4. Biodémo : Biodémographie Humaine

Le portfolio de l'équipe Biodémographie humaine met en exergue trois aspects de son activité : l'analyse de données de terrain en anthropologie démographique, son expertise en modélisation mathématiques, son ouverture auprès de la société. Il montre en outre comment la biodémographie permet d'informer des défis majeurs des sociétés contemporaines :

4.1 L'article de Pavard & Coste (2021) montre qu'il est important de prendre en compte les comportements sociodémographiques pour mieux comprendre la prévalence des maladies du vieillissement.

4.2 L'article de Ramirez-Rozzi (2018) décrit la fertilité d'une population de chasseurs cueilleurs du Cameroun et alerte sur les changements environnementaux brutaux vécus par cette population du fait de l'introduction massive d'alcool à bas prix.

4.3 Le Guide Photographique de Portions Alimentaires (Cohen, 2022) est un outil important, scientifique et de santé publique, pour mieux comprendre la transition nutritionnelle au Cameroun et prévenir l'épidémie d'obésité.

ARTICLES
https://doi.org/10.1038/s41559-020-01355-2
nature ecology & evolution

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Evolutionary demographic models reveal the strength of purifying selection on susceptibility alleles to late-onset diseases

Samuel Pavard[1]✉ and Christophe F. D. Coste[1,2]

Assessing the role played by purifying selection on a susceptibility allele to late-onset disease (SALOD) is crucial to understanding the puzzling allelic spectrum of a disease, because most alleles are recent and rare. This fact is surprising because it suggests that alleles are under purifying selection while those that are involved in post-menopause mortality are often considered neutral in the genetic literature. The aim of this article is to use an evolutionary demography model to assess the magnitude of selection on SALODs while accounting for epidemiological and sociocultural factors. We develop an age-structured population model allowing for the calculation of SALOD selection coefficients (1) for a large and realistic parameter space for disease onset, (2) in a two-sex model in which men can reproduce in old age and (3) for situations in which child survival depends on maternal, paternal and grandmaternal care. The results show that SALODs are under purifying selection for most known age-at-onset distributions of late-onset genetic diseases. Estimates regarding various genes involved in susceptibility to cancer or Huntington's disease demonstrate that negative selection largely overcomes the effects of drift in most human populations. This is also probably true for neurodegenerative or polycystic kidney diseases, although sociocultural factors modulate the effect of selection in these cases. We conclude that neutrality is probably the exception among alleles that have a deleterious effect in old age and that accounting for sociocultural factors is required to understand the full extent of the force of selection shaping senescence in humans.

The role played by purifying selection in shaping the allelic spectra of common late-onset genetic diseases remains poorly understood. There is increasing evidence that susceptibility alleles to late-onset diseases (SALODs) are subject to purifying selection, with most of them being recent and rare. However, population genetics is not yet able to quantify precisely the force of such selection from genetic data (mostly because detecting selection for alleles under weak negative selection is difficult). Furthermore, it is still poorly understood how purifying selection operates on alleles whose deleterious effects occur late in life at ages when death or incapacitation is thought not to compromise an individual's reproductive success. The aim of this study is to use carefully parameterized models from evolutionary demography to predict the magnitude of selection on SALODs, and to disentangle the biological and social phenomena that may explain such persisting negative selection in advanced age.

This question is especially fundamental in regard to genetic epidemiology, since the magnitude of purifying selection distinguishes the two main hypotheses for the evolution of SALOD spectra: the common disease common variant (CDCV) and the common disease rare variant (CDRV) hypotheses[1,2]. In the former hypothesis, SALODs are considered close to neutrality. Thus, genetic drift is the dominant evolutionary force driving their fate and the prevalence of most diseases is expected to result from a limited number of alleles at moderate/high frequency, as theorized in Box 1 and in ref. [3]. In contrast, the CDRV hypothesis emphasizes the importance of numerous rare variants in disease prevalence resulting from a balance between mutations and weak purifying selection at a large number of loci. The CDRV hypothesis has been theorized by Pritchard[4] and compared to the CDCV hypothesis[5]. Estimating the fitness of SALODs carriers is, therefore, crucial to assessment of the relative importance of these two mechanisms in shaping late-onset disease prevalence in humans, as well as to the design and interpretation of genome-wide association studies[6,7]. However, estimating this fitness first requires establishment of the relationship between late-onset diseases—that is, SALOD phenotypic effects, and reproductive success—that is, the fitness of carriers.

Several lines of evidence argue for the existence of purifying selection on SALODs. The first line of evidence comes from the fact, mentioned above, that the allelic spectrum of common late-onset diseases is mainly characterized by a multitude of rare and recent variants. This pattern, which is more compatible with the CDRV hypothesis than with the CDCV hypothesis, also yields a missing heritability problem for common diseases[7,8]. This missing heritability is notably the case for familial forms of cancer, coronary artery disease and Alzheimer's dementia[9,10]. The most frequently cited example is that of familial forms of breast and ovarian cancers. More than two thousand mutations in the genes *BRCA1* and *BRCA2* have been associated with increased risk of such cancers. Most of these mutations are found at very low frequencies, and most reaching high frequencies do so because of the history of populations and, in particular, founder effects[11]. The existence of purifying selection on SALODs has also received support from the comparison of genetic and epidemiological data, which demonstrate that allele frequencies decrease as a function of allele effect size in the case of late-onset diseases[12–14], suggesting that there are different levels of selection of different SALODs. Finally, a selection test found no difference in selection magnitude between mutations responsible for early- versus late-onset disorders, which may suggest that SALODs remain under substantial selection[15]. Despite the accumulation of

[1]Unité 7206 Eco-anthropologie, Muséum National d'Histoire Naturelle, CNRS, Université de Paris, Paris, France. [2]Department of Biology, Centre for Biodiversity Dynamics, Norwegian University of Science and Technology, Trondheim, Norway. ✉e-mail: samuel.pavard@mnhn.fr

Box 1 | Theory behind the CDCV (late-onset) hypothesis

In the late 1990s, the quest to unravel the allelic spectrum of common genetic diseases took a new turn with the development of DNA sequencing and micro-array. Great effort has been invested in genetic and epidemiological research in the hope of eventually 'mapping' individual genetic susceptibility to common genetic diseases—especially for late-onset diseases in the context of ageing populations. Together with these technological developments, this drive has been supported by the theoretical prediction that most of the prevalence of common late-onset diseases is associated with a small number of allelic variants coexisting at large frequencies in a given population.

This CDCV hypothesis postulates that common diseases are complex and/or late-onset[69]. Complex diseases, in which susceptibility alleles modify only a single element of an intricate molecular circuitry regulated by epistatic relationships between many loci, are opposed to diseases in which the transmission of alleles obeys Mendelian segregation rules[1]. Susceptibility alleles to complex diseases are thought to lead to low disease penetrance, which does not importantly compromise the carriers' reproductive success, and are therefore considered to be under negligible purifying selection. Late-onset diseases are generally defined as those for which the mean age at onset is >40 years[15], and are incorporated into the CDCV hypothesis whether complex (such as Alzheimer's dementia) or quasi-Mendelian (such as the *BRCA1* and *BRCA2* forms of breast cancer)[17]. This is because the magnitude of selection is predicted to decrease with age: the later in life an allele's deleterious effect occurs, the lower the proportion of carriers surviving to these ages and the smaller the fraction of reproductive success compromised by the deleterious effect[18,70]. In humans, it has long been thought that purifying selection past the age of 45 years is low in pre-industrial populations because of their low life expectancy and menopause (a woman's post-menopause death does not compromise her reproductive success).

Because negative selection is negligible, the fate of alleles involved in complex and/or late-onset diseases is, therefore, mainly driven by genetic drift, which tends randomly to eliminate most genetic variants, while the persisting ones reach high frequencies[3]. More precisely, it is predicted that, in a growing population, the selective disappearance of alleles with a slightly deleterious effect (that is, with a selection coefficient (s) at or below 10^{-6}) is sufficiently slowed by genetic drift, allowing the emergence of common variants. As a consequence, the CDCV hypothesis predicts that a small number of alleles at high frequency are expected to account for most of the prevalence of familial forms of common diseases. By contrast, the CDRV hypothesis assumes a purifying selection, albeit mild (at an order of magnitude of $s=10^{-4}$), which, combined with genetic drift within a multi-loci Wright–Fisher model, can lead to the accumulation of rare variants and the persistence of a few variants at intermediate frequencies[4].

evidence for the selection on SALODs, the dominant idea is still that late-onset diseases do not compromise reproductive success. When discussed, evidence for selection is instead mostly explained by either antagonistic pleiotropy in past human populations or selective effects due to recent environmental changes[15–17].

Estimating the magnitude of selection of SALODs is, therefore, crucial to understanding how evolutionary processes have shaped the current allelic spectrum of late-onset diseases. For these estimations, evaluation is required of how rapid purifying selection decreases with SALOD-specific mean age at disease onset. This estimation is needed to assess the ages at which alleles reach neutrality and, consequently, whether the disease lies within the 'selection shadow'[18], as well as to investigate the potential for positive selection caused by antagonistic pleiotropic effects. Indeed, a rapid decline with age implies that a small beneficial effect at a young age can be positively selected together with a strongly deleterious effect at an older age. To do this, however, one has to account for the distribution of the age at onset of diseases resulting from the deleterious effect of a given SALOD, together with the sociocultural behaviours of the population in which selection occurs. Indeed, three phenomena may explain why some SALODs are under negative selection.

Variance in age at disease onset

A particular familial form of late-onset disease does not occur at exactly the same age for all SALOD carriers. Rather, the onset of such a disease is distributed across a range of ages and should be characterized, at least, by a mean and variance (see Fig. 1a for the case of *BRCA1* susceptibility alleles in breast and ovarian cancer, and additional data in Supplementary Methods). It was first suggested that late-onset diseases may occur in a non-negligible proportion of young individuals even though the mean age at onset is late in life[4], a proportion that could substantially compromise the average reproductive success of SALOD carriers. This suggestion has been proved to be true in the case of *BRCA1* alleles[19]: although the mean age at onset occurs after menopause, in approximately 30% of cases the disease begins before 45 years of age allowing negative selection to occur. To our knowledge, the variance in age at disease onset was not accounted for in previous tests of selection on SALODs[13,15]. This variance partly reflects the influence, on the age at onset, of the type and location of mutations in susceptibility genes (for example, in the case of polycystic kidney diseases linked to *PKD1* and *PKD2* (ref. [20])), as well as of epistatic relationships between mutations and risk-modifying loci (for example, for Alzheimer's dementia linked to *PSEN2* (ref. [21]), for breast and ovarian cancer linked to *BRCA1* (ref. [22]) or for Huntington's disease linked to *HTT* (ref. [23])). A large variance at onset is, therefore, a ubiquitous characteristic of any SALOD, as exemplified by Huntington's disease where variance in age at onset increases with mean age at onset[24].

Late male human reproduction

Although women stop reproducing at menopause, men can continue reproducing until late in life (Fig. 1b). Tuljapurkar et al.[25] showed that male fertility provides a non-negligible selective force against autosomal deleterious mutations acting at ages far past female menopause. The proportion of children born to old men depends on population survival and matrimonial behaviours. In contrast to the great apes, in which males seem to favour reproduction with older females[26], males are more frequently older than females in human couples. First, men are on average older than women at first marriage and first reproduction (for example, 6 years older on average[27]; see the additional data in Supplementary Methods), even in societies in which sexuality is not prohibited before marriage[28] and in matrilineal/matrilocal societies[29,30]. Second, widowed or divorced men can remarry even at old ages. In the absence of modern medicine, approximately 20% of men surviving past 50 years of age have lost their first wife. Divorce, nearly absent in historical Western Christian populations, is allowed in most ethnological populations[31] and may reach very large frequencies (for example, in Ache, 61% of marriages are terminated within the first year[32]). Third, human populations were most probably mildly polygynous in the past[33]. Polygyny is often associated with large age differences between husbands and wives. This is the case, for instance, when men have to 'queue' to access the matrimonial market (that is, 'wealth-increasing' polygyny) or when they are more likely to marry the younger sisters of their first wife (that is, sororal polygyny).

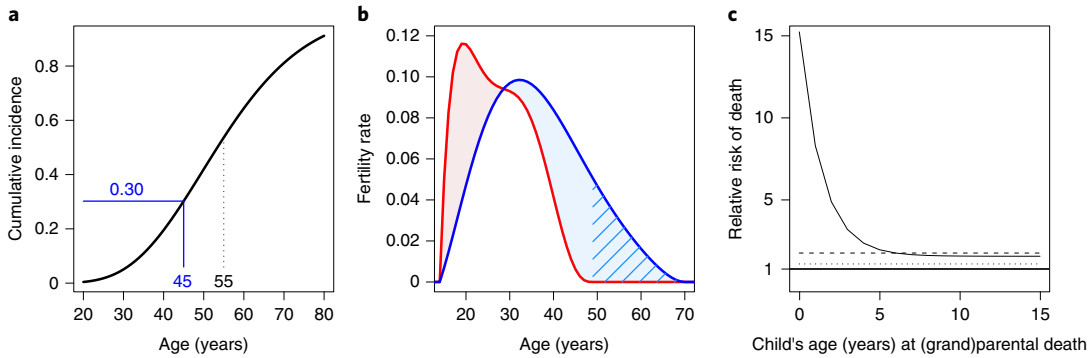

Fig. 1 | Factors that might explain the persistence of purifying selection on SALODs. a, Cumulative incidence of breast and ovarian cancer, with the age of females carrying a mutation in the *BRCA1* gene fitted by ref. [19] using data from ref. [56]. The mean age at onset was 55 years, but approximately 30% of cases arose in females aged <45 years. Variance in disease onset means that disease may occur during female reproductive life although mean age onset is after menopause. **b**, Scaled, age-specific fertility rates for women (red) and men (blue) fitted with a Brass polynomial function from published estimates for non-industrialized populations (that is, Kung, Ache, Tsimane, rural Gambia, Peul Bandé and French Canadians of the seventeenth and eighteenth centuries). The data and modelling are detailed in Supplementary Methods. The blue area denotes the ages at which male fertility is greater than female fertility, and the cross-hatched area is the part of this where female fertility is decreased to zero. The parameters for males are fine-tuned to allow the finite rate of population increase to equal 1.004 in the case of a particular population mortality (here, that of an average hunter-gatherer population[39]). Males can reproduce at older ages in most non-industrialized societies due to older age at marriage, remarriage or polygamy. **c**, Relative risk of death of a child having lost its mother (solid line), grandmother (dashed line) or father (dotted line) compared to non-orphans according to the child's age at (1) maternal death, (2) paternal or maternal grandmaternal death or (3) paternal death (denoted as y_1, y_2 and y_3 in the model, respectively). Maternal, paternal and grandmaternal deaths increase child mortality throughout infancy and childhood. Data are fitted from published estimates from 31 articles detailed in Supplementary Methods.

Parental and grandparental care

Humans are mammals and, as such, their neonates are altricial: a newborn that is not taken care of is doomed to die. However, humans are also cooperative breeders where the mother is the primary caregiver but not the only one. Maternal care as well as, to a lesser extent, paternal and grandmaternal care have been shown to keep children alive[34,35]. In demographic terms, this means than an infant or a child who has lost his or her mother, father or maternal and/or paternal grandmother is less cared for and has a lower chance of surviving until adulthood than a child who has not experienced such a loss (Fig. 1c and Supplementary Methods). From the (grand) parental perspective, this means that an individual may continue to increase his or her reproductive value by enhancing his or her children's chance of survival, even if he or she stops reproducing. Disease morbidity and incapacitation, therefore, incur an additional cost besides the prohibition of future reproduction: they also compromise the chances of children already born to reach adulthood and to reproduce, and this effect may be substantial. For example, maternal care has been proved to be sufficient to maintain purifying selection for 10 years after menopause[36] (but see ref. [37]). To estimate the phenotypic effect of a SALOD, one therefore has to measure the magnitude of the direct and indirect genetic effects of the carriers' increased adult mortality through different 'social paths'[38]. Direct genetic effects are measured by estimating the extent to which carriers' increased adult mortality compromises their reproductive success, and indirect genetic effects are measured by estimating the extent to which carriers' increased mortality compromises the survival of their children through depleted maternal and paternal care, as well as depleted grandmaternal care if the grandmother also carries the SALOD.

In this study, we calculate selection coefficients (s) thus: (1) for SALODs leading to diseases with an age-at-onset distributed across ages; (2) in a two-sex model in which men are able to reproduce until old ages; and (3) in a three-generation model in which child survival depends on maternal, paternal and grandmaternal care. The predictive value of these calculations lies in the careful choice of input parameters (Supplementary Methods). The assumptions made by the model and caveats are also fundamental (Box 2). Some effects have indeed been omitted when their effects on the magnitude of selection are expected to be negligible, when empirical data are too scarce to carefully parameterize the model or vary too much between populations to be generalizable, or to limit the complexity of the model.

Results

Old ages are not selectively neutral, but outflank the selection shadow. Most SALODs, in the absence of pleiotropic effects and considering a large disease penetrance, are unlikely to be neutral but rather are under purifying negative selection.

This situation is due first to the epidemiology of late-onset diseases. Variance in disease onset means that a non-negligible proportion of cases may occur at reproductive ages even if the mean age at onset (MAO) is after menopause. In the absence of variance in age at onset, SALODs with a MAO beyond 48 years of age are not negatively selected (Fig. 2a). However, SALODs are purified up to MAO of 57 years of age if the first age at onset (FAO) is 20 years earlier (this corresponds to standard deviation in age at onset of s.d. = 6.32 years; Fig. 2b) in all human populations (that is, for effective size, $N_e > 100$).

Second, selection of SALODs is also inflected by sociocultural factors (Fig. 2a,b). Deaths occurring past 45 years of age do not vanish into the selection shadows[18] where selection has no leverage. This is because, even in populations with a low life expectancy, most individuals surviving until the age at first reproduction are likely to survive past 45 years of age (63% for hunter-gatherers[39]). Individuals may then enhance their selective value past this age. Maternal care has a large effect in magnitude but is limited in duration to 10–15 years after menopause[36]. Grandmaternal care has a persistent and large effect up to old ages because, although it is much less important for child survival than maternal care (Fig. 1c), grandmothers have more grandchildren than mothers have children and, most importantly, the risk of late-onset disease is much greater at grandmaternal ages than at maternal ages.

Finally, if paternal care has little effect on child survival, males' ability to reproduce at ages at which women have already reached

Box 2 | Main assumptions and caveats

Mutations are considered to be at an initial low frequency. This assumption is required by the model. Incorporation of frequency dependence (that is, when the selection coefficient of an allele depends on the frequency of the allele in the population) is difficult, and data for parameterization are missing. This hypothesis is, however, reasonable since most SALODs are rare or de novo. Our model would, however, fail to predict the fate of mutations reaching high frequency (for example, because of a founder effect).

Antagonistic pleiotropy is unaccounted for, but could be incorporated in such a model. However, if this has been shown to occur at the genome level[13] it has been demonstrated for only a small number of specific gene–disease pairs (for example, *BRCA1* (ref. [41])), and data on allele-specific effect sizes are still missing for parameterization.

Epistasis, epigenetic and environment–gene interactions are unaccounted for. These mechanisms may modulate late-onset gene expressions; see, for example refs. [21–23] for epistasis or ref. [16] for environmental changes. However, the incorporation of these mechanisms is not trivial, and data for parameterization are mostly missing.

The disease is lethal or fully incapacitating when it occurs. Many late-onset diseases are slowly degenerative and/or not lethal (for example, age-related macular degeneration or neurodegenerative diseases). Data are, however, missing for the pace at which the disease compromises an individual's age-specific fitness through decreased fertility (direct genetic effect) or (grand)parental care (indirect genetic effect[38]). Diseases can also lead children to invest time and energy in caring for their parents (a phenomenon referred to as 'filial piety'[71]) and, as such, will reduce their fitness.

Population is at a demographically stable state. This common assumption facilitates access, for the model, to the population age structure. Incorporation of transient dynamics (for example, because of density dependence or stochasticity) is, however, an interesting future prospect.

Cost of reproduction and effect of parental care on the adult life of children are not incorporated, and the effect of care is similar on sons and daughters. This assumption allows ready solving of the Euler–Lotka stable-state equation and general conclusions to be drawn from the model. The incorporation of these phenomena would require the addition of traits categorizing individuals. The recent development of multi-trait population projection matrix model theory[72] may, however, allow such an extension. It would also be interesting to incorporate the effects of transfers of behaviour or knowledge on offspring survival and reproduction.

Potential heritability of demographic traits is not incorporated. Breaking this assumption would mean modelling the population substructure where reproduction, survival (beyond the effect of SALOD) and even maternal and grandmaternal care could vary between families and can be heritable through genes or because of a shared environment.

Possible differences in survival between males and females are not incorporated. These could, however, be easily incorporated. Sex-specific survival data are scarce for hunter-gatherers but, for other pre-industrial or contemporary populations, further work may alleviate this assumption.

The effect of maternal and paternal age on offspring fitness is not incorporated. It remains unknown how parental age compromises children's fitness because of an increased gamete mutation load. In contrast, some social factors correlate with better offspring survival, such as parent's age (because of parental experience, influence and wealth).

Only maternal grandmaternal care is considered. Although this assumption is not required by the model, data suggest that, for a given population, one of the two grandmothers provides the primary care for her grandchildren and this grandmother is more frequently the maternal one (Supplementary Methods).

menopause increases selection coefficients to a large extent. As a consequence, when all sociocultural factors are incorporated, an allele with a large variance in age at onset (that is, for which MAO − FAO ≥ 20) will be under significant purifying selection in most human populations ($N_e > 100$), even if MAO is as late as 72 years of age (Fig. 2b; Extended Data Fig. 1 gives results for the whole FAO and MAO parameter space).

We further demonstrate that the magnitude of purifying selection remains a linear function of disease penetrance, even when complex sociocultural factors are incorporated into the calculation (Extended Data Fig. 2). Approximately speaking, an allele with a MAO of 40 years of age and only 1% penetrance is selected against as strongly as an allele with a MAO of 70 years of age but penetrance of 100%. We also demonstrate that large selection coefficients are found for autosomal alleles responsible for sex-specific diseases or for loci on the Y chromosome (because of late male reproduction) or in mitochondrial DNA (because of the effects of (grand)maternal care; Extended Data Fig. 3). Finally, we show that when all sociocultural factors are accounted for, contrary to common opinion, changes in the mortality regime during early demographic transition have little effect on the magnitude of selection with age (Extended Data Fig. 4 with data from refs. [39,40]).

Predictions for specific late-onset diseases. Figure 2c shows the estimated selection coefficients calculated from distribution of disease onset for various susceptibility genes to common late-onset diseases. These genes can be roughly categorized into two classes. Mutations in susceptibility genes to cancers, as well as in *Huntington*, *SNCA* and *PDK1*, are always predicted to be strongly selected against, independently of sociocultural factors, because of their large penetrance and early FAO (<35 years of age). For most genes involved in neurodegenerative diseases, however (such as Parkinson's, Alzheimer's or frontotemporal dementia), as well as for the susceptibility gene *PKD2* to polycystic kidney diseases, sociocultural factors do matter. These SALODs could be under strong purifying selection or may not, depending on old male reproduction or the effective population size. It must be stressed that we did not perform calculations for cardiovascular and metabolic diseases, since epidemiological data at the gene level are still lacking. For instance, >38 genes are associated with susceptibility to type II diabetes and age-specific data are lacking, even for the most common genes (including *TCF7L2* and *CAPN10*).

Our model yields results that seldom correspond to the levels of selection considered by Reich and Lander[3] (approximately 10^{-6}) and largely discard, in our opinion, the CDCV hypothesis in the case of late-onset diseases. Although our results tend to favour the CDRV

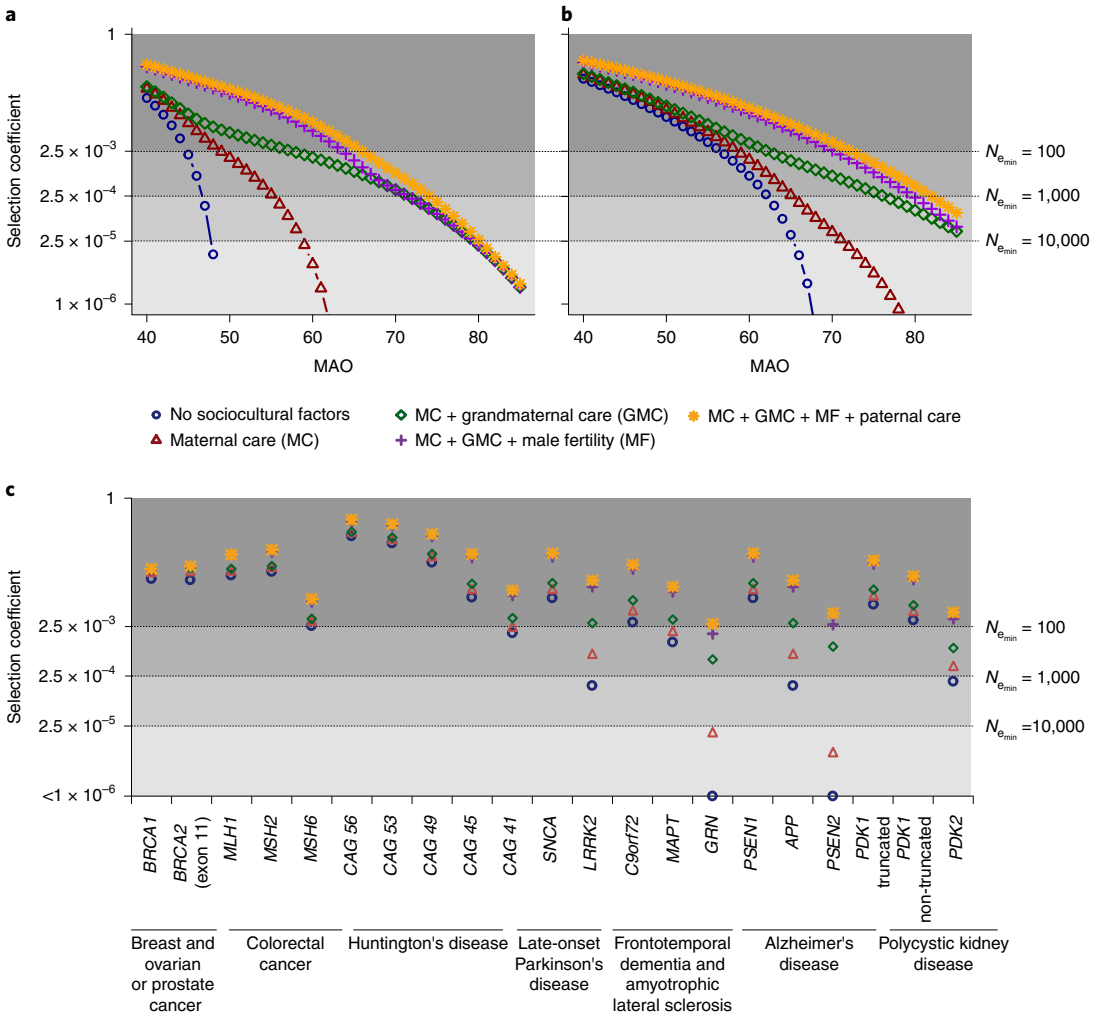

Fig. 2 | Estimated coefficient of selection (*s*). a,**b**, Selection coefficient *s* as a function of MAO in the case when disease onset has no variance (**a**, disease occurs at a unique age) and when FAO is observed 20 years before the mean (**b**, constant variance; modelled by a logistic distribution of s.d. = 6.32 years), respectively; when all alleles are rare, autosomal, dominant disease occurs in both sexes and penetrance is complete. **c**, Estimated value of *s* for different genes involved in susceptibility to late-onset diseases. The parametrization is detailed in Methods. Calculations are performed for various sociocultural scenarios. Horizontal lines indicate the level of selection for which alleles become neutral ($4N_e s < 1$) for populations of $N_e = 10^2$, 10^3 and 10^4; that is, the minimum N_e for which the effect of selection overcomes that of genetic drift, holding that 10^4 is the N_e estimated at our species level. Mortality is that of a mean hunter-gatherer population[39] and fertility is that shown in Fig. 1b.

hypothesis, they are mostly of a larger magnitude than those considered by Pritchard[5] and would increase in mutation frequency only for populations with a strong founder effect and a very small effective size (for example, *BRCA2 999del5* in Iceland, *MSH2 A636P* and *BRCA1 185delAG* in Jewish Ashkenazi, *LRRK2 R1441G* in Basques and so on). Are our estimates of selection coefficients thus too large to explain the observed allelic spectrum?

Perhaps not. First, the currently observed penetrance may not reflect that in past populations[17] but may be the outcome of recent environmental changes. For instance, suppose that the penetrance of susceptibility genes to breast and ovarian cancer was 1% in the past. In the case of *BRCA1* and *BRCA2*, for example, this would make the selection coefficients s_{BRCA1} and s_{BRCA2} approximately 10^{-4} at the time when their allelic spectrum was shaped, which agrees with previous findings[4]. To further assess this finding, it is crucial to better understand the epidemiological genetics of late-onset diseases across environments and societies. Second, our results gather all mutations of the same gene 'under the same umbrella', while current theoretical and empirical efforts investigate the ways in which selection operates in networks of genes and for complex phenotypes, as well as in the case of epistatic and epigenetic gene regulation and expression. For instance, it is still an open question, to our knowledge, as to why there are >1,800 loci of *BRCA1* that increase susceptibility to female-specific breast cancer while there are only approximately five loci that increase susceptibility to male-specific prostate cancer. Third, antagonistic pleiotropy may be more common than previously thought[13], which is important, for example, in the case of *BRCA1*. Smith et al.[41] find a large beneficial impact of *BRCA1* mutations on carrier fertility, which has led to the suggestion that grandmaternal effects, which maintain deleterious effects under significant negative selection, were the most likely explanation as to why these alleles had not reached fixation[42]. Our model validates this prediction and goes further, showing that grandmaternal care is an important, but not the sole, factor maintaining SALODs out of the selection shadow. Finally, it may be that N_e *is* overestimated in a species that is spatially and socially highly structured with a large cultural heritability of reproductive success, allowing drift to overcome the quite large levels of negative selection[43].

In contrast, the effects of age, sex and kin structure on the force of selection on SALODs, as shown by our results, may be somehow underestimated because we incorporate only the effect of (grand) parental care on child survival (Box 2). There is indeed some evidence that (grand)parental care also enhances fitness components during children's adult lives. For instance, it has been shown that post-reproductive mothers allow their children to breed earlier and/or more frequently in the case of historical populations[44,45]. Such an additional positive correlation between (grand)parental survival and offspring fitness is expected to further increase the strength of negative selection on SALODs. However, Sear[46] demonstrated that the extent to which the presence of kin (parents, parents-in-law, siblings) is correlated with adult fertility is mainly a matter of environment and culture, resulting in potential variance in the selection of SALODs among populations.

Importance of detecting selection on SALODs and finding new mutations. Our results provide evidence primarily for the fact that variance in age at onset has to be accounted for to characterize the phenotype of SALODs. Accounting for variance in age at onset may allow one to review results from studies characterizing alleles according to the mean age at onset and effect size only—for instance, the tests of selection from ref. [15] or the conflicting results aiming at detecting accumulation mutations and antagonistic pleiotropy by Genome-Wide Association Study (GWAS) approaches[13,47]. Second, because most SALODs are expected to be under negative selection and therefore recent and rare, accounting for variance in age at onset validates current efforts to design new techniques (not only technological but also in the sampling design and statistics used) to detect low-frequency genetic variants—for instance, in sampling age-at-onset variations that are large as possible[48] and accounting for the spatial distribution of variants and the history of the population[7]. We would go even further and argue that the epidemiology of a disease has to be contemplated in view of the social and demographic parameters of the population considered. For instance, we showed that the allelic spectrum is expected to differ more strongly according to these factors among populations for neurodegenerative diseases than for cancer. Then, GWAS approaches detecting allele changes in frequency among age classes[49], and that have been successful in detecting common alleles at a large scale (which have a frequency in young age classes of approximately 0.15–0.2), could prove more powerful in detecting lower-frequency variants at a finer scale. More generally, at the disease level, we expect the allelic spectrum to be shaped by the disease type and onset trajectory; by the history, geography and past demography of the population considered (affecting its effective population size); and by knowledge about marriage practices, fertility age trajectories for men and women, and intergenerational behaviours.

Importance of evolution in regard to ageing in humans. The decreased force of selection with age is the founding effect of the main evolutionary genetic theories of ageing: antagonistic pleiotropy and mutation accumulation. However, in practice, selection gradients are not estimated from empirical data but are rather a conceptual calculation mainly inferred from life tables (considering theoretical alleles with deleterious effects at a specific age). We show here that this practice hides many layers of biological and demographic complexity[50]. This is because, from an allelic perspective, selection operates on an epidemiological space with at least three axes: the mean, variance and cumulative onset. We show here that the steepness of the selection gradients is probably largely overestimated in humans and, by extension, in most long-lived species for which disease onset may be spread over several age classes. From a phenotypic perspective, a disease-specific selection gradient encompasses the multiplicity of loci from potentially different genes that have different epidemiological outputs. At the species level, ageing encompasses the accumulated incidence with age of many disorders projected over a unique age-specific mortality trajectory.

Consequently, inferring senescence patterns from averaged mortality trajectories sweeps much of this complexity under the carpet, and further theoretical studies are required to incorporate age-specific causes of death and their genetic variance into evolutionary theories of ageing[51]. In contrast, however, focusing on selection coefficient s for a given allele, in a model in which the selective effect is scaled over generation time, does not account for the importance of the timing of reproduction on population dynamics. Further studies could, however, use our model to investigate discrepancies between decreases in selection coefficient s by age and age-specific selection gradients based on Malthusian fitness.

Furthermore, in humans, we show that selection is not only related to lifetime reproductive success (overall number of children produced) but also depends on the number of children that have been cared for and educated during a protracted infancy and childhood (by several kin). As they slow the decline of selection with age, these sociocultural factors tend to both prevent the accumulation of deleterious mutations and decrease the effect of antagonistic pleiotropy in humans, therefore promoting an extended lifespan. This probably has another consequence. Purifying selection at the locus level leads to lower genetic variance at the disease level and therefore lower genetic variance over the adult lifespan. It may then explain why the heritability of the adult human lifespan is low (approximately 25%) and increases substantially only past 65 years of age (approximately 36% (ref. [52])). Because genetic variance in mortality is low at the age when (grand)mothers care for their (grand)children, it may also be one of the reasons why small indirect genetic covariance is found between maternal and grandmaternal survival on the one hand and child survival on the other[37].

Together, our findings emphasize the fact that, in humans, the evolution of life history and sociality is intertwined and that genomics, genetics, epidemiology, demography and anthropology are all essential fields that contribute to our understanding of the allelic spectrum of late-onset diseases.

Methods

General framework of the model. We aimed to calculate the selection coefficient s for a SALOD in a two-sex, three-generation model in which SALOD carriers exhibit an excess of either mortality due to allele-specific disease morbidity or any incapacitation that fully compromises reproductive success. Such a model requires accounting for the full population age structure, which is not the case for most population genetics models in which selection on alleles is usually evaluated in populations with non-overlapping generations. We therefore model a two-sex, three-generation, age-structured population model from which we compute the selective values (defined as the expected number of children surviving until maturity produced by a mean individual during their lifetime) of female and male (indicated by superscripts fm and m, respectively) carriers of a SALOD and of non-carriers (indicated by subscripts C and NC, respectively): W^{m}_{NC}, W^{fm}_{NC}, W^{m}_{C}, W^{fm}_{C}. In the stable state, male and female subpopulations grow at the same (asymptotic) finite growth rate, λ; otherwise, one sex would dominate the population. However, because age-specific fertility schedules are different with males reproducing at older ages than females, males produce, on average, a larger number of offspring during their lifetime than females but over a longer generation time.

Assuming that the SALOD is autosomal, dominant and rare (Box 2) and a sex ratio at birth of 1:1, its purifying selection coefficient s is:

$$s = 1 - \left(W^{fm}_{C} + W^{m}_{C}/\left(W^{fm}_{NC} + W^{m}_{NC}\right)\right) \quad (1)$$

Selective value of non-carriers. We now aim at expressing W^{fm}_{NC} and W^{m}_{NC} as functions of survival probabilities to maturity $S(x_1)$ and $S(x_3)$ of children (irrespective of whether they are boys or girls) born to a mother of age x_1 and a father of age x_3, such that:

$$\begin{aligned} W^{fm}_{NC} &= \int_{x_1=\alpha}^{\omega} L(x_1)F(x_1)S(x_1)\mathrm{d}x_1, \\ W^{m}_{NC} &= \int_{x_3=\alpha}^{\omega} L^{m}(x_3)F^{m}(x_3)S(x_3)\mathrm{d}x_3, \end{aligned} \quad (2)$$

where α is the age at first reproduction, ω is the maximal age at death, $L(x)$ and $L^{m}(x)$ are the adult female and male probability, respectively, of remaining alive at

age x conditional on survival to maturity (and therefore $L(\alpha)=L^{m}(\alpha)=1$), and $F(x)$ and $F^{m}(x)$ are female and male fertility rates at age x, respectively. In this case, the selective values are composite and correspond to the adult lifetime mean number of children of individuals weighted by the expected survival to maturity of these children.

How does one calculate $S(x_1)$ and $S(x_3)$ in equation (2) in the case where survival depends on maternal, grandmaternal and paternal care? Here, these effects are incorporated to the extent that the death of a mother, grandmother or father compromises an immature child's survival via $\sigma(y_1, y_2, y_3)$, which is the survival probability to age at maturity α of a child who has lost his or her mother, grandmother and father when he or she was y_1, y_2 and y_3 years old, respectively (Supplementary Methods). A child for whom y_1, y_2 and y_3 are greater than α is fully cared for and therefore exhibits a maximal chance of surviving until maturity. A child with any one of y_1, y_2 or y_3 lower than α has lost one of his or her parents before reaching maturity and exhibits compromised survival.

Consequently, child survival is a function of the age of his or her mother, grandmother and father at the time of birth (denoted as x_1, x_2 or x_3, respectively): the older the child's (grand)parents at the time of birth, the higher their risk of the (grand)parents dying (or being already dead in the case of grandmothers) in the years following the birth of the child[36,53]. The distribution of child survival thus depends on the distribution of x_1, x_2 and x_3 in the population (a demographic relationship first explored in ref. [54]). In a constant environment with infinite resources, these distributions are stable and depend on the male and female age structure in the population. Assuming that there is no heritability of fertility schedules between mothers and daughters, the distributions of x_1 and x_2 are independent in a given population: a mother's age at the birth of a child does not depend on the age of her own mother at her birth. However, the distributions of x_1 and x_3 are not independent when matrimony is age structured.

The probability $S(x_1)$ is thus calculated as the sum over all possible child's ages at the mother's, grandmother's and father's death (y_1, y_2 and y_3, respectively) of the product between (1) the probability of a child born to a x_1-year-old mother losing its mother when it is y_1, its maternal grandmother when it is y_2 and its father when it is y_3 (that is, the probability of a given $[y_1, y_2, y_3]$ combination) and (2) the survival probability $\sigma(y_1, y_2, y_3)$:

$$S(x_1) = \iiint p(y_1|x_1)p(y_2|x_1)p(y_3|x_1)\sigma(y_1, y_2, y_3)\mathrm{d}y_1\mathrm{d}y_2\mathrm{d}y_3 \quad (3)$$

A similar formula yields $S(x_3)$ (the derivations performed to obtain $S(x_1)$ and $S(x_3)$ are detailed in Supplementary Methods). Because they depend on a stable population structure (related to λ) which, in turn, depends on $S(x_1)$ or $S(x_3)$, these quantities must be solved simultaneously by iteration (Supplementary Methods).

Selective value of SALOD carriers. *Incorporating the morbidity of SALOD carriers.* If the SALOD is sufficietly rare, the proportion of carriers relative to that of non-carriers is negligible at all ages and the population's age-specific mortality hazard (that is, the instantaneous rate of mortality) is that of non-carriers, $h_{NC}(t)$[19]. Assuming that carriers' age-specific mortality hazard resulting from disease morbidity, $h_d(t)$, is independent from any other causes of death existing in the population, the mortality hazard of carriers during adulthood is $h_C(t) = h_{NC}(t) + h_d(t)$, where $t \geq \alpha$ and their adult survival probability is $\exp\left[-\int_0^x h_C(t)\mathrm{d}t\right] = \exp\left[-\int_0^x (h_{NC}(t) + h^d(t))\mathrm{d}t\right] = L(x)L^d(x)$.

Incorporating segregation coefficients in the familial structure. The SALOD can be carried by either a man or a woman with a probability equal to the sex ratio (here, 1:1). If the mutation is carried by a man, because the mutation is rare we can consider that his wife (wives) and his mother(s)-in-law are not carrying the mutation (the plural indicates that we do not assume strict monogamy). Similarly, if the mutation is carried by a woman, her husband(s) is considered free of mutation. In this case however, the woman may have inherited her mutation from her mother or father with a probability equal to 0.5. On average, the selective value of carriers can be written as:

$$W_C = \tfrac{1}{2} W_C^{m}\left[\text{wife(wives)}_{NC}, \text{wife(wives)}' \text{mother}_{NC}\right] + \tfrac{1}{2}\begin{pmatrix} \tfrac{1}{2} W_C^{fm}\left[\text{husband(s)}_{NC}, \text{female's mother}_{NC}\right] \\ +\tfrac{1}{2} W_C^{fm}\left[\text{husband(s)}_{NC}, \text{female's mother}_{C}\right] \end{pmatrix} \quad (4)$$

where individuals carrying the SALOD are at risk of developing the disease and exhibit an excess of mortality due to disease morbidity, $L^d(x)$. For instance, and assuming that the mutation has no antagonistic pleiotropic effect (Box 2), the selective value of a carrier female who has inherited the SALOD from her mother would be:

$$W_C^{fm}\left[\text{husband(s)}_{NC}, \text{female's mother}_{C}\right] = \int_{x_1=\alpha}^{\omega} L(x_1)L^d(x_1)F(x_1)S^*(x_1)\mathrm{d}x_1 \quad (5)$$

with $S^*(x_1)$ being the survival of a carrier female offspring calculated by replacing $L(x_1)$ and $L(x_2)$ with $L(x_1)L^d(x_1)$ and $L(x_2)L^d(x_2)$, respectively, in equations (2), (5) and (6) of Supplementary Methods. Equation (4) makes it easy to calculate s in the case of other genetic compartments or for a sex-specific disease (Box 2). The selective value W_c is therefore a composite value incorporating both the direct genetic effect (how increased mortality $L^d(x)$ affects the number of children produced by carriers) and indirect genetic effect (how $L^d(x)$ compromises children's survival by affecting parental and grandmaternal care).

Demographic parameterization. Age-specific fertility and the effects of maternal, grandmaternal and paternal care on child survival are shown in Fig. 1b,c and Supplementary Methods. All the results are provided for a population mortality corresponding to that of an average hunter-gatherer population fitted with a Siler mortality model[39]. In this case, $l(15)=0.57$ and $l(45)=0.36$, which means that $l(45)/l(15)=63\%$ of survivors at 15 years of age survive until 45 years of age. While life expectancy at birth is $e_0=31$ years of age, the remaining life expectancy at 45 years of age is $e_{45}=20.7$ years. Using female fertility, as shown in Fig. 1b and considering no (grand)parental care, we obtain a population growth rate of $\lambda=1.004$ and a mean number of daughters produced by females of 2.004. The proportion of children born to a father older than 50 years of age is 12%.

Distribution of age at disease onset. The results shown in Fig. 2a,b assume that the distribution of cumulative disease incidence $1-L^d(x)$ is logistic shaped, as detailed in Supplementary Methods (with $1-L^d(\text{FAO})=0.01$ and $1-L^d(x<\text{FAO})=0$), and that the disease is lethal (or fully incapacitating at age at onset). The age-specific survival, L^d, is used to estimate the gene-specific selection coefficients shown in Fig. 2c as follows.

For SALODs in the *HTT* gene leading to Huntington's disease (autosomal dominant, disease in both sexes), the formula for the distribution of disease onset with age and as a function of the number of CAG repeats is taken from ref. [24], to which we add 10 years (the typical latency from diagnosis to death is 20 years[55], but dependence on care occurs approximately 10 years sooner).

For SALODs in the *BRCA1* gene leading to breast and ovarian cancer (autosomal dominant, disease is considered in females only), the distribution of disease onset is the two-parameter gamma function fitted by ref. [19] to data from ref. [56] (MAO = 55 years, FAO = 20, $1-L^d(70)=81\%$).

For SALODs in the *BRCA2* exon 11 gene, which leads to breast and ovarian cancer in females and breast and prostate cancer in males (different autosomal dominant diseases with sex), we extracted the female age-specific onset distribution of breast and ovarian cancers from ref. [57] and that of male breast and prostate cancers from ref. [58] (the MAO, FAO and $1-L^d(80)$ are 44.75, 21.3 and 83%, respectively, for female breast cancer; 55.1, 32.4 and 34% for female ovarian cancer; 61, 37 and 12.5% for male breast cancer; and 67, 52 and 18.8% for male prostate cancer).

For SALODs in the genes *MLH1*, *MSH2* and *MSH6* leading to hereditary non-polyposis colorectal cancer (autosomal, dominant disease in both sexes), we considered a logistic-shaped distribution fitted from ref. [59], considering that the minimum age at disease onset is no younger than 20 years (MAO, FAO and $1-L^d(70)$ are 44, 20 and 41% for *MLH1*, respectively; 44, 20 and 48% for *MSH2*; and 55, 24 and 12% for *MSH6*).

For SALODs in genes *APP*, *PSEN1* and *PSEN2*, which lead to Alzheimer's dementia (autosomal, dominant disease in both sexes), we considered a logistic-shaped distribution fitted from ref. [60] bearing in mind that disease penetrance is nearly complete (MAO and FAO are 51.3 and 35 for *APP and* 42.9 and 24 for *PSEN1*, respectively; and 57.1 and 47 for *PSEN2*) and add 8 years as the mean age between disease diagnosis and death[61].

For SALODs in genes *LRRK2* and *SNCA* leading to Parkinson's disease (autosomal, dominant disease in both sexes), we considered a logistic-shaped distribution fitted from ref. [60] (MAO and FAO are 56 and 24 for *LRKK2*, respectively, and 48 and 31 for *SNCA*). Penetrance varies widely for *LRRK2* between populations (including for the single-mutation *G2019S*), and we arbitrarily set it at 50% by 80 years of age. For *SNCA* we set $1-L^d(100)=100$ from ref. [62] on the basis that the distribution of onset varies with the number of gene copies rather than penetrance. The average disease duration to death is set at 12.6 years[63].

For *C9orf72 (G4C2)n* expansion and SALODs in genes *MAPT* and *GRN* leading to frontotemporal dementia and amyotrophic lateral sclerosis (autosomal, dominant disease in both sexes), we considered a logistic-shaped distribution fitted from ref. [60] (MAO and FAO are 57.4 and 30 for *C9orf72*, respectively[64]; 47 and 28 for *MAPT*; and 59 and 42 for *GRN*[60]). Penetrance is considered to be complete for all three genes[65]. The mean survival time from onset of symptoms is approximately 8 years for frontotemporal dementia[66].

For SALODs in genes *PDK1* and *PDK2* leading to autosomal dominant polycystic kidney disease, the distribution of age at renal failure is extracted from ref. [20] (MAO, FAO and $1-L^d(90)$ are 58, 30 and 100% for *PDK1*, respectively, and 79, 41 and 70% for *PDK2*). Along with the authors of these studies, we make the distinction between mutations that truncate or do not truncate the *PKD1* protein.

Scaling selection to genetic drift in humans. In population genetics, selection coefficients are scaled by the factor $4N_e$, where N_e is the effective population size, to account for the stochastic effect of genetic drift in determining the fate of an allele. This scaling is crucial in the case of alleles under weak selection or close to

neutrality, when $4N_e s < 1$ (that is, 1 is the value for which genetic drift and selection are equal[67]). In humans, the population size N_e refer to a spatially or culturally defined population over a given time and with a given demographic history for which the allelic spectrum is observed. For example, refs. [3–5] aimed to explain the allelic spectrum defined at the level of humanity since its origin and considered that $N_e = 10{,}000$. In contrast, if one wants to explain the allelic spectrum of the descendants of French Canadian settlers, one would consider a founder population that has undergone massive population growth for 300 years (that is, $N_e = 1{,}000$ (ref. [43]). Finally, for human populations, N_e rarely fall below 100, which is the range of size found for very isolated insular populations[68].

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

No new data were generated for this study.

Code availability

The code in R language that supports the findings of this study is available on GitHub's 'SPavard/Code-for-SALOD' repository with the identifier https://doi.org/10.5281/zenodo.4032278.

Received: 21 March 2020; Accepted: 22 October 2020;
Published online: 4 January 2021

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Acknowledgements

This study is supported by a grant from the Agence Nationale de la Recherche (no. ANR-18-CE02-0011, MathKinD).

Author contributions

S.P. designed the study and wrote the manuscript. S.P. and C.F.D.C. developed the model together.

Competing interests

The authors declare no competing interests.

Additional information

Extended data is available for this paper at https://doi.org/10.1038/s41559-020-01355-2.

Supplementary information is available for this paper at https://doi.org/10.1038/s41559-020-01355-2.

Correspondence and requests for materials should be addressed to S.P.

Peer review information Peer reviewer reports are available. *Nature Ecology & Evolution* thanks the anonymous reviewers for their contribution to the peer review of this work.

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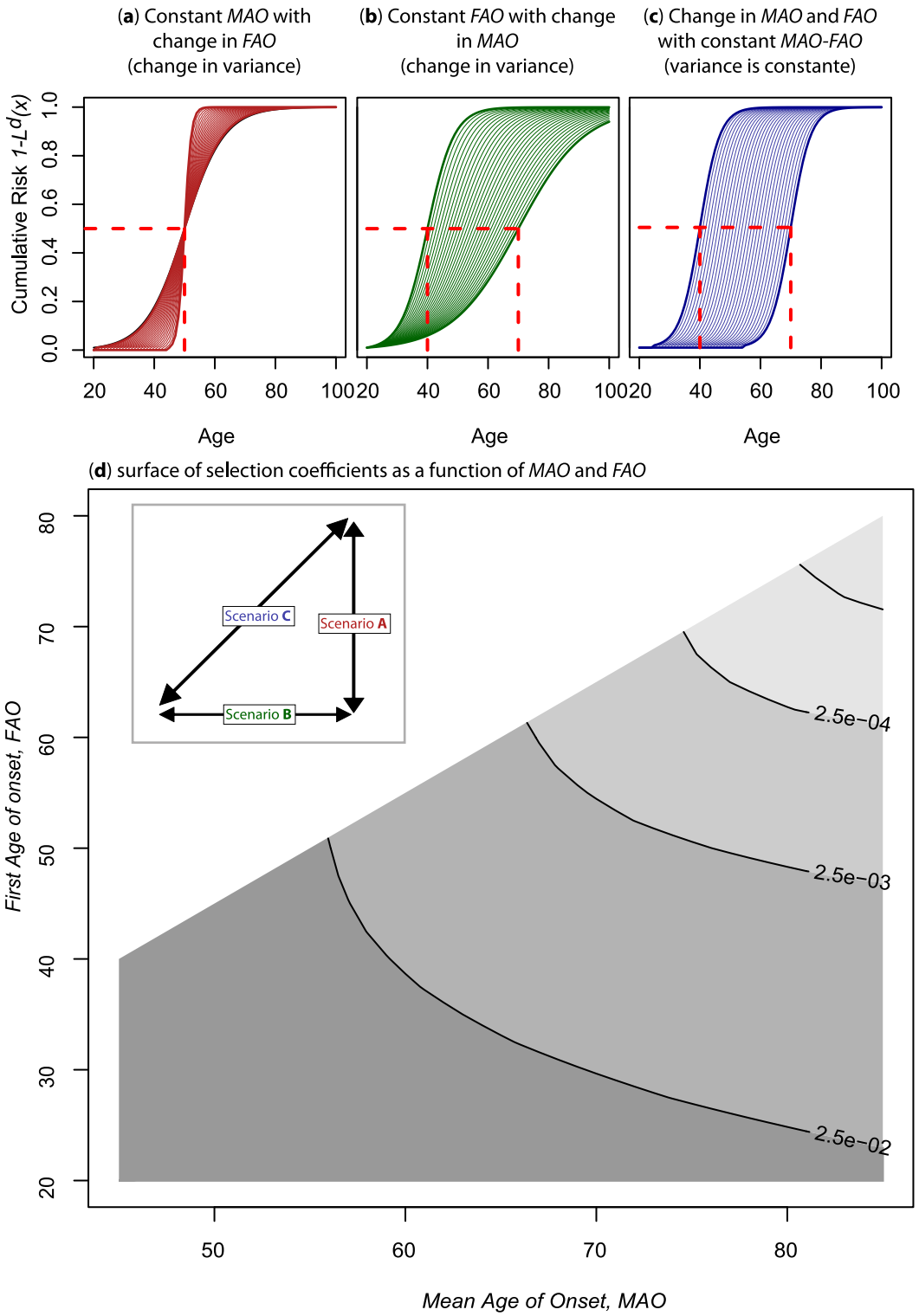
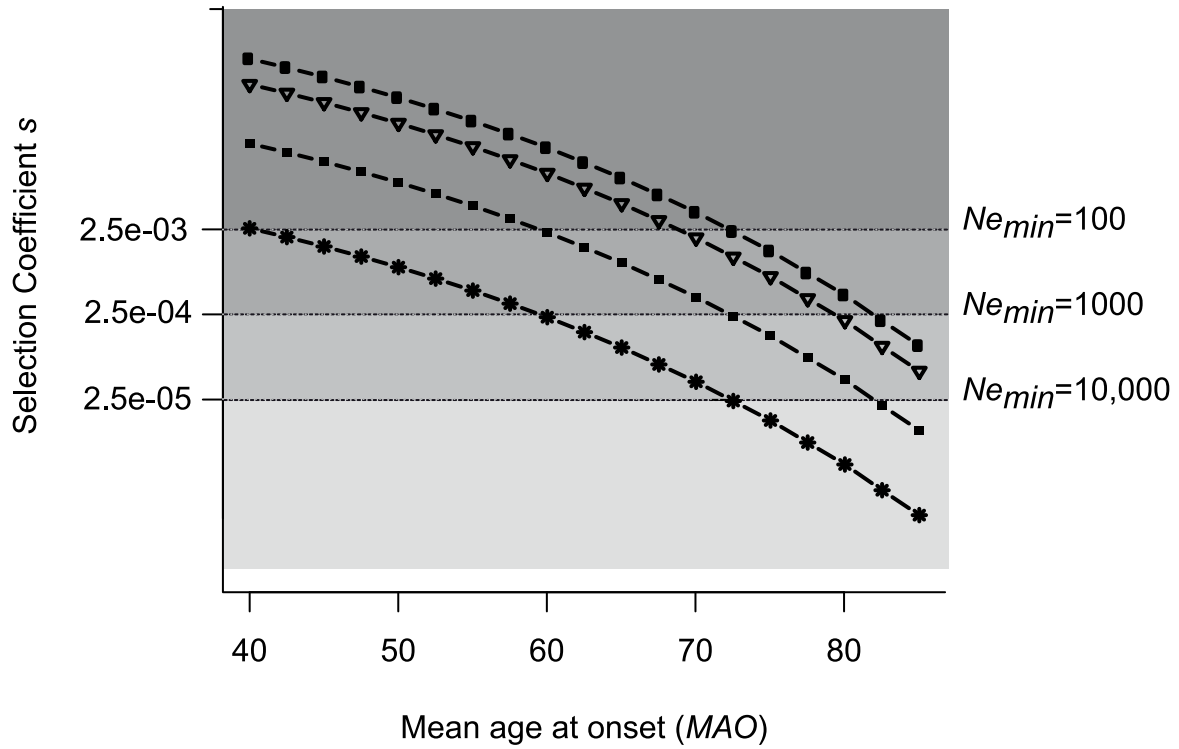
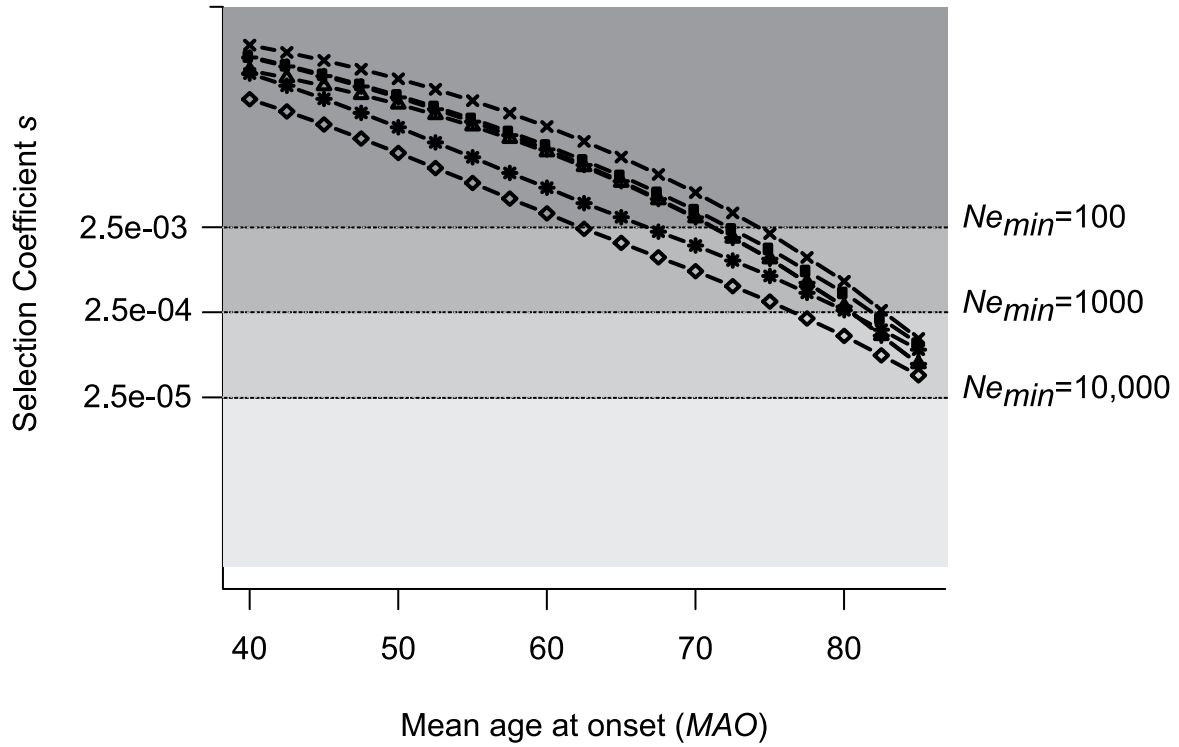


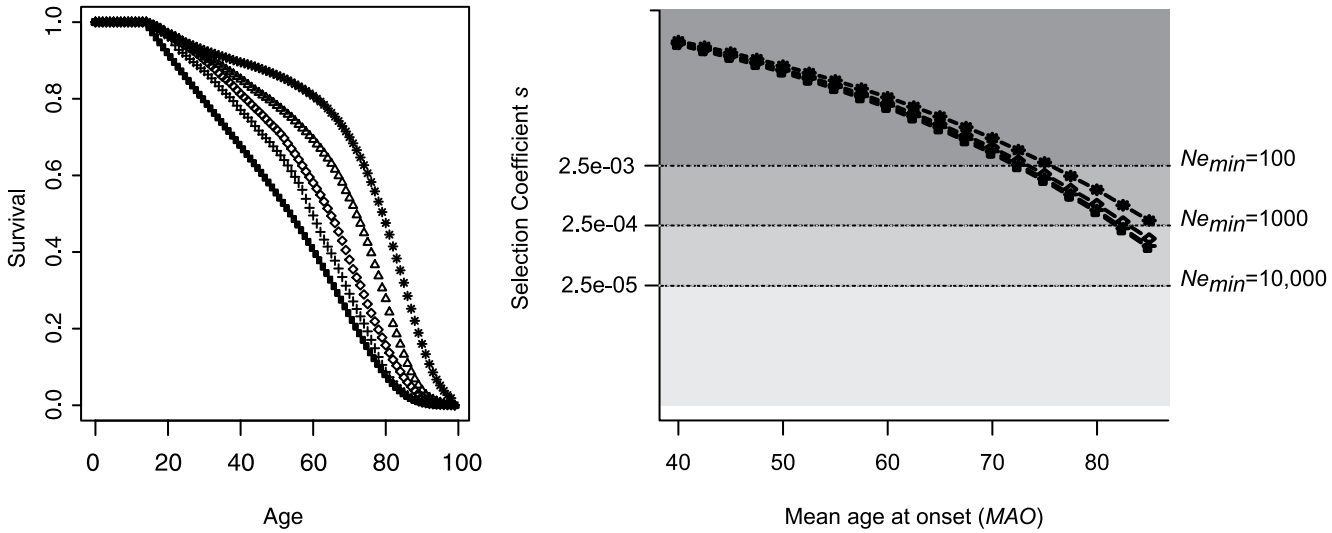
Extended Data Fig. 1 | Selection coefficients for a large parameter space of onset. a–c, Cumulative incidence of disease onset with age according to change in Mean Age at disease Onset (*MAO*) and First Age at disease Onset (*FAO*, with *FAO* from age 20 to *MAO* − 5 *yrs*). If disease onset is confounded with morbidity or full incapacitation, cumulative risk is $1\text{-}L^d(x)$, where $L^d(x)$ is the disease-specific survival at age *x*. Dashed red lines indicate the median age at disease onset. Age at onset distribution if fitted with a two parameters logistic function (see Supplementary Information 2.2). *FAO* is defined as the age at which 1% of SALOD carrier have develop the disease ($1\text{-}L^d(x) = 0.01$ and setting $1\text{-}L^d(x < FAO) = 0$). **d**, Coefficient of selection *s* as a function of *MAO* and *FAO*. Levels of grey indicate relation of selection to drift. Above *s* = 2.5e-02 (darker grey) selection is expected in all human populations (all of them having *Ne* > 100). Below *s* = 2.5e-04, alleles are neutral in most human populations (for which *Ne* < 10,000). In between selection levels of selection will vary of 'small' (dark grey) or large '*Ne*' (light grey). Allele is rare, autosomal, dominant, disease in both sexes and penetrance is complete.



Extended Data Fig. 2 | Selection coefficients with respect to disease cumulative risk. Selection coefficients as a function of Mean Age at disease Onset (*MAO*), First Age at Onset (*FAO*) being 20 years earlier, in the case of an autosomal allele leading to disease's cumulative risk at age 100 [a measure of the genotype penetrance] of 100% (circles), 50% (triangles), 10% (squares) and 1% (stars). In this case, *FAO* is defined as the age at which of the cumulative distribution respectively reaches 1, 0.5, 0.1 and 0.01; the risk of disease onset being zero before this age. Horizontal lines indicate the level of selection for which alleles become neutral ($4.Ne.s < 1$) for populations of *Ne* equal to 10^2, 10^3 and 10^4, that is, the minimum *Ne* for which effect of selection overcome that of genetic drift, holding that 10^4 is the *Ne* estimated at our species level. Mortality is that of a mean hunter-gatherer population and fertility that of Fig. 1b. Selection coefficient is a linear function of penetrance (estimated here by the cumulative risk at age 100). This makes a genotype penetrance a fundamental parameter for estimating magnitudes of selection, even for SALOD leading to a *MAO* after age 45 (by contrast with a model without variance in disease onset and cultural factors where alleles are neutral after age 45 years, even if penetrance is 100%). Roughly, an allele with *MAO* at 40 but 1% of penetrance is selected against as an allele of *MAO* at 70 but penetrance at 100%.



Extended Data Fig. 3 | Selection coefficients for sex-specific diseases and genetic compartments. Selection coefficients as a function of Mean Age at Onset (*MAO*), First Age at Onset (*FAO*) being 20 years earlier, when maternal, grandmaternal and paternal care are incorporated, as well as both females and males reproduction; in the case of: (circles) a dominant autosomal allele (equation [7]); (pluses) a recessive autosomal allele (the probability for the mother of a female homozygous carrier of being herself homozygous is considered as negligible and the female's mother is considered as non-carrier in equation [7]); (diamonds) an autosomal allele leading to disease in females only (W^C of male carriers is equated to W^{NC} in equation [7]); (triangles) an autosomal allele leading to disease in males only (W^C of female carriers equated to W^{NC} in equation [7]); (stars) an allele carried by the mitochondrial chromosome (canceling the male element of equation [7]); and (crosses) an allele carried by the Y-Chrom (canceling the female element of equation [7]). Horizontal lines indicate the level of selection for which alleles become neutral ($4.Ne.s < 1$) for populations of *Ne* equal to 10^2, 10^3 and 10^4, that is, the minimum *Ne* for which effect of selection overcome that of genetic drift, holding that 10^4 is the *Ne* estimated at our species level. Mortality is that of a mean hunter-gatherer population and fertility that of Fig. 1b. When variance in disease onset and all socio-cultural factors are accounted for, there are no large difference in magnitude of selection on these alleles for population of medium or large *Ne*: they all cross the $Ne_{min} = 1000$ line for $75 < MAO < 85$. A differential of selection may however be expected for population of small *Ne* (between 100 and 1000) between alleles in the Y-Chromosome or leading to disease in males only (more prone to purification when there is large differences in reproductive schedules between men and women) and alleles in the *Mt*-Chromosome or leading to disease in females only (less prone to purification). This is because coefficient of selection *s* is less impacted by (grand) maternal care than by male reproduction. No large difference is expected between recessive alleles, autosomal dominant alleles, or allele leading to disease in male only, which all exhibit intermediary level of selection. A decrease in cumulative risk of disease onset at age 100 (here equaled to 100%) would proportionally scale down all these selection coefficients (see Extended Data 2).



Extended Data Fig. 4 | Selection coefficients for various demographic regimen. *Right panel* - Selection coefficients as a function of Mean Age at disease Onset (*MAO*), First Age at Onset (*FAO*) being 20 years earlier, in the case of different adult survival shown in the left panel: average Hunter-gatherer (squares) from [39], estimates of females of Sweden 1751 (crosses), 1800 (diamonds), 1850 (triangles) and 1900 (stars) from [40]. Horizontal lines indicate the level of selection for which alleles become neutral ($4.Ne.s < 1$) for populations of *Ne* equal to 10^2, 10^3 and 10^4, that is, the minimum *Ne* for which effect of selection overcome that of genetic drift, holding that 10^4 is the *Ne* estimated at our species level. Mortality is that of a mean hunter-gatherer population and fertility that of Fig. 1b. Large increase of adult survival has little effect on the decrease in magnitudes of selection coefficients with *MAO*. This is because selection is always proportional on population mean and increased mortality of carriers compared to that of non-carriers within a population is not that dependent on the age-specific survival in a model where carriers may develop the disease over a large range of ages.

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Last updated by author(s): Sep 16, 2020

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Reproduction in the Baka pygmies and drop in their fertility with the arrival of alcohol

Fernando V. Ramirez Rozzi[a,1]

[a]UMR 5288 Laboratoire Anthropologie Moléculaire et Imagerie de Synthèse, CNRS, Faculté de Chirurgie Dentaire, 92120 Montrouge, France

Edited by James O'Connell, University of Utah, Salt Lake City, UT, and approved May 21, 2018 (received for review November 10, 2017)

To understand the diversity of human growth and development from an evolutionary point of view, there is an urgent need to characterize the life-history variables of vanishing forager societies. The small body size of the Baka pygmies is the outcome of a low growth rate during infancy. While the ages at sexual maturity, menarche, and first delivery are similar to those in other populations, fertility aspects are unknown. In the Le Bosquet district in Cameroon, thanks to systematic birth records kept from 1980 onwards, we were able to assign ages to individuals with certainty. This study, based on chronological records and on data collected from 2007 to 2017, presents life-history variables related to fertility and mortality among the Baka pygmies: total fertility rate, age-specific fertility rate, completed family size, reproductive span, age at menopause, and infant and juvenile mortality. The Baka present low infant and juvenile mortality, and their fertility pattern differs from that of other forager societies in the higher age-specific fertility rates found in the two lower age classes. Future studies will need to assess whether this particular pattern and the short interbirth interval are related to highly cooperative childrearing, which in the Baka is associated with slow growth. The fertility rate has fallen drastically since 2011, and this matches the arrival of cheap alcohol in the community. Our data provide a first-hand record of the impact of alcohol on fertility in a hunter-gatherer society which appears to be seriously compromising the survival of the Baka.

Baka pygmies | hunter-gatherers | fertility | mortality | alcohol

Our species, *Homo sapiens*, is the most polymorphic species of primate and is distinct from all others in the wide range of contrasting environmental conditions it inhabits. Although culture in the broad sense is largely responsible for the broad geographical distribution of our species, biological plasticity has certainly played a fundamental role in our adaptation (1). Biological adaptation to environmental conditions depends on the allocation of an organism's energy to growth, maintenance, reproduction (including raising offspring to independence), and avoiding death. The timing of key developmental events that determine the pace at which these factors play out within the lives of humans is called "life history" and is described by a suite of life-history variables (LHVs) that include age at first reproduction, number of offspring, interbirth interval (IBI), age at menopause, infant mortality, and survival to maturity (2).

LHVs are well known for several modern human groups (3), and their variability through time can be tracked over several decades. However, a broad knowledge of the variability of life history in our species requires studies of LHVs in many human societies. Along this line of reasoning, as argued by Hill and Hurtado (4), the adaptive functional significance of human life history can be understood better by studying forager societies (5). Although variation in life history has been studied across several forager societies, these studies have shown that significant differences exist between societies living under dissimilar environmental conditions (4, 6–8). This has led to the suggestion that no single society can be taken as representative of all hunter-gatherers (4) and, more importantly, that we need broad-ranging studies of LHVs in more societies to understand the variation we observe across hunter-gatherer societies.

Particular attention has been paid to populations with a small adult body size (6, 7). From an evolutionary developmental perspective, adult size is the final product of growth. Energy acquired throughout life must be allocated to growth, on the one hand, and reproduction, on the other (9). A small adult body size therefore implies a specific growth pattern with low energy allocated to it but enough to ensure an adult size capable of producing the necessary energy for reproduction. Migliano et al. (10) have suggested that small body size in the Aeta results from precocious reproduction due to a high mortality rate; in other words, small body size might be a by-product of growth ceasing at an early age to divert energy away from growth and toward reproductive activity. However, this observation cannot be extrapolated to all forager societies with a small body size. For instance, among the Baka pygmies in Cameroon (*SI Appendix*, *Text S1*), a low rate of growth from birth to 2.5 y of age accounts for the pygmy phenotype, and this process is not followed by any change in the timing of sexual maturation (i.e., age at menarche and age at first reproduction) (11). However, it is not known whether fertility parameters such as the total fertility rate (TFR), age-specific fertility rate (ASFR), and age at menopause are affected by the particular growth pattern that produces a small adult size. Knowledge of these parameters is fundamental to understand life-history variations since a small adult body size produces less energy to be allocated to reproduction by lowering the fertility rate or by advancing the age at menopause. The aim of this study is thus to characterize fertility in the Baka.

The relationship between fertility and mortality is often used to build models for demographic transitions and is essential to understand population dynamics (12). Any change in fertility is associated with a change in mortality. At the population level, a

Significance

Humans are a polymorphic species with a broad geographical distribution. Diversity in growth and development plays an important role in biological adaptation and can be addressed through studies of life-history variation across different populations, particularly in hunter-gatherer societies. This paper reports the results from our study on fertility and mortality in the Baka pygmies based on individuals of known age. The Baka are characterized by low infant and juvenile mortalities, slow growth, and high fertility at an early age. However, the arrival of cheap alcohol has drastically reduced fertility early in life, which seriously compromises this population's survival. We provide empirical evidence of the effects of alcohol consumption on the fertility rate of a hunter-gatherer society.

Author contributions: F.V.R.R. designed research, performed research, analyzed data, and wrote the paper.

The author declares no conflict of interest.

This article is a PNAS Direct Submission.

[1]Email: fernando.ramirez-rozzi@cnrs.fr.

This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1719637115/-/DCSupplemental.

Published online June 18, 2018.

reduction in the fertility rate is expected after a drop in the infant mortality rate; conversely, a rise in fertility can be observed after high mortality due to natural disasters (13). At the family level, the average birth interval is substantially shorter following an infant death than when an infant survives (14). Mortality in infants and mothers is complementary to data on fertility aspects.

During our 10-y study, we witnessed the arrival of cheap alcohol which became widely available to the community. We observed that changes in human fertility occurred at that point. The relationship between these two phenomena is discussed.

Overview: Moange Le Bosquet

Most studies on life-history variation as an aspect of the demographics of forager societies have been hampered by the lack of chronological data for individuals. This is a fundamental problem because our understanding of population dynamics and evolution revolves around processes that occur at known chronological stages. Except for Early and Headland's work (7) on the Agta, in which the ages of 271 of the 857 individuals (31.6%) were known (117 individuals to within a year, 80 to within a month, and 74 exactly to the day; see table 4.1 in ref. 7), authors have had to develop various methods to estimate the missing chronological information (15). From data provided by many scholars, Weiss (16) built model life tables to infer, from a limited number of variables, many demographic/life-history parameters, such as life expectancy or the ASFR for each 5-y age cohort. Until recently, these tables were widely used to characterize all forager societies. The lack of chronological data available to benchmark his models means his data should be viewed as preliminary and used cautiously.

Because we were aware of the limitations imposed by the lack of chronological dates, we carried out field studies at Moange Le Bosquet, a Baka pygmy village in southeastern Cameroon where birth records had been kept for many years. Le Bosquet was founded in 1973 by Sister Marie-Albéric of the Congregation of Holy Spirit. Given the complex socioeconomic relationships that the Baka have with their Bantu-speaking farming neighbors (17), Sister Marie-Albéric invited those Baka living in camps attached to nearby Bantu villages to move to a new locality to found a village where, for the first time, the chief would be a Baka. One of the first buildings erected by the Catholic mission was a medical center run by nuns with medical training, who provided health care for the community, kept birth records, and carried out regular censuses to integrate the Baka into the organizational structure of the civilian community in Cameroon (e.g., helping them obtain identity cards and land titles). By the end of 1973, about 700 Baka were living at the village of Le Bosquet.

Le Bosquet comprises an aggregate of Baka camps. As people come in from different camps attached to nearby Bantu villages, they form different neighborhoods, each keeping the name of the original village, possessing its own meeting hut, and organized socially around a family chief. Le Bosquet extends over approximately 5 km from east to west along the road from Lomié to Messok. The neighborhoods near the Catholic mission are very close to one another, while others are separated by large tracts of forest and look like the camps attached to Bantu villages.

Although the Baka are inhabitants of Le Bosquet, their way of life has remained seminomadic. Many individuals and family groups arrive or leave from one year to the next with no particular pattern: Some families leave and return a few years later, while other families leave after staying at Le Bosquet for a time and never return. During each field season we met some Baka who spent several months of the year away from the village, moving to camps in the middle of the forest where they feel "at home." Hunting and gathering are the main activities in the forest camps. When at Le Bosquet, the main activity for women is gathering, on top of other chores including housekeeping, childcare, and fishing; the men's activities include agricultural work for farmer neighbors, carrying logs cut by clandestine timber companies, hunting, and sometimes gathering (18). Many Baka also cultivate their own banana and/or manioc crops. According to several censuses carried out by the nuns and our own records kept over 11 y, the number of Baka individuals at Le Bosquet has remained more or less constant at around 800 individuals.

Birth records with both parents identified are available from 1980 to 1983 and from December 1987 until the present (*SI Appendix*, Table S1). Demographic records had previously been kept in the 1960s and 1970s by Father Dhellemmes (19), who lived and traveled in the region. Dhellemmes built up an enormous database from individual index cards identifying people by family and clan links, including a large number of Baka living in the wider area of southeastern Cameroon. The nuns used these index cards to provide identity cards for the first inhabitants at Le Bosquet, a strategy that allowed us to determine exact ages for a subset of people approximately 50+ y of age.

Ages are not known for all the people living at Le Bosquet. The nuns constantly encourage the Baka to declare births. Because of the fluid residential pattern mentioned above, many families live at Le Bosquet for only a short period, while others may have lived at a forest camp at the time of birth and forgotten to formally declare the baby later as part of the census exercise. To further complicate census efforts, if a newborn dies during the first year of life and another baby follows within a short time ($\leq$2 y), the new baby is considered to be the former baby who has "left for a while and returned a little later," so the parents believe it is enough to declare the first birth. A consequence of this cultural belief is that the number of deliveries, both live and dead, is not the same as the total number of offspring for a couple during their entire reproductive period. Births may also not be declared because of the wishes of one or both parents: For instance, one father stopped declaring births after his fourth girl and opted in the future to declare a new birth only if it was a boy.

With around 800 Baka inhabitants, Le Bosquet is not a Baka settlement, because these settlements are made up of only 45 people on average (20–22). We are aware that the social and economic situation at Le Bosquet is probably not the same as that described for the camps; however, it should be remembered that the main characteristic of Baka society is the heterogeneity of its camp environments and its patterns of economic and social organization (23). While the social and economic aspects of Baka society have been investigated many times (24–26), variations in key reproductive aspects of their life history have never been explored. Thanks to the birth records available at Le Bosquet, we were able to describe growth and LHVs based on an absolute chronology in a hunter-gatherer society. Although our analysis centers on the subpopulation at Le Bosquet (only individuals with a known date of birth are included), we believe the results presented here are representative of the entire population at Le Bosquet, that they reflect a transition to a period increasingly affected by external influences, and that they provide a basis for studies of other pygmy groups that are genetically close to the Baka (e.g., the Aka from the Central Africa Republic).

Results

Timing of Reproduction and Family Size. Conjugal relationships do not occur immediately after menarche: There is a gap while young adult Baka enjoy different kinds of friendly relationships. In the past, the choice of partner could have been directed by clan membership (avoiding a partner from the same clan), but almost all clans in and around Le Bosquet have abandoned this practice. Some constraints do exist in the case of widowhood, since widows and widowers must choose a new partner among members of the deceased partner's family; the widow or widower can make a different choice only if the deceased partner's family refuses to provide a new partner. There are no cultural factors

Table 1. Reproductive aspects in hunter-gatherer societies

Hunter-gatherer population	H F	H M	CFS	IBI, y	Age at first birth, y	Age at last birth, y	RS, y	IM	PS F, %	PS M, %
Ache Forest (4, 29)	149*	158*	8.15	3.1	19.5	42.1	22.6	11	68* (61)	79* (71)
Hiwi (29, 30)	145	154	5.13	3.76	20.5	37.8			45	51
Ju/'hoansi (6)	150	161	4.7	4.12	18.8	34.4	15.6	20.2	60	56
Yanomamo (3, 27, 28)	142	152	7.8	3.3	18.4	37.9	19.5	19	70 (48†)	70 (48†)
Agta (7)	143	153	7.6	2.82–2.85	19.5	early 40s	24	29	42	42
Aka (3, 50)	145	153		3.5					55	55
Efé (3, 31, 32)	136	144	2.7	3.1					78	
Pumé savanna (33–35)	151.5	163.2		3.1	15.5					
Pumé river (33)				2.87						
Hadza (3, 29)	150	160			19				54 (58)	54 (55)
Baka	147	154	7.3	2.77	18	39.9	22	5.2	66–92	66–92

CFS, completed family size; F, female; H, height (cm); IM, infant mortality (%); M, male; PS, proportion of survival to maturity; RS, reproductive span (the difference between mother's age at last and first births). For the Baka, the difference between mother's age at last and first births gives an RS of 22 y, but from the full reproductive history of 15 women RS is 20.2 y.
*From Reserve (3).
†See ref. 3.

regulating delayed or precocious conception: The first birth therefore reflects fecundity. In the Baka at Le Bosquet, the earliest first births occurred at 16 y of age, and the average age at first birth was at 18 y. The age at latest birth varies widely (from 25 to 51 y) and averages 39.9 y. The average age at menopause is estimated to be around 42 y.

The average completed family size for postmenopausal women ($n = 15$, *SI Appendix*, Table S2) in this sample is 7.3 living offspring, varying from 4 to 10 children per woman. Nine of 16 women declared they had lost one baby in its infancy (at or before 1 y of age), while three women had each lost two infants. Four women said they had experienced a miscarriage. The difference between the average age at first and last birth suggests a reproductive span of 22 y, although the average reproductive period for the 15 women is 20.2 y. An average family size of 7.3 people therefore generates an average IBI of 3 y or 2.77 y, the latter figure being very close to the modal value of 2.5 and 2.75 y obtained in a previous study on the Baka (11). Comparisons with other hunter-gatherer societies (3, 4, 6, 7, 27–35) show that results for the Baka are similar to those suggested for the Aché, the Agta, and the Yanomamo, although the Baka have the shortest IBI (Table 1).

TFR and ASFR. The TFR by year is shown in Fig. 1 and Table 2. The average TFR is very close to the average completed family size of 7.3 individuals. Clearly, two periods can be distinguished, one from 2007–2010, when the TFR values are high (>7) and another from 2011–2015 when the TFR decreases markedly ($P = 0.008$). The TFR values are not associated with any variation in the number of women or in the number of births ($P > 0.05$). The TFR for the Baka during the first period (2007–2010), which varies from 7.71 to 11.03 ($\bar{x} = 8.8$), is close to that for the Aché forest and reserve populations ($\bar{x} = 8.08$ and 8.53, respectively) and Yanomamo ($\bar{x} = 8.1$) but is a little higher than for the Agta ($\bar{x} = 7.04$) (Table 3). During the second period (2011–2015), the TFR for the Baka is much lower ($\bar{x} = 5.53$), higher than for the Ju/'hoansi ($\bar{x} = 4.69$) but much lower than for all other hunter-gatherer populations reported here.

The Baka present the same pattern in the ASFR in all years (2007–2015), with the highest value occurring in the second age class (20–24 y). In general, the highest values occur in the first two age classes, declining throughout a woman's reproductive life (Fig. 2, Table 4, and *SI Appendix*, *Text S2*). Longitudinal ASFR data reinforce the identification of two different periods, as suggested by the TFR data. Births were recorded for mothers 45–49 y of age during the first period (2007–2010) but not during the second period (2011–2015). Furthermore, ASFR values in the two younger age classes are much higher in the first period than in the second ($P < 0.05$). The proportion of births per woman declines during the second period but only in the two youngest age classes ($\bar{x} = 0.55$ and 0.45, respectively, for the first period; $\bar{x} = 0.21$ and 0.26, respectively, for the second period).

Compared with other hunter-gatherer societies reported here, the Baka have the highest ASFR values in the first two age classes, although the values for the second period are closer to those reported for other populations (Fig. 3 and Table 3). For the third age class the low values for the Baka are close to those observed for the Ju/'hoansi. In other hunter-gatherer societies, the ASFR increases from the first years of reproductive activity and reaches the highest values in the third age class (25–29 y) in the Yanomamo and the Aché living in the reserve and in the fourth age class (30–34 y) in the Aché living in the forest. Weiss (16) suggested that the highest values in the third or fourth age classes are "virtually universal among human females" (ref. 16, p. 31), and he followed this pattern to establish his models of anthropological fertility rates. However, the Ju/'hoansi, like the Baka, have the highest value in the second age class (age 20–24 y). The Baka thus have a very characteristic ASFR pattern that clearly distinguishes them from other hunter-gatherer societies, with a high rate of reproduction from age 15–29 y and a lower rate in the older age classes (Fig. 3).

ASFR enables estimations of the mean annual probability of birth in the last two reproductive age classes (40–49 y). In forager societies, this ranges from 0.044 (Ju/'hoansi) to 0.158 (Aché). In the Baka it falls between those two populations, with a probability of 0.081 during the first period (2007–2010) and 0.045 for the second period (2011–2015).

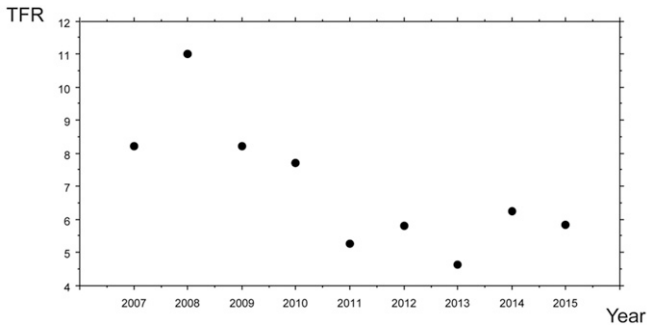

Fig. 1. TFR in the Baka from 2007–2015. High values during the first years of the study are followed by a drop in the TFR. The year 2011 marks a significant change in the TFR in the Baka.

Table 2. TFR in the Baka

Year	TFR	Log	No. women	No. births
2007	8.21	0.9143	95	17
2008	11.03	1.0426	113	37
2009	8.23	0.9156	163	40
2010	7.71	0.8873	167	37
2011	5.26	0.7213	157	26
2012	5.82	0.7648	180	33
2013	4.62	0.6651	155	21
2014	6.25	0.7959	189	35
2015	5.83	0.7658	177	30
Average	7	0.8303		

Infant and Juvenile Mortality. Table 5 shows the number of births, the number of infant deaths during the first year of life, the number of infants who survive the first year of life, and the number of infants who moved away from Le Bosquet from 2007–2015 (and whose survival after leaving Le Bosquet is unknown). The infant mortality rate from 2007–2015 is extremely low, as only six infants died before the first year of life out of 229 births (this number was obtained by subtracting the number of infants reported as "out" from the total number of births). This corresponds to an infant mortality rate of 2.62%. It is possible that infants who died within a few days after birth were not declared. In the reproductive history of the 44 women used to obtain parity-specific infant mortality (see below) we observed that four infants who died a few days after birth were not declared, which corresponds to 50% of cases. Even with this correction, the estimated infant mortality rate, at 5.24%, remains extremely low compared with infant mortality in other hunter-gatherer societies (Table 1). Marlowe (36) reported a mean infant mortality rate of 23.29% for 12 hunter-gatherer groups living in a warm climate. It is worth noting that no infant death is recorded from 2007–2010: The first evidence of infant mortality appears in 2011 (Table 5). There is no difference between the two periods in weight during the first 2 mo of life (*SI Appendix*, Table S3).

Among the 44 mothers with a known full reproductive history used to obtain infant mortality per woman by parity (Table 6), 13 miscarriages were recorded. Two mothers had two successive miscarriages. The abortion indicated in Table 6 was produced deliberately because the woman became pregnant when her last child was still "too small," which for the Baka means less than 1.5 y old. Abortions recorded for other women or at other periods and thus not included in this analysis were performed for the same reason. Parity-specific infant mortality per woman obtained for the Pumé (35) shows that Pumé mothers can have five children by 25 y of age. None of the Baka mothers 15–25 y of age had five infants, and only one mother 25 y of age had four infants. This difference with the Pumé can be related to the age at first pregnancy, the average being 15.5 y for the Pumé (35) but 18 y for the Baka (11). Parity-specific infant mortality per woman was obtained in June 2010 and in June 2014. Two main differences can be observed: The number of miscarriages was higher in 2010 than in 2014, while infant mortality in first-time mothers was 0% in 2010 but reached 50% in 2014. In 2010, 9 of 12 mothers with a first live infant were 19 y of age or less. In 2014, however, the three mothers with one live infant were 21–23 y of age, whereas two of the mothers with one dead infant were 18 y old, and one was 21 y of age. Infant mortality in mothers with more than one infant was much lower than in mothers with only one infant, which probably suggests that high infant mortality is a new phenomenon.

The average IBI for mothers 15–25 y of age in 2010 was 2.85 y ($n = 19$), but in three cases the IBI may have been affected by particular factors: Two high IBIs occurred when the mothers suffered miscarriages, and the other high IBI happened when the woman was not married for a while. When these particular IBIs are excluded, the average IBI for 2010 is 2.36 y. For mothers 15–25 y of age in 2014, the average IBI is 2.77 y ($n = 11$). Only one IBI was very long, almost certainly due to two miscarriages. When this is excluded, the average IBI is 2.56 y. When these two IBIs are compared, no significant difference is found ($P = 0.384$).

Mortality was estimated for Baka children born from 1996–2001 and reaching 15 y of age in 2011 and later. The high mobility of the Baka prevented an accurate estimation. As shown in Table 7, 60 children (30 girls and 30 boys) out of 212 births (28%) were no longer living at Le Bosquet, and it was not possible to find out whether they had lived to age 15 y. If these children are considered dead, juvenile mortality in the Baka varies from 29 to 41% with a mean for the six years of 34% (66% probability of survival to maturity). If only known alive and dead infants are considered (excluding those classified as out), juvenile mortality drops to 8% (92% probability of survival to maturity). The values are the same for males and females (Table 7). Among the hunter-gatherer groups compared with the Baka, only the Ache present a high probability of survival (68% in female, 79% in male) (Table 1). Walker et al. (3) reported values of around 80% for the Tsimane and Turkana. However, the lower value of 66% for the Baka is certainly an underestimation of the probability of survival in this group because it assumes that all the young adults who left Le Bosquet are dead. A 92% probability of survival to maturity in the Baka is much higher than in any other hunter-gatherer group and must be considered with caution. Table 5 also provides some information on juvenile mortality. It is surprising that the number of children that died is as high among those who were born in 2011–2015 as it is in the 2007–2010 cohort.

Only four cases of death of young Baka mothers were recorded. If a mother dies during the first year of an infant's life, the infant is abandoned by the family and dies (*SI Appendix*, Fig. S1).

Table 3. Comparison of TFR and ASFR in the Baka and other hunter-gatherer societies

	Baka		Aché (4)				
Age, y	Period 1	Period 2	Forest	Reserve	Ju/'hoansi (6)	Agta (7)	Yanomamo (28)
15–19	0.550	0.212	0.151	0.253	0.135	0.126	0.295
20–24	0.448	0.259	0.275	0.333	0.242	0.299	0.267
25–29	0.233	0.220	0.298	0.341	0.203	0.344	0.361
30–34	0.200	0.210	0.318	0.333	0.152	0.282	0.364
35–39	0.168	0.109	0.279	0.265	0.119	0.213	0.205
40–44	0.088	0.090	0.219	0.157	0.071	0.144	0.063
45–49	0.073	0.000	0.069	0.019	0.016	0	0.063
>50	0.000	0.012	0.000	0.000	0	0	
TFR	8.797	5.558	8.081	8.529	4.69	7.04	8.098

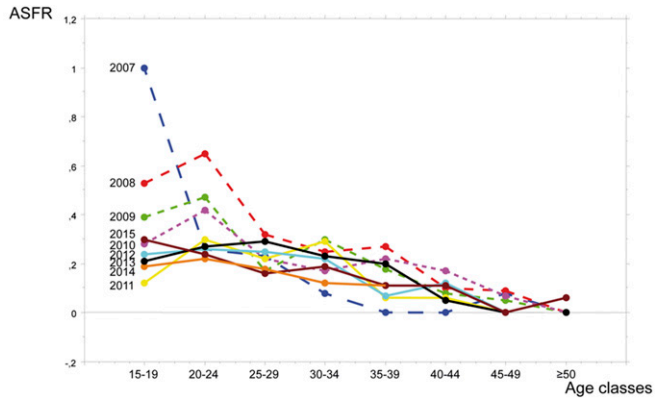

Fig. 2. ASFR over 9 y among the Baka (one color for each year). From 2007–2010 (period 1, dashed lines) the lower age classes have much higher values than the next classes; these values dropped from 2011–2015 (period 2, solid lines), suggesting a major change in the reproduction capacities of young adults.

Discussion

The first pregnancy marks an abrupt change in the life of any mammal, since the energy used for growth until this point is allocated from then on to reproduction (9). Given the intersection of ecology and demography in any population, natural selection can presumably act on the timing of this important life-history event, resulting in either an earlier or a later age at first reproduction. Any organism will favor growth to reach its maximum size, which is closely linked to energy production: A larger size will produce more energy for reproduction and survival. However, each time unit of delay before the onset of reproduction decreases the organism's chances of surviving to reproductive age (37). The average age at first birth thus appears to be the best compromise that a population can achieve between allocating surplus energy to growth or to reproduction.

The hunter-gatherer populations compared in this study have a small average adult size and an average age at first reproduction of 18–19 y, which is similar to that of European populations. Thus, the small body size with the limited amount of surplus energy it provides for reproduction does not appear to be related to the age at first delivery in these populations. Results for the Pumé point to the same conclusion. The Pumé are relatively tall compared with other hunter-gatherer populations referred to here (Table 1), and the first birth occurs at a much younger age (15.5 y) (34). This seems to be coupled with rapid juvenile growth, which produces greater gains in stature in youth than in adolescence to achieve a body size close to that of neighboring populations. As adult stature may not be associated with age at first birth (35), short stature is not necessarily linked with early maturation. Variations in adult size (height and weight) probably play some role in the age at maturation among individuals from the same population (4), but extrapolating this relationship to entire populations seems hazardous.

However, Kramer (38), like Migliano et al. (10) for the Aeta, sees faster growth as an adaptive response in high-mortality environments where early reproduction is advantageous. This links up with the suggestion made by Walker et al. (3) that a high survival rate is associated with slower and later development. The Baka show a very low infant mortality rate and a high, even extremely high, probability of survival to maturity (Table 1). The environmental conditions of the Baka thus do not appear to be challenging in terms of mortality and offer appropriate conditions for a slow growth pattern. This agrees with the pattern of growth described for the Baka, who reach maturity (menarche, first reproduction) at a similar age as nonforager populations (11). The short stature of the Baka is not a consequence of early cessation of growth, as has been suggested for the Aeta, but results from a slower rate of growth during infancy (11), which has a genetic foundation (39–41). Therefore, high mortality rates (infant, juvenile, or adult) may influence the timing of development (38, 42) but do not seem to be linked with adult body size.

Walker et al. (3) propose that Pygmies (as well as Negritos and Hiwi) have a faster growth rate and that this is related to high juvenile mortality. Our results suggest, on the contrary, a low infant mortality and a high proportion of survival to maturity which agree with slow growth in the Baka (11). This difference in results certainly comes from the methodology and data samples, as these authors recognize (3). Based on cross-sectional data, Walker et al. assume a linear growth rate from 3–10 y of age, suggesting that this is one of the best measures for comparisons across societies, although the assumption of linear growth in humans is much criticized (43, 44). Furthermore, sample size is limited to a few individuals with considerable uncertainty as to their estimated age, and the 0.78 probability value for survival to maturity for the Eastern Pygmies is disregarded (32). High-quality data (longitudinal data based on many individuals whose ages are known from birth to adulthood) are needed for an appropriate assessment of life-history variation in human populations.

Table 4. ASFR by year

Age, y	2007	2008	2009	2010	2011	2012	2013	2014	2015	X 1°P	X 2°P
15–19	1.00	0.53	0.39	0.28	0.12	0.24	0.19	0.21	0.30	0.55	0.21
	4/4	*8/15*	*7/18*	*8/29*	*3/26*	*9/37*	*5/26*	*6/28*	*8/27*		
20–24	0.26	0.65	0.47	0.42	0.30	0.26	0.22	0.27	0.24	0.45	0.26
	6/23	*11/17*	*15/32*	*10/24*	*7/23*	*7/27*	*4/18*	*8/30*	*7/29*		
25–29	0.23	0.32	0.17	0.22	0.22	0.25	0.18	0.29	0.16	0.23	0.22
	5/22	*7/22*	*6/35*	*8/37*	*8/36*	*8/32*	*5/28*	*9/31*	*5/31*		
30–34	0.08	0.25	0.30	0.17	0.29	0.22	0.12	0.23	0.19	0.20	0.21
	1/13	*5/20*	*6/20*	*4/23*	*6/21*	*6/27*	*3/26*	*7/30*	*5/26*		
35–39	0.00	0.27	0.18	0.22	0.06	0.07	0.11	0.20	0.11	0.17	0.11
	0/11	*4/15*	*4/22*	*4/18*	*1/16*	*1/14*	*2/19*	*4/20*	*2/19*		
40–44	0.00	0.10	0.08	0.17	0.06	0.12	0.11	0.05	0.11	0.09	0.09
	0/8	*1/10*	*1/12*	*2/12*	*1/16*	*2/17*	*2/18*	*1/22*	*2/18*		
45–49	0.08	0.09	0.05	0.07	0.00	0.00	0.00	0.00	0.00	0.07	0.00
	1/13	*1/11*	*1/19*	*1/14*	*0/8*	*0/12*	*0/10*	*0/8*	*0/10*		
>50	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.06	0.00	0.01
	0/1	*0/3*	*0/5*	*0/10*	*0/11*	*0/14*	*0/10*	*0/20*	*1/17*		

Ratios in italics show number of births/number of women. X 1°P, average for the first period; X 2°P, average for the second period.

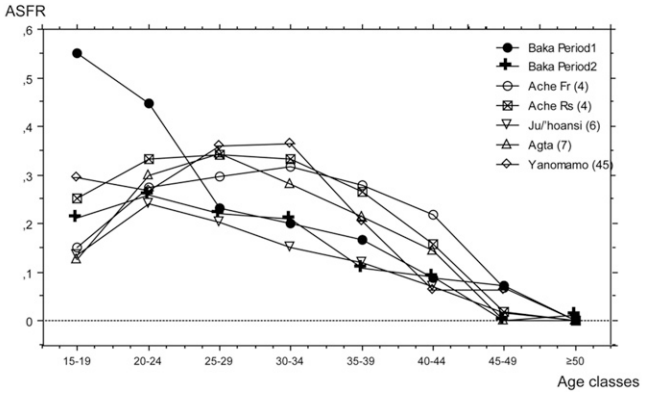

Fig. 3. Pattern of the ASFR in the Baka compared with other hunter-gatherer societies. In contrast to ASFR variations in other forager societies, for which the curve is bell-shaped, the highest values for the Baka are found in the lower age classes, producing a particular pattern of reproduction. Fr, forest; Rs, reserve.

Low infant and juvenile mortality rates in the Baka contrast with fertility aspects, as shown by the ASFR and the short IBI. The pattern of shifting ASFR shown by the Baka, with high values in the lower age classes and lower values in the higher age classes, suggests that the main reproductive period for Baka women is between 15 and 29 y of age. The age of menopause at around 42 y is close to the ages reported by Goodman et al. (43.9 y) (45) and by Early and Headland for the Agta (early 40s) (7) (Table 1). Therefore, the age of reproductive senescence in the Baka is not a constraint that induces a high rate of reproduction in the lower age classes. Furthermore, the Baka have an average IBI of approximately 33 mo (2.77 y), which is shorter than the IBI for the Aché, Batek, Inuit, Ju/'hoansi, and Pumé from savannah areas (4, 6, 11, 33, 46, 47) but not the Batak (48), Agta (7), and the Pumé from the river (33). It is well known that cooperative childrearing benefits mothers by redistributing the energy cost of raising offspring, which allows shorter birth intervals, higher maternal fertility, or increased infant survival (49). In the geographically and genetically closely related Aka pygmies, Meehan (50, 51) has quantified the parental and alloparental assistance a mother receives during the period of bride service (approximately 1 y). Fathers and grandmothers provide the second and third highest frequency of direct care to infants, but unlike the father's presence, which increases the mother's energy expenditure by increasing her work, a grandmother's presence is a substitute for maternal care and allows the mother to invest energy in other activities, including those that increase maternal reproductive success. Another Pygmy group, the Efé from the Ituri forest, have a child-rearing system in which infants receive a remarkably high level of parental and alloparental assistance (52). Childcare is mainly provided by nonreproductive women and is characterized primarily by intermittent play and physical contact, whereas mothers invest in more demanding forms of care and economic tasks. Interestingly, mothers are also relieved of competing childcare demands and can engage in subsistence activities from which children and others benefit (52); the help received by mothers seems to translate into infant survival and not into fertility. It is possible that the Baka share a high level of parental and alloparental assistance in childrearing with the Aka and the Efé. The high rate of reproduction in the lower age classes, the short IBI, and the low infant mortality rate might be favored by the help that other adult individuals are able to provide to young mothers by caring for newborns and infants or sharing resources. However, unlike the Aka and the Efé, Baka mothers can probably engage more time and energy in increasing reproductive success, which would explain why the Baka have the lowest IBI (Table 1). If parental and alloparental investment in the Baka is confirmed by empirical data, it is worth noting that such a childrearing system would not be exclusively associated with fast growth, as has been suggested for the Pumé (34) and speculated for the Aka and Efé (3).

It is worth noting that if the mother dies when the infant is younger than 1 or 1.5 y of age, no one replaces the mother in caring for the child, not even members of the family, including the child's father. Even if a close member of the family is breastfeeding, she does not invest in the survival of the orphaned baby. As a result, this infant dies a few months after its mother (*SI Appendix*, Fig. S1).

From 2007 to 2010 (period 1), the ASFRs in the lower age classes were higher than those observed in any of the other hunter-gatherer societies, but they dropped from 2011–2015 (period 2), resulting in a 37% reduction in the TFR. This drop in fertility in the lower age classes during period 2 is also observed in the results concerning infant mortality per woman by parity (Table 6), because the mothers with one infant in period 1 were 19 y of age or less, whereas in period 2 five of the six mothers were at least 21 y of age. Several studies on forager societies made at intervals over a long period have enabled us to observe various changes in LHVs that can be related to new living conditions (4, 7). Hill and Hurtado (4) reported a lower age at menarche and at first reproduction for the Aché when they settled in a reserve, developing a horticulturalist economy and reducing hunting treks in the forest. They also showed that ASFR increased in the lower age classes but decreased later, producing a minimal increase in the TFR in the reserve. Many factors can lead to a change in the fertility rate of a population. Physiological causes can alter fertility as a result of reproductive failure or reduced fecundity. Various social or environmental constraints, such as migration, war, work stress, epidemics, and starvation, can reduce access to mating or increase the energy cost of childbearing.

A change in the frequency of miscarriages or in the IBI may lead to a change in the fertility rate. However, even if they are associated with fertility, they do not explain the underlying cause of the change in fertility. The number of miscarriages was higher in period 1 (2007–2010) than in period 2 (2011–2015) (Table 6). Tables 6 and 7 show that infant mortality was higher in period 2. Higher infant mortality is associated with a shorter IBI (14). However, in the Baka, neither the IBI nor infant weight in first 2 mo of life differed between the two periods. The number of miscarriages, the IBI, and weight in early infancy are not associated with the drop in fertility during period 2. It would be expected that the drop in fertility during period 2 would be associated with a drop in mortality (12, 14), but infant and juvenile mortality seems, on the contrary, to have increased during this period compared with the previous one.

From the foundation of Le Bosquet in 1977 until our first field study in 2007, and during the 11 y of our regular visits to Le Bosquet, there is no record of epidemics, mass mortality, or starvation (a word that does not exist in the Baka language). There was no demographic change: The population of Baka at Le Bosquet has remained at around 800 individuals since the

Table 5. Mortality in Le Bosquet

Data	2007	2008	2009	2010	2011	2012	2013	2014	2015
No. births	17	38	38	37	25	33	22	35	30
No. infant deaths					1	2		3	
No. child deaths		1		2			3	2	1
No. out	3	10	6	6	4	3	5	3	6

No. out: number of individuals not met again and whose status is not known.

Table 6. Infant mortality per woman by parity

	Parity			
Infant deaths	1 (%)	2 (%)	3 (%)	4 (%)
2010 (n = 32)				
0	12 (100)	8 (80)	7 (78)	1
1		2 (20)	2 (22)	
2+				
Miscarriage	3	3	4	
Abortion				
2014 (n = 24)				
0	3 (50)	12 (92)	4 (80)	
1	3 (50)	1 (8)	1 (20)	
2+				
Miscarriage		3		
Abortion		1		

1970s. The Baka have no access to clinics, and vaccination programs are random. Basic health care and education are provided by the health center and the school established by the nuns in the 1970s. A drop in fertility is sometimes associated with parental investment in child skills, and investment in education is a particularly favored option in transitional conditions. Records of school attendance in Le Bosquet are scattered over the years, but they show 131 enrolments in 1989–1990, 125 in 2010–2011, and 129 in 2015–2016. Analysis of school attendance has not revealed any change in parental investment from period 1 to period 2 (*SI Appendix*, *Text S3*).

One change in the lives of the Baka relates to logging, both legal and illegal. Both activities obey the same dynamic, advancing along forest tracks to fell only well identified trees and moving on when all of these have been cut. Legal and illegal logging companies employ local villagers, preferably the Baka since they know the forest very well and can penetrate deep into the interior. The villagers do not move on with the employers: They are not welcome in neighboring villages because they would deprive local people of work. Legal timber felling ended in the Le Bosquet area at the end of 2006 and moved away in 2007, and illegal logging with chainsaws that could be dismantled for easy transport was present at Le Bosquet during 2010 and 2011. In 2012, illegal logging moved away to the east. The impact of legal and illegal logging therefore has been irregular and limited in time.

One major event occurred in the last month of 2010, when cheap alcohol arrived in the community. Local wine and beer were already consumed by the Baka: A bottle of palm wine cost 500 Central African francs (CFA) (€0.75; $0.87), and beer cost around 800 CFA (€1.20; $1.40). Salaried employment is very uncommon among the Baka, but when available the daily wage for working in a plantation is 300 CFA (€0.45; $0.52). The high cost of these alcoholic beverages thus prevented widespread consumption on a daily basis. In 2010, a bar was set up within the confines of Le Bosquet with cheap alcohol sold in plastic bags as the main commodity, costing 50 or 100 CFA (€0.07–0.15; $0.08–0.17) per bag, a lower price than that of any other consumer product and corresponding to the lowest value coins in the country. Although very little money circulates among the Baka, occasional work in plantations, for illegal loggers and for nuns or researchers produces some monetary income for the Baka community, which they mainly use to buy alcohol (53). From the end of 2010, consumption of these newly introduced alcoholic drinks, called "*nofia*" locally and "*whisky*" in general, became widespread among individuals of all ages: Even infants were picking up the bags from the floor, opening them, and sucking on them. Although this is anecdotal evidence, as we have no data on the frequency of such behavior, we observed it several times (ref. 53, minute 25:22). During each field season, the first comments from our Baka collaborators were always about people who had died in Le Bosquet since our last visit. Never previously mentioned as such, alcohol poisoning has become one of the main causes of death since 2011. The chemical composition of *nofia* has never been studied in detail, but it is a mixture of ethanol and methanol whose main purpose is to make people drunk as quickly as possible. Government authorities have recognized that these drinks are causing major disorders of the nervous system, cancers, and death, even when consumed in small quantities. Their production has been banned, but traders are still allowed to sell them until current stocks are exhausted (54–56).

The impacts of alcohol in encounters between different cultures have been widely analyzed (e.g., ref. 57). The effects of drinking alcohol are determined largely by the rate at which it and its main by-products are metabolized after consumption. It is well established that the main metabolic pathway for ethanol involves a variety of enzymes and that their presence and proportions vary among populations (58). It is also well established that the consumption of alcohol has a direct impact on reproduction by increasing the risk of infertility in women or altering semen quantity or quality (59–61), even in people with a low level of alcohol intake (e.g., ref. 62). At Le Bosquet, the consumption of cheap alcohol that

Table 7. Juvenile mortality in the Baka

						% reaching age 15 y	
Sex	Year	No. births recorded	No. reaching age 15 y	Dead	Out	Minimum	Maximum
Males	1996	15	9	2	4	60	82
	1997	8	7		1	88	100
	1998	17	9		8	53	100
	1999	19	14		5	74	100
	2000	19	10	2	7	53	83
	2001	28	21	2	5	75	91
		106	70	6	30	66	92
Females	1996	26	17	1	8	65	94
	1997	17	10	1	6	59	91
	1998	10	7		3	70	100
	1999	20	12	3	5	60	80
	2000	20	16	1	3	80	94
	2001	13	8		5	62	100
		106	70	6	30	66	92
Total		212	140	12	60	66	92

began in the last month of 2010 has continued until now. It is not a one-off phenomenon whose effects would dissipate over time: Its arrival changed the behavior of people at Le Bosquet because buying alcohol has become one of the main motivations for taking on any kind of work to earn cash. Alcohol has also shifted the center of activities in Le Bosquet. For years, the Catholic Mission was the main place where people converged to discuss matters concerning the village. Since 2010, the main place has become the bar, where people meet at any time and talk while drinking. It is difficult not to infer a direct link between the arrival and mass consumption of cheap alcohol and the drop in the TFR in the Baka.

During a meeting with Baka women, we asked them if they had noticed any change in fertility over time and, if so, whether they had any idea about its cause. They said that there probably was a change in fertility due to living close to the road. This implied a need to give more care to children, mainly by giving more attention to clean clothes: Having more children implies having more resources, which they do not have, to pay for clean clothes for themselves and the children. Asked about how they could control the number of children, they said they could reduce the number of times they have intercourse. We then asked about the alcohol. After a great many exclamations, they said that the arrival of alcohol had affected everybody, even the children who would rush to buy some when they obtained a coin. About the possible link between fertility reduction and alcohol, they said that alcohol was now very cheap and consumption was massive. They said that men coming back from the field spend a few coins on alcohol before going home and arriving there drunk, and that the women refused to have sexual relations when the men are in this condition. This situation persists during the entire period of wage labor, which can last from a few days to several weeks. The women then added that this situation was mainly affecting young mothers who, even if intercourse is easier now than before, took longer to become pregnant. They thought that young mothers were probably more affected than older ones because they had been drinking alcohol since they were young.

It is very interesting to note that these Baka women have realized that fertility in younger women has become more problematic. The lower age classes are the most important in the reproductive cycle of the Baka and make the largest contribution to the TFR. Reproduction in the lower age classes is the most distinctive aspect in the Baka and probably reflects a particular adaptation that we cannot elucidate at the moment. Surprisingly, these are the age classes most affected by the drop in fertility. There is no record of any major and enduring change in Le Bosquet, except for the arrival of cheap alcohol at the end of 2010, which coincides with the drop in fertility in the Baka. Alcohol consumption could thus be the main reason for the drop in fertility in the younger age classes. Our results provide clear, first-hand evidence of the damaging effects on fertility produced by alcohol in a hunter-gatherer society. Downward trends in TFR such as those seen in the Baka will have the long-term impact of reducing the number of Baka individuals.

Materials and Methods

The data presented in this article were obtained over 11 y from 2007–2017. At least one field study was conducted each year in May–June, and a second field study in October was added from 2011–2015. Informed consent was obtained from all participants and from both parents of any participants aged under 18. This study obtained approval of the Centre National de la Recherche Scientifique, Agence National de la Recherche (France) and Institut de Recherche et Développement and was carried out as part of the international agreement between the L'Institut de Recherche pour le Développement (IRD) and the Ministry of Scientific Research and Technology of Cameroon. Only individuals whose age was known or could be estimated accurately were included in the study. Thanks to Dhellemmes' records, the age of some women more than 25 y old is known to within a year. By combining census and birth records with our questionnaires, we were able to establish the first birth and the total number of infants for each woman very accurately. The modal IBI in the Baka is 2.5 y (11), and we worked on this assumption for children for whom we had no birth record. Similarly, since 18 y is the average age for the first delivery (11), this was the age assumed for the mothers at first birth. For instance, if we knew that the first record of the birth of a sibling was for the third infant, we assumed that the first infant was born 5 y earlier (two IBIs of 2.5 y each) and that the mother was 18 y old at the first birth. We are aware that this procedure introduces some bias, but when it was applied to mothers and infants whose real chronology was known, the differences were never greater than 2 y. The bias therefore has a minimal impact, if any, on the distribution into 5-y age classes. Many analyses were performed in this study, and the sample size varies from one to another (*SI Appendix*, Table S2).

Timing of Reproduction and Family Size. To obtain these variables, only 16 women whose birth records were available were included in the analysis. These were women born between 1952 and 1970. The majority had already begun their reproductive life when systematic recordkeeping started at Le Bosquet in 1988, except for two whose first baby was born during the earlier period when records had been kept. The birth dates were recorded, and full personal histories detailing the numbers of live births, stillbirths, and miscarriages were established by questionnaires. Among the women whose reproductive history is fully recorded ($n = 16$), one woman had only one child, which is very rare among the Baka; she was not included in the calculation of the average completed family size. The reproductive period was obtained by subtracting the mother's age at the first birth from her age at the last birth. For these women, the last birth had occurred several years previously, which implied that their reproductive life was over. An estimated age at menopause is suggested, which we obtained by averaging the ages at last birth of the 15 women. The full family history is also known for many other women, but it was not certain that their reproductive life was already over.

TFR and ASFR. The TFR and ASFR were obtained every year from 2007–2015. For each year, the number of births was taken from the records in the medical center, and we used questionnaires to establish the number of women present at Le Bosquet (Table 2).

It is important to emphasize that the ASFR does not mean the same thing to all authors (*SI Appendix, Text S4*). In our study, as in Hill and Hurtado (4) and Howell (6), the ASFR is the number of women in a 5-y age group who gave birth during a given year, divided by the total number of women in that age group; the TFR corresponds to the sum of all ASFRs multiplied by 5.

Since two periods can be distinguished, one from 2007–2010, and the other from 2011–2015, the ASFR and the TFR were compared using the Mann–Whitney *u* test (SPSS) to establish the significance of any changes. The same test was used to observe whether the TFR values are related to changes in the number of women or in the number of births.

The ASFR and TFR for the Baka were compared with those for other hunter-gatherer populations with a low average adult stature: the Agta, Yanomamo, Ju/'hoansi, and Aché. The ASFR values for the Yanomamo are those reported by Melancon (28) and used by Hill and Hurtado (4); for the TFR we used Neel and Weiss' (27) results, which we multiplied by 2.05. Hill and Hurtado (ref. 4, p. 255) provided the basis for choosing Melancon's study for the ASFR by pointing out problems in previous studies. They do not reject a variation in ASFR among Yanomamo populations (see variation in the Baka), but none has been accurately observed to date.

Infant and Juvenile Mortality. The infant mortality rate (the percentage of children who die within the first year of life) and the juvenile (or child) mortality rate (the percentage of children who die within the first 15 y of life) were obtained for the Baka. Their seminomadic lifestyle makes it difficult to measure mortality: Families move at any time of the year, and whether an infant or child has died can be established only when the family is found again at a later date. To estimate the infant mortality rate, we recorded, for each year from 2007–2015, the number of births, the number of infant deaths during the first year of life, the number of infants who survived beyond the first year of life (we know this because we met them), and the number of infants who moved away from Le Bosquet and whom we never met again.

Deliveries take place in private at home, so it was not possible to obtain birth weights, but many mothers go to the health center a few days later to declare the birth and have the baby weighed. Infant weight is monitored by the nuns for several months. We used these measurements to compare weight during the first 2 mo of life for infants born between 2008 and 2010 and between 2012 and 2014 to observe any differences in birth weight between period 1 (2007–2010) and period 2 (2011–2015). The Mann–Whitney *u* test (SPSS) was used to compare the significance of results.

To estimate infant mortality per woman by parity (33), we used the individual reproductive histories of 44 mothers between 15 and 25 y of age whose age at birth was recorded or well established because their deliveries were recorded. Some children were not declared at birth, but we were able to place them thanks to siblings whose age was known. Since fertility seems to change from 2011, suggesting the probability of two distinct periods, infant mortality per woman by parity was obtained in May 2010 for mothers born between June 1985 and May 1995 ($n = 32$) and in May 2014 for mothers born between June 1989 and May 1999 ($n = 24$). Mothers 15–21 y of age in 2010 are those who were 19–25 y of age in 2014. Miscarriages and abortions were also recorded. IBIs were obtained for both periods when exact chronological data for successive deliveries were available.

We estimated juvenile mortality for children who were born from 1996–2001 and had reached 15 y of age. Again, mobility prevented us from obtaining exact values because several families had moved away, and we did not know if their children were alive. When we never met the children and could not find out whether they were still alive, they are referred to as "out."

Deaths of young mothers can affect infant survival. We report here what happens with infants when the mother dies, but the number of such cases is very small among the Baka at Le Bosquet.

ACKNOWLEDGMENTS. We thank X. Garde, B. Bordage, and all the personnel of IRD Yaounde for logistical support; the nuns at the Le Bosquet mission for their kind hospitality; S. Pavard, S. Gallois, and two anonymous reviewers for helpful comments; A. Froment and L. Maget, my buddies in the field; and especially P. Kalo, J. B. Etoa, and other Baka collaborators for their help, assistance, and friendship. This study was supported by L. Di Giorgio (Dental Film), the CNRS, the IRD, Wenner–Gren Foundation Grant 7810, National Geographic Grant 8863-10, and the Agence Nationale de la Recherche Blanc SVSE7-2011 GrowinAP programme.

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4.3 Guide Photographique de Portions Alimentaires (GPPA)

Emmanuel Cohen (CR CNRS, équipe Biodémographie humaine)

Avec le phénomène d'urbanisation mondialisée, favorisant une pandémie d'obésité sans précédent, l'étude des régimes alimentaires et modes de consommation adoptés par les populations devient un enjeu crucial. De ce fait, de nombreuses méthodes d'évaluation de l'alimentation ont été développées durant les dernières décennies, même si elles se basent majoritairement sur le déclaratif des enquêtés, alors même que seule la caractérisation des ingérés alimentaires donne une représentation objective de la consommation. Néanmoins, l'évaluation objective de l'alimentation n'est pas applicable pour des enquêtes quantitatives à grandes échelles devenues indispensables pour comprendre les dynamiques de la transition nutritionnelle obésogène engendrée par l'urbanisation.

Les manuels photographiques de portions alimentaires constituent des compromis entre la rigueur de l'évaluation et la portée de celle-ci sur le terrain. Ils se basent en effet sur le déclaratif des enquêtés devant se prononcer sur des portions alimentaires consommées durant les dernières 24 heures (Rappel 24heures) donnant une approximation fiable des ingérés alimentaires, contrairement à d'autres méthodes comme le questionnaire de fréquence alimentaire. Dans cette perspective, de nombreux manuels photographiques de portions alimentaires ont été réalisés dans différents pays comme le Mozambique (« Food photographs in portion size estimation » 2013) ou le Sri-Lanka (« The Food Atlas » 2017), ou encore dans les Balkans (« The food atlas for portion size estimation » 2018), pour mener des enquêtes nutritionnelles quantitatives fiables.

Le Cameroun étant largement frappé par la pandémie d'obésité, Emmanuel Cohen (équipe Biodémographie humaine) a construit dans le cadre du projet ANR ANTRAC (Anthropologie nutritionnelle des migrants d'Afrique centrale à la ville et en France), en partenariat avec le Centre de Recherche en Alimentation et Sécurité Alimentaire (CRASAN), et avec l'appui du Ministère de la Santé camerounais, le Guide Photographique de Portions Alimentaires (GPPA) pour adultes et enfants (publié en 2020). Le GPPA a ainsi été créé et validé pour évaluer la consommation alimentaire des Camerounais afin de mesurer ses changements et ses effets sur leur santé nutritionnelle dans un contexte de développement rapide de l'obésité avec l'urbanisation intensive du pays (Figure 1).

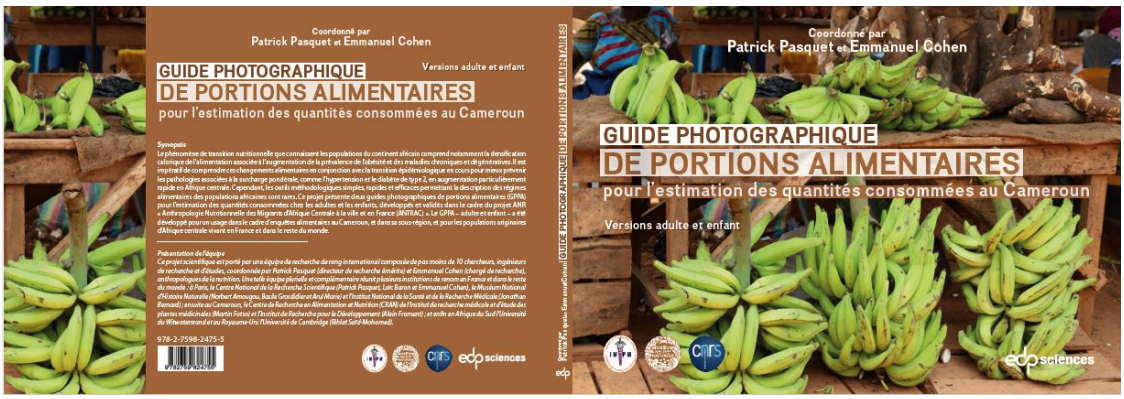

Figure 1 : Le GPPA

Cet outil scientifique a donc une visée méthodologique permettant aux spécialistes en nutrition (médecins, chargés d'étude, etc.), dans le cadre de leurs enquêtes nutritionnelles, d'évaluer la consommation alimentaire des Camerounais.

Par ailleurs, puisqu'il est d'intérêt public en matière de santé que la population camerounaise puisse elle-même évaluer en accès libre son alimentation afin de mieux prévenir les maladies cardiométaboliques associées à l'obésité, une version en ligne du GPPA a été réalisée en 2021 pour répondre à ce besoin (Figure 2). Le GPPA en ligne a été réalisé sur le modèle des programmes d'évaluation alimentaires réalisés préalablement au Royaume-Uni : Intake24 (2014) et MyFood24 (2015). Il est en cours de validation dans le cadre d'une étude de terrain à Yaoundé depuis 2022.

Figure 2 : Le GPPA en ligne

Le GPPA version papier comme sa version en ligne ont été réalisés en collaboration étroite avec les institutions camerounaises : l'Institut de Recherches Médicales et d'Etudes des Plantes Médicinales (dont le CRASAN) et le Ministère de la Santé, car ce sont des outils d'intérêt public pour l'amélioration de la santé de la population.