DG contributed to the analyses and interpretation. All authors critically revised the paper, provided final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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REVIEW

Pivoting the Plant Immune System from Dissection to Deployment

Jeffery L. Dangl,[1,2,3,4,5]*† Diana M. Horvath,[6]* Brian J. Staskawicz[7]*

Diverse and rapidly evolving pathogens cause plant diseases and epidemics that threaten crop yield and food security around the world. Research over the last 25 years has led to an increasingly clear conceptual understanding of the molecular components of the plant immune system. Combined with ever-cheaper DNA-sequencing technology and the rich diversity of germ plasm manipulated for over a century by plant breeders, we now have the means to begin development of durable (long-lasting) disease resistance beyond the limits imposed by conventional breeding and in a manner that will replace costly and unsustainable chemical controls.

Plants turn sunlight into sugar. Thus, plants are rich sources of nutrients and water that are, to no one's surprise, host to diverse microbial communities both above and below the ground. Microbes are likely to have accompanied the first plants that emigrated from water to land 400 to 500 hundred million years ago. Many of their descendant contemporary microbes are adapted to take advantage of the nutrient niches afforded to them by the huge diversity of plants all over the earth. Plants are protected from infection by a "skin," a waxy cuticular layer atop the cell wall. Would-be pathogens breaching this barrier encounter an active plant immune system that specifically recognizes pathogen and altered-self molecules generated during infection. Consequent regulation of a network of inducible defenses can halt pathogen proliferation and signal distal plant organs to become nonspecifically primed against further infection.

Nevertheless, fungal, oomycete, bacterial, and viral pathogens cause devastating epidemics that have affected human civilizations since the dawn of agriculture (*1*). The late blight Irish potato famine of the 1840s was caused by the oomycete *Phytophthora infestans* (*2*); the loss of the world's first mass-cultivated banana cultivar *Gros Michel* in the 1920s to Panama disease was caused by the fungus *Fusarium oxysporum* (*3*); and the current wheat stem, leaf, and yellow stripe rust epidemics spreading from East Africa into the Indian subcontinent caused by rust fungi *Puccinia graminis* and *P. striiformis* (*4*) are all testament to the recurring impact of plant diseases. Plant pathogens can spread rapidly over great distances, vectored by water, wind, insects, and humans (http://rusttracker.cimmyt.org/). Despite various cultural practices, crop protection chemicals, and available disease-resistant crop varieties, an estimated 15% of global crop production is lost to preharvest plant disease (*5*).

Plant Breeding and Disease Resistance

Humans have selected for disease-resistant crops throughout the history of agriculture, at times unwittingly (*6*). As a practiced science, plant breeding for disease resistance originated with Sir Rowland Biffen in Cambridge, England, who

[1]Department of Biology, University of North Carolina, Chapel Hill, NC 27599, USA. [2]Howard Hughes Medical Institute, University of North Carolina, Chapel Hill, NC 27599, USA. [3]Curriculum in Genetics and Molecular Biology, University of North Carolina, Chapel Hill, NC 27599, USA. [4]Department of Microbiology and Immunology, University of North Carolina, Chapel Hill, NC 27599, USA. [5]Carolina Center for Genome Sciences, University of North Carolina, Chapel Hill, NC 27599, USA. [6]Two Blades Foundation, 1630 Chicago Avenue, Evanston, IL 60201, USA. [7]Department of Plant and Microbial Biology, 111 Koshland Hall, University of California, Berkeley, CA 94720–3120, USA.

*These authors contributed equally and are listed alphabetically.
†Corresponding author. E-mail: dangl@email.unc.edu

identified a single recessive gene for resistance to wheat yellow rust caused by *P. striiformis* (*7*). The ensuing century of breeding in nearly every crop species resulted in deployment of disease resistance (*R*) genes, many of which were introduced by introgression from sexually compatible wild relatives. Dominant or semidominant *R* genes were easier to breed into existing crop cultivars, as they could be selected functionally in each generation. We now know that *R* genes are present in multigene clusters and can occur as true alleles across naturally variant genetic backgrounds. The function of each R protein is activated by the product of a specific pathogen virulence gene (*8*), now generically termed "effector genes." Each pathogen isolate can express an array of effectors, and the diversity of effectors across the population of any pathogen species can be stunning (*9*, *10*).

Unfortunately, the utility of most *R* alleles can be short-lived in the field, because their deployment in monoculture selects for pathogen variants, wherein the corresponding effector allele has suffered mutation or been lost. Effectors are virulence factors, but each typically contributes only partially to virulence. Unrelated effectors can act redundantly by altering the same host signaling pathway. Therefore, effector genes can often be lost without significant impact on pathogen virulence. Likely exceptions to this principle are "core effectors," defined operationally by their wide distribution across the population of a particular pathogen and their substantial contribution to pathogen virulence. Genomics-based identification of core effectors and their utilization to functionally define new *R* alleles that they activate in diverse plant germ plasm is a particularly promising strategy for research and deployment that we discuss below.

The Plant Immune System

Research using both tractable experimental systems (*Arabidopsis*) and the irreplaceable germ plasm toolkits provided by plant breeders and plant pathologists (notably in flax, tomato, and barley) led to the isolation of the first pathogen effector genes (*11*) and plant *R* genes (*12*). Additional fundamental discoveries demonstrated that plants could perceive diverse structures generally encoded by microbes via high-affinity cell surface pattern-recognition receptors (PRR) (*13*). These lines of research converged to describe a plant immune system that consists of two interconnected tiers of receptors, one outside and one inside the cell, that govern recognition of microbes and response to infection (*14*–*18*).

The first tier of the plant immune system is governed by extracellular surface PRRs that are activated by recognition of evolutionarily conserved pathogen (or microbial)–associated molecular patterns (PAMPs or MAMPs). These receptors are typically leucine-rich repeat kinases and lysine motif (LysM) kinases (although some lack the kinase domain and thus require a co-receptor to provide signaling function) and are broadly analogous to Toll-like receptors in animals. Activation of PRRs leads to intracellular signaling, transcriptional reprogramming, and biosynthesis of a complex output response that limits microbial colonization (*13*) (Fig. 1, step 1).

Successful pathogens use their effector repertoire to subvert PRR-dependent responses, to facilitate nutrient acquisition, and to contribute to pathogen dispersal. Effector repertoires have been described from pathogens with diverse lifestyles. These include effectors from extracellular plant bacterial pathogens that are delivered into host cells by the type III secretion system (TTSS) (*9*, *19*); effectors from oomycetes and fungi (*10*, *20*) that invaginate specialized feeding organelles, called haustoria, into host cells; and salivary proteins delivered to plant cells during aphid and nematode feeding (*21*) (Fig. 1, step 2). Effector suites from at least two evolutionarily diverse pathogens interact with a limited set of plant "targets," a high proportion of which have immune system functions (Fig. 1, step 3) (*22*).

Most *R* genes encode members of an extremely polymorphic superfamily of intracellular nucleotide-binding leucine-rich repeat (NLR) receptors, which function intracellularly and anchor the second tier of the plant immune system (*14*–*18*). Specific NLR proteins are activated by specific pathogen effectors. This can be via direct interaction, as receptor and ligand, respectively (*23*) (Fig. 1, step 4a). Alternatively, an effector can modify its host cellular target (or a molecular decoy of that target), and a specific NLR associated with the target or decoy can be activated by the modification (*14*, *24*) (Fig. 1, steps 4b and 4c). NLR activation coordinates effector-triggered immunity, a rapid and high-amplitude reboot of effector-suppressed, PRR-dependent outputs that limits pathogen proliferation (Fig. 1, step 5). Animal NLR proteins are likely to follow similar activation models (*25*).

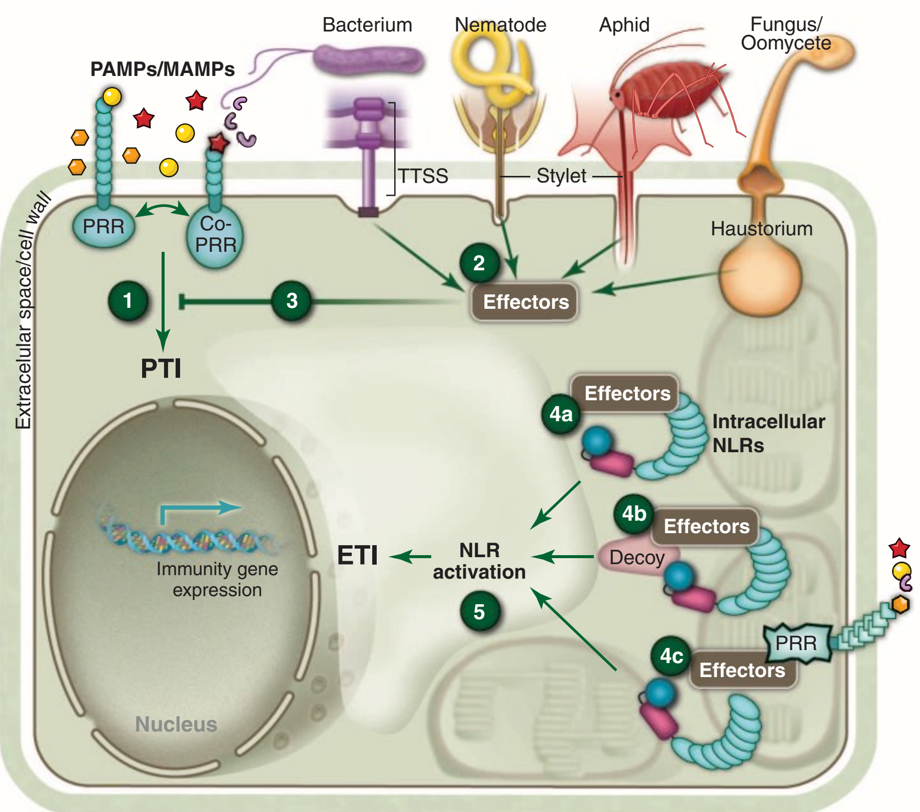

Fig. 1. Schematic of the plant immune system. Pathogens of all lifestyle classes (color coded and labeled) express PAMPs and MAMPs as they colonize plants (shapes are color coded to the pathogens). Plants perceive these via extracellular PRRs and initiate PRR-mediated immunity (PTI; step 1). Pathogens deliver virulence effectors to both the plant cell apoplast to block PAMP/MAMP perception (not shown) and to the plant cell interior (step 2). These effectors are addressed to specific subcellular locations where they can suppress PTI and facilitate virulence (step 3). Intracellular NLR receptors can sense effectors in three principal ways: first, by direct receptor ligand interaction (step 4a); second, by sensing effector-mediated alteration in a decoy protein that structurally mimics an effector target, but has no other function in the plant cell (step 4b); and third, by sensing effector-mediated alteration of a host virulence target, like the cytosolic domain of a PRR (step 4c). It is not yet clear whether each of these activation modes proceeds by the same molecular mechanism, nor is it clear how, or where, each results in NLR-dependent effector-triggered immunity (ETI). [Modified from (*17*) by Sarah R. Grant]

Table 1. Published examples of transgenic disease resistance in crops and development status.

Pub. year	Crop	Disease resistance	Mechanism	Development status	Ref.
2012	Tomato	Bacterial spot	*R* gene from pepper	8 years of field trials	(*46*)
2012	Rice	Bacterial blight and bacterial streak	Engineered *E* gene	Laboratory	(*56*)
2012	Wheat	Powdery mildew	*R* gene from wheat, overexpressed	2 years of field trials at time of publication	(*82*)
2011	Apple	Apple scab fungus	Thionin gene from barley	4 years of field trials at time of publication	(*83*)
2011	Potato	Potato virus Y	Pathogen-derived resistance	1 year of field trial at time of publication	(*84*)
2010	Apple	Fire blight	Antibacterial protein from moth	12 years of field trials at time of publication	(*85*)
2010	Tomato	Multibacterial resistance	PRR from *Arabidopsis*	Laboratory scale	(*43*)
2010	Banana	*Xanthomonas* wilt	Novel gene from pepper	Now in field trial	(*86*)
2009	Potato	Late blight	*R* genes from wild relatives	3 years of field trials	(*87*)
2009	Potato	Late blight	*R* gene from wild relative	2 years of field trials at time of publication	(*88*)
2008	Potato	Late blight	*R* gene from wild relative	2 years of field trials at time of publication	(*89*)
2008	Plum	Plum pox virus	Pathogen-derived resistance	Regulatory approvals, no commercial sales	(*90*, *91*)
2005	Rice	Bacterial streak	*R* gene from maize	Laboratory	(*92*)
2002	Barley	Stem rust	*RLK* gene from resistant barley cultivar	Laboratory	(*93*)
1997	Papaya	Ring spot virus	Pathogen-derived resistance	Approved and commercially sold since 1998, sold into Japan since 2012	(*94*, *95*)
1995	Squash	Three mosaic viruses	Pathogen-derived resistance	Approved and commercially sold since 1994	(*96*)
1993	Potato	Potato virus X	Mammalian interferon-induced enzyme	3 years of field trials at time of publication	(*97*)

Fig. 2. Hawaiian papaya plot in 2011. Hawaiian papaya plot showing diseased, devastated, nontransformed trees in the foreground and healthy transgenic trees behind. [Photo courtesy of Dennis Gonsalves, Agricultural Research Service, U.S. Department of Agriculture, Hawaii]

The molecular architectures of NLR proteins in their resting, transition, and active signaling states are poorly defined (*26*, *27*). There are limited and conflicting data on the role of self-association or oligomerization for sensor NLR protein function, at both pre- and postactivation steps (*28*). Resting state oligomerization (in some cases), activation-dependent intramolecular rearrangements (in essentially all cases), and activation-dependent N-terminal signaling domain dimerization (in many but not all cases) have been documented. Some effector-triggered responses require a pair of NLR proteins (*28*): One is activated by the effector and is a "sensor NLR"; the other is required for its function and is a "helper NLR" (*27*, *29*). Heteromeric pairing could expand NLR repertoires (*30*, *31*). Similar NLR pairs can function in animal NLR systems (*32*, *33*). Exceptions abound, and generalizable models for NLR activation may not exist; evolution may have favored a mix of mechanisms that were refined by coevolutionary conflict between effectors, targets or decoys, and sensor NLRs.

The cellular site(s) of NLR activation and action are likely to be diverse. Some NLRs may require nucleocytoplasmic shuttling for function, whereas others appear to be activated at the plasma membrane (*18*, *27*). These different sites of activation suggest a more idiosyncratic model for NLR function, dictated in part by the localization of, and functional constraints on, the effector targets whose integrity each NLR monitors.

The presence of NLRs with diverse N-terminal signaling domains in both plants and animals suggests that this architecture confers a fundamental advantage in host defense. This advantage may include recruitment of diverse cofactors after activation, as suggested by the functionally relevant interaction of NLR N-terminal domains with transcription factors in some cases (*34*). NLRs may facilitate tightly regulated "cooperative" threshold responses to ligands within an evolutionarily flexible scaffold that permits innate immune systems with limited germ line–encoded repertoires to keep pace with functionally diverse pathogen effectors acting at a variety of intracellular sites.

Engineering Disease Resistance in Crops: Early Successes

Successful transgenic disease resistance was demonstrated in 1986. Constitutive *in planta* expression of viral coat protein gene sequences conferred virus resistance via small RNAs, now understood to be a widely applicable mechanism for inhibiting viral replication (*35*). By combining coat protein genes from three different viruses, scientists developed squash hybrids with field-validated, multiviral resistance (Table 1). The Asgrow Seed Company obtained regulatory approvals for transgenic commercial squash in 1994, and these continue to be sold by Seminis today. Similar levels of resistance to this variety of viruses had not been achieved by conventional breeding.

A similar strategy was deployed to combat papaya ringspot virus, which, by 1994, threatened to destroy Hawaii's papaya industry. Field trials demonstrated excellent efficacy and high fruit quality (Table 1), and by 1998, the first transgenic virus-resistant papaya was approved for sale in Hawaii. Disease resistance has been durable for over 15 years of commercial use, and transgenic papaya currently accounts for ~85% of Hawaiian production (Fig. 2). The fruit is now approved for sale in Canada and Japan.

Since the approval and commercialization of these two crops in the late 1990s, not a single new crop with engineered disease resistance has reached the market. Research successes exist (Table 1), and there is still potential to reduce yield losses and chemical inputs associated with crop disease.

Effector-Targeted Strategies for Durable Disease Resistance—An Emerging Paradigm

R gene isolation using genetics and genomics is now a reality in even the most complex plant genomes (*36*, *37*). Rapid and inexpensive DNA-sequencing technologies can provide the genomes of natural field isolates of plant pathogens with impact on breeding strategies for durable control of plant diseases (*38*). It is now possible to define the genomes, and thus the effector complement, of plant pathogens isolated from infected plants in a rapid and efficient manner. Defining core effectors facilitates identification of suites of corresponding *R* genes from wild germ plasm by using transient coexpression assays, followed by either marker-assisted breeding or transgenic deployment (Box 1). Validation of these new *R* genes could be enhanced by new genome-editing methods that use transcription activator–like effector nuclease (TALEN) (*39*) and clustered regulatory interspaced short palindromic repeat (CRISPR) technologies (*40*, *41*).

The function of any particular *R* gene is likely to be durable only if the effector that activates it is present and important for virulence in the pathogen strains that one is trying to control. Knowledge of the effector content in local pathogen isolates can inform *R* gene deployment or chemical treatment in the control of potato late blight (*38*). Another exmaple is *Xanthomonas axonopodis* pv. *manihotis* (*Xam*), the causal agent of cassava bacterial blight (*42*). This disease devastates a staple crop in East Africa. The sequence of ~65 *Xam* strains collected over a 70-year time frame, from 12 countries and three continents, revealed a core effector set that can now serve as targets to define *R* genes activated by them in wild species of *Manihot* and potentially other related plants in the *Euphorbiaceae.*

Deployment of Immune System Receptors

Research aimed at deployment of the two classes of immune receptors currently follows two main strategies. One is to transfer PRRs that detect common microbial products into species that lack them. For example, the *Arabidopsis* PRR EF-Tu receptor (EFR) recognizes the bacterial translation elongation factor EF-Tu. Deployment of EFR into either *Nicotiana benthamiana* or *Solanum lycopersicum* (tomato), which cannot recognize EF-Tu, conferred resistance to a wide range of bacterial pathogens (*43*). The expression of EFR in tomato was especially effective against the widespread and devastating soil bacterium *Ralstonia solanacearum*. Also, the tomato PRR *Verticillium 1* (*Ve1*) gene can be transferred from tomato to *Arabidopsis*, where it confers resistance to race 1 isolates of *Verticillium* (*44*). Identification of functional PRRs and their transfer to a recipient species that lacks an orthologous receptor could provide a general pathway to additional examples of broadened PRR repertoires (*13*).

The second strategy exploits immune responses in contexts where multiple *NLR* genes are deployed simultaneously, a breeding strategy known as stacking. Such cultivars, generated by either DNA-assisted molecular breeding or gene transfer, should provide more durable disease resistance because pathogen evasion would require mutations in multiple effector genes. Recent breakthroughs in DNA sequencing allow access to the huge genetic diversity of our major crops and their relatives to functionally "mine" *NLR* genes directed against different core effectors. This approach will ultimately overcome inherent barriers to traditional crop breeding (Box 1). Illustrative examples follow.

The first "effector-rationalized" search for a potentially durable *R* gene was predicated on the finding that the *avrBs2* effector gene from *Xanthomonas perforans,* the causal agent of bacterial spot disease of pepper and tomato, is found in most species of *Xanthomonas* that cause disease and is required for pathogen fitness (*45*). The *Bs2* NLR gene from the wild pepper, *Capsicuum chacoense,* was transformed into tomato, where it inhibited growth of pathogen strains that contained *avrBs2*. Successful field trials of transgenic tomato plants that express *Bs2* demonstrated robust resistance to *X. perforans* without bactericidal chemicals (*46*). However, rare strains of *Xanthomonas* have overcome *Bs2*-mediated resistance in pepper by acquisition of *avrBs2* mutations that avoid recognition but retain virulence (*47*). Stacking of multiple *R* genes that each recognize a different core effector could delay or prevent this problem.

The oomycete *Phytophthora infestans* causes late blight disease of potato (*2*). Cultivated potato, *Solanum tuberosum*, is tetraploid and clonally propagated via cuttings, which significantly hampers introgression of disease resistance from diploid wild species in the genus *Solanum.* Furthermore, the pathogen is aggressive and has repeatedly adapted to evade host resistance mediated by single *R* genes and chemical treatments. Most potato cultivars are thus susceptible to *P. infestans* infection, which necessitates continual updating of chemical treatments.

Genome-wide definition of effector suites across pathogen isolates collected worldwide and of *R* gene distribution across *Solanum* sp. will have a major impact on management of resistance to *P. infestans* (*38*). Sequencing of several *P. infestans* genomes has identified a core set of effectors that can now be used to identify new sources of disease resistance across the genus *Solanum*. This approach has been validated in the potato cultivar *Sarpo mira*, which contains four naturally stacked *R* genes activated by already known *P. infestans* effectors (*48*). Rational stacking of *R* genes is a general approach (*49*, *50*) and the method of choice for producing sustainable, durable disease resistance that will require fewer chemical inputs.

In modern wheat and its many relatives, more than 50 different loci have been described that confer disease resistance against wheat stem, leaf, and yellow stripe rust pathogens. A few were known to confer resistance to the pandemic wheat rust isolate Ug99 and its derivatives, but these were not readily incorporated into hexaploid wheat or provide only partial resistance. The *Stem rust 35* (*Sr35*) NLR gene was very recently cloned from a diploid relative of cultivated wheat, *Triticum monococcum*, and transferred into cultivated hexaploid wheat to derive resistance to Ug99 (*36*). Similarly, the *Stem rust 33* (*Sr33*) NLR gene from the wheat relative *Aegilops tauschii* was also very recently cloned and shown to encode a wheat ortholog to the barley *Mla* powdery mildew–resistance genes (*37*). Both *Sr35* and *Sr33* are fairly rare in wheat and its relatives, which accentuates the importance of diverse germ plasm screening to identify useful new *R* genes. It is hoped that *Sr35* and *Sr33,* combined with the *Sr2* gene that is known to act additively with at least *Sr33* (*51*), could provide durable disease resistance to Ug99 and its derivatives.

Deployment of Executor-Mediated Disease Resistance

In contrast to PRRs and NLRs, another class of plant disease resistance genes has evolved to coopt pathogen virulence functions and open a "trap door" that stops pathogen proliferation. *Xanthomonas* and *Ralstonia* transcription activator–like (TAL) effectors are DNA-binding proteins delivered into plant cells, where they activate host gene expression to enhance pathogen virulence (*39*). In a neat evolutionary trick, however, both the rice and pepper lineages independently evolved TAL-effector binding sites in the promoters of genes whose products induce hypersensitive host cell death when up-regulated and thus inhibit pathogen proliferation. The known "executor" genes, *Xa27* from rice (*52*) and *Bs3* and *Bs4c* from pepper (*53*, *54*), encode plant proteins of unknown function that share no homology. Executor genes are not expressed in the absence of infection, but expression of each is strongly induced by a specific TAL effector.

Engineered executor genes provide unique opportunities to deliver enhanced and potentially durable disease resistance. This was demonstrated by successfully redesigning the pepper *Bs3* promoter to contain two additional binding sites for TAL effectors from disparate pathogen strains (*55*). Subsequently, an engineered executor gene was deployed in rice by adding five different TAL effector binding sites to the *Xa27* promoter. The synthetic *Xa27* construct was activated by TAL effectors from, and conferred resistance against, both bacterial blight and bacterial leaf streak species of *Xanthomonas* (*56*) (Table 1).

Defining and Deploying Altered Host "Susceptibility Alleles" to Control Plant Diseases

Most plant pathogens reprogram host plant gene expression patterns to directly benefit pathogen fitness, as exemplified above for TAL effectors. Host genes reprogrammed by pathogens that are required for pathogen survival and proliferation can be thought of as "disease-susceptibility genes." Identification and isolation of these would provide useful sources for breeding disease resistance: their loss or alteration of function would deprive the pathogen of a host factor required for its proliferation (*57*, *58*). We highlight a few here.

Recessive disease-resistance genes, long known to breeders, are candidates for disease-susceptibility genes. For example, a loss-of-function mutation in an *Arabidopsis* gene encoding pectate lyase, an enzyme involved in cell wall degradation, conferred resistance to the powdery mildew pathogen *Golovinomyces* (syn. *Erysiphe*) *cichoracearum* (*59*). Similarly, the Barley *mlo* gene has been deployed against powdery mildew for more than 70 years, and it is required for pathogen invasion (*60*). Spontaneous mutations in pea and tomato *MLO* orthologs confer resistance to powdery mildew pathogens of these plants (*61*, *62*). And the *Pseudomonas syringae* bacterial effector HopZ2 targets the *Arabidopsis* ortholog, *MLO2*, to contribute to bacterial virulence (*63*).

Similarly illustrative is the cloning and deployment of *Lr34*, a gene that provides partial resistance to leaf and yellow rusts and powdery mildew in wheat and that has been durable for nearly a century. *Lr34* encodes an adenosine triphosphate (ATP)–binding cassette (ABC) transporter. The dominant allele that provides disease resistance was recently derived in cultivated wheat (it is not present in wild progenitors of wheat) and, like *mlo*, is associated with ectopic plant cell death that may establish a "sensitized" defense state or accelerate senescence. Transfer of the wheat *Lr34* resistance allele provides broad-spectrum resistance in barley, although with the expected cell death–lesion formation (*64*–*66*). It is unclear whether the wheat allele that provides durable resistance is also functional for the inferred ABC transporter activity of Lr34, and thus, the mechanism by which Lr34 confers disease resistance remains obscure.

Naturally occurring alleles of the host translation elongation initiation factors *eif4e* and *eif4g* double as recessive viral-resistance genes. Some have been deployed to control important potyviruses in barley, rice, tomato, pepper, pea, lettuce, and melon (*67*). The discovery of natural recessive alleles prompted a successful mutant screen for chemically induced *eif4e* alleles in tomato (*68*).

Natural variation in the promoters of key plant-susceptibility genes can also lead to the evolution of recessive disease-resistance alleles. For example, the recessive resistance gene *xa13* in rice is an allele of *Os-8N3*. *Os-8N3* is transcriptionally activated by *Xanthomonas oryzae* pv. *oryzae* strains that express the TAL effector PthXo1. The *xa13* gene has a mutated effector-binding element in its promoter that eliminates PthXo1 binding and renders these lines resistant to strains of the pathogen that rely on PthXo1 as their essential virulence factor. This finding also demonstrates that Os-8N3 is required for susceptibility (*69*).

The deployment of mutant alleles of host disease-susceptibility genes can be problematic if the disease-susceptibility phenotype comes at the cost of altered function in other cellular and developmental processes. This is the case for *Xa13/Os-8N3*, which is also required for pollen development (*70*). Nevertheless, it is possible to separate disease susceptibility from normal development. For example, mutations in the *Os11N3* (*OsSWEET14*) TAL effector–binding element were made by using TAL effectors fused to nucleases (TALENs). Genome-edited rice plants with altered *Os11N3* binding sites were resistant to *Xanthomonas oryzae* pv. *oryzae* infection, but they were unaltered for the normal *Os11N3* (*OsSWEET14*) developmental function (*71*).

The identification of new susceptibility genes in crops will come from forward genetic screens that uncover new recessive disease-resistance genes—which may, indeed, turn out to be host-susceptibility genes—and from identification of host targets of effectors. For example, mutant screens in *Arabidopsis* identified additional recessive mutations that confer recessive resistance to the obligate biotrophs, *G. cichoracearum* (*72*) and *Hyaloperonospora arabidopsidis* (*73*). These genes have orthologs in other plants, thus making them obvious targets for identification of mutant alleles in crop species (Box 1).

Box 1. Breeding for disease resistance.

Current practices involved in breeding for disease resistance

1. Discover single *R* genes in wild relative species and cross into agronomic cultivars by interspecific hybridization, followed by successive generations of recurrent selection for resistance. This process is slow.
2. Use pathogen inoculations to test plant germ plasm for resistance without a priori knowledge of which effector is being detected by the new *R* gene.
3. *R* gene–mediated disease resistance can be short-lived, as pathogens can mutate to evade activating *R* function.
4. Interspecific hybrid breeding is sometimes difficult because of sexual incompatibilities and/or linkage drag of undesirable traits.

Improved practices for breeding durable resistance by genomic strategies

1. Use next-generation sequencing technologies to sequence and assemble pathogen genomes causing disease in local fields.
2. Use computational biology to identify the most highly successful core effectors in these strains.
3. Identify *R* genes that are activated by those effectors.
4. Deploy multiple, stacked *R* genes that recognize defined core effectors to reduce the chance that pathogens will overcome resistance.
5. Identify and edit within the genome disease-susceptibility genes to reduce pathogen growth and symptom development.
6. Identify and deploy antipathogenic probiotic and/or antipathogenic microbial mixtures as seed coats.

Looking Forward: Future Challenges, Technical and Societal

In the past century of disease-resistance breeding, we were largely limited to germ plasm from sexually compatible wild species that can recognize and resist infection, without a priori knowledge of the effector *R* gene mediating the outcome (Box 1). This strategy is slow, and field efficacy is often shortened by selection of effector gene mutants that evade host recognition. Our current challenge is to leverage evolutionary genomic information stored in the worldwide germ plasm diversity. The goal is to define and to stack multiple resistance specificities active against the daunting array of economically important pathogens, including *Phytophthora*, *Magnaporthe*, *Fusarium*, *Pseudomonas*, *Ralstonia*, *Xanthomonas*, and gemini and potyviruses (*74*). At the same time, we must maintain complex agronomic traits—such as yield, form, and flavor—and avoid yield penalties. The precision offered by transgenic and genome editing technologies offers considerable advantages over conventional breeding (Box 1).

Prospects for the development of durable disease resistance have improved markedly because of the ongoing molecular dissection of the plant immune system and the advent of ever-faster, ever-cheaper genome-sequencing technologies. Many exciting challenges are emerging to exploit that knowledge. We can contemplate rational, stacked deployment of multiple NLRs that each recognize a different core effector (Box 1). We will eventually be able to engineer novel NLR recognition specificities, though this requires detailed structural knowledge only now beginning to be unraveled (*75*). Combinations of stacked NLRs, new PRRs, and genome-edited disease-susceptibility alleles that reduce or stop pathogen proliferation are realistic possibilities. We can now monitor pathogen populations and their effector complements in the field over space and time to inform deployment of better-suited cultivars requiring less chemical control (*38*). We harbor ambitions to enhance plant immune system function by managing defined probiotic, antipathogenic microbial consortia isolated from the plant's own microbiome (*76*, *77*). A holistic, mechanism-based approach will ultimately improve plant immune system function to deliver durable and sustainable disease resistance, with minimum or no chemical input, where it is needed most in the future.

Among the greatest challenges remaining for deployment of next-generation disease-resistant plants are those posed by regulatory and consumer acceptance hurdles. Virus resistance in modified papaya and squash has been durable, and the crops have been safely consumed for nearly 20 years, with no negative environmental impacts (*78*). Nevertheless, significant anxiety remains. Sadly, commercial deployment by BASF Corporation (Badische Anilin Soda Farbrik, AG) of a potentially valuable potato cultivar, Fortuna, containing two stacked and potentially durable *NLR* genes from a wild potato species, was canceled because of pressure from lobbies opposing genetic modification, despite the fact that it would likely eliminate some or all of the up to 25 fungicide treatments required in Northern Europe per year to control late blight (*79*). If the examples of the introduction of coffee as a beverage, and the use of hybrid crops, such as corn, serve as guidelines, acceptance of transgenic crops should become mainstream in about 50 to 200 years (*80*, *81*). That timeline is simply too long to wait to confront the issues of food security and environmental sustainability posed by the plethora of microbes that value our crops as food sources as much as we do.

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