HHS Public Access

Author manuscript

Cold Spring Harb Perspect Med. Author manuscript; available in PMC 2016 December 04.

Published in final edited form as:

Cold Spring Harb Perspect Med. ; 6(1): . doi:10.1101/cshperspect.a025098.

Dissecting the Mechanisms Underlying Unusually Successful Human Healthspan and Lifespan

Sofiya Milman[1,2] and **Nir Barzilai**[1,2,3]

[1]Department of Medicine, Division of Endocrinology, Albert Einstein College of Medicine, Bronx, NY 10461.

[2]Institute for Aging Research, Albert Einstein College of Medicine, Bronx, NY 10461.

[3]Department of Genetics; Albert Einstein College of Medicine, Bronx, NY 10461.

Abstract

Humans age at different rates and families with exceptional survival provide the opportunity to understand why some people age slower than others. Unique features exhibited by centenarians include a family history of longevity, compression of morbidity with resultant extension of healthspan, and biomarkers such as low circulating insulin-like growth factor-1 (IGF-1) and elevated high-density lipoprotein (HDL) cholesterol levels. Given the rarity of the centenarian phenotype, it has not been surprising that the use of discovery methods that relied on common population single nucleotide polymorphisms (SNPs) to unlock the genetic determinants of exceptional longevity have not yielded significant results. Conversely, gene sequencing has resulted in discoveries of functional gene variants that support several of the centenarian phenotypes. These discoveries have led to the strategic developments of drugs that my delay aging and prolong healthspan.

Introduction

1. The rationale for studying human exceptional longevity

The Unites States government annually publishes a report on the rate of death from individual diseases, stratified by age groups. What's striking about these reports is that the rate of death increases logarithmically with advancing age for all diseases associated with aging, including heart disease, cancer, stroke, diabetes mellitus type 2 (T2DM), and Alzheimer's disease (Figure 1). This demonstrates that aging is a major risk factor that all these age-related diseases have in common. To put these statistics in perspective, elevated low-density lipoprotein (LDL) cholesterol level, which is one of the best known and aggressively treated risk factors for heart disease, which is the most common cause of death among older adults, is associated with a three-fold increase in the risk for heart disease. However, advancing the age from 30 years to 80 years raises the rate of death from each of the age-related disease by as much as 100 to 1,000 fold. If we accept the notion that aging is

Corresponding Author: Nir Barzilai M.D., The Rennert Chair of Aging Research, Director of The Institute for Aging Research, Albert Einstein College of Medicine, 1300 Morris Park Ave, Belfer Bld #701, Bronx NY 10461, Tel: 718-430-3144, Fax: 718-430-8557, nir.barzilai@einstein.yu.edu.

the common and major risk factor for all age related diseases then we conclude that unless aging itself is delayed, our best attempts at preventing each disease individually will result in exchanging one disease for another. The return for curing individual diseases is small. For example, statistical models project that delaying cancer would result in an increase of only 0.8% in the population of older adults over a 50 year period, whereas delaying aging would lead to an increase of about 7% in the population, with most of theses individuals being free of disability (Goldman et al. 2013). Furthermore, this delay in aging would yield approximately $7.1 trillion in social benefit to the population (Goldman et al. 2013).

When thinking about aging, it is important to recognize that chronological and biological age are not the same. It is well recognized by all that some individuals appear younger than their chronological age, whereas others appear older. This observation highlights an opportunity for scientific discovery that until recently has been missed, that is to try to understand the biology of why some age faster while others age slower. At one extreme of the spectrum of the rate of aging are rare segmental progeroid syndromes that are thought to accelerate various aging phenotypes. The responsible gene mutations have suggested genomic instability as an important mechanism of aging (Martin 2005). More recently, scientists have become interested in studying people with exceptional longevity, which are located at the other end of the rate of aging spectrum, in an effort to discover the genetic and biological determinants of delayed aging.

Centenarians are a unique group of individuals that constitute an example of delayed aging. This delay in aging can only be accomplished if it results in the extension of disease-free survival and indeed this appears to be the case in many centenarians. Analyses from the New England Centenarian Study (Andersen et al. 2012), the Long Life Family Study (Sebastiani et al. 2013) and the Longevity Genes Program (Ismail K 2014) have provided evidence that individuals with exceptional longevity manifest compression of morbidity, meaning that they spend a smaller percentage of their life being ill, and as a result their health span approximates their lifespan. These studies revealed significant delay in the ages of onset for most age-related diseases among individuals with exceptional longevity, including hypertension, cardiovascular disease, cancer, T2DM, stroke, osteoporosis, and Alzheimer's disease. Thus, not only do centenarians live longer, they live healthier. Although a large proportion of centenarians delay or escape from age-related diseases altogether (Evans et al. 2014), a number of individuals achieve exceptional longevity despite having developed one or several of these diseases (Andersen et al. 2012; Ailshire et al. 2015). This suggests that these people likely possess protective factors that allow them to be resilient and survive in spite of health ailments.

The inherent differences between chronological and biological age, and between the diverse rates of aging, offer scientists opportunities to study the variations in the biology and genetics among these different groups. As exemplified in other chapters of this book, several mechanisms have already been identified that can delay aging in a variety of animal models. Investigating whether these same mechanisms apply to humans with exceptional longevity serves to validate these discoveries as important for human aging. Furthermore, studies are underway for discovery of age-delaying mechanisms that are specific to humans by using centenarian populations. The rationale for studying centenarians is that they are the “poster

children" for what we are ultimately trying to achieve-extension of healthspan and not merely lifespan.

2. The evidence that longevity is inherited

Demographers and epidemiologists have attributed ~15–30% of the variation in lifespan to heritable factors. Several studies have found positive correlations between the lifespans of the parents and their biological children (Atzmon et al. 2004; Schoenmaker et al. 2006; Westendorp et al. 2009). However, the advances of modern medicine that include preventive measures and treatments, have extended the lifespans of the newer generations beyond what would have been predicted based on their inheritance. Thus, offspring whose parents died from cardiovascular disease resulting from hereditary hyperlipidemia, can now enjoy an extension of their lifespan through treatment with cholesterol lowering medications and interventions such as coronary artery bypass graft surgery or revascularization of coronary arteries with angioplasty. Despite these significant medical advances, achievement of exceptional longevity remains a rare occurrence. Yet, in spite of its rarity, exceptional longevity clusters in families, pointing to a strong relationship between genetics and longevity.

Data suggests that the offspring of parents who achieved a lifespan of at least 70 years have a much greater probability of living longer compared to the offspring of parents with shorter lifespans, with this association becoming stronger as the parental lifespan lengthens (Gavrilov et al. 2001). This relationship is even more pronounced in families with exceptional longevity. Siblings of centenarians have been shown to be approximately 4–5 times more likely to achieve longevity, with male siblings being 17 times more likely to become centenarians themselves (Perls et al. 1998; Perls et al. 2002). The parents of centenarians were found to be seven times more likely to have survived to age 90 and beyond, compared to parents of those with usual lifespan (Atzmon et al. 2004). Even if genetics account for smaller differences observed in the rate of aging, identification of these genes is important for planning strategies that can delay the aging process. Furthermore, since exceptional longevity is heritable, studying the families of centenarians to identify genetic determinants of exceptional longevity offers great promise for discovery.

Familial longevity is likely mediated through protection from age-related disease, which is inherited by the offspring from their parents. Centenarians and their offspring have a lower prevalence and later age of onset of heart disease, stroke, hypertension, T2DM, Alzheimer's disease, and cancer (Anderson et al. 1991; Atzmon et al. 2004; Adams et al. 2008; Lipton et al. 2010; Altmann-Schneider et al. 2012). This heritable protection from disease has also been demonstrated in several large studies. A prospective population based study found that the incidence of Alzheimer's disease was 43% lower in offspring of parents with exceptional longevity compared to offspring of parents with more usual lifespans over a 23 year follow-up (Lipton et al. 2010). A similar association was also found in a study conducted in a population whose parents achieved more modest longevity. In a secondary analysis of the Diabetes Prevention Program (DPP), a large clinical trial designed to compare strategies for T2DM prevention in individuals at high risk for T2DM, parental longevity was associated with a delay in the incidence of T2DM of the offspring, with the children of parents with

longest lifespans experiencing the greatest delay in disease onset (Florez et al. 2011). The effect of parental lifespan on diabetes prevention was found to be just as strong as the effect of metformin, an anti-diabetic drug used in this study (Florez et al. 2011). These results demonstrate that extended parental lifespan is strongly associated with better health outcomes in the offspring, even in populations who achieve less extreme degrees of longevity.

Although environmental influences may have a significant effect on health and lifespan in the general population, this does not seem to be the case in centenarians. A study that compared individuals with exceptional longevity to their contemporaries who did not achieve longevity found that centenarians were as likely as their shorter-lived peers to have been overweight or obese (Rajpathak et al. 2011). Furthermore, the proportion of centenarians who smoked, consumed alcohol daily, had not participated in regular physical activity, or had not followed a low calorie diet throughout their middle age was similar to that among their peers from the same birth cohort. In fact, as many as 60% of male and 30% of female centenarians had been smokers (Rajpathak et al. 2011). Thus, the centenarians had not engaged in a healthier lifestyle compared to their peers. This supports the notion that people with exceptional longevity possess genomic factors that protect them from the environmental influences that may be detrimental to health.

3. Genetics of Exceptional Longevity

For over a decade, centenarian populations of diverse Americans, as well as, ethnically homogeneous populations of Mormons, Ashkenazi Jews, Icelandics, Okinawan Japanese, Italians, Irish and Dutch, among others, have served as cohorts for studies to identify longevity genes or longevity-associated biological pathways. These studies relied on candidate genes and genome-wide association study (GWAS) that included genotyping of large populations. One of the strengths of GWAS compared to the candidate gene approach is that these studies are un-biased. Their results may provide insights into novel mechanisms of longevity. Several research groups have conducted GWASs for longevity (Beekman et al. 2010; Sebastiani et al. 2012), yet none yielded significant results after appropriate statistical corrections for multiple comparisons were applied. One exception was the finding of the *APOE2* genotype, although its identification may have been the result of ascertainment bias, since individuals with the *APOE4* allele, who are at higher risk for developing Alzheimer's dementia, are less likely to be recruited into population studies (Nebel et al. 2011).

There are several explanations for these disappointing results. First, relying on common genetic variants that occur at frequencies between 5–49% in the population in order to study such a rare event as exceptional longevity (one that occurs at a rate of 1/6,000–1/10,000 in the general population) may result in missing the rarer longevity-associated genotypes. This also underscores the need for exon or whole genome sequencing in order to discover rare mutations. Second, applying GWAS to genetically diverse populations requires a very large study cohort in order to account for genomic diversity and to identify relatively rare genetic variants. Thus, most studies have lacked sufficient power for such discoveries.

Following this logic, it is not surprising that many important genetic discoveries were made in populations that exhibit comparatively small levels of genetic diversity. One such example is the Icelandic population, which originated from a small number of founders and expanded to ~500,000 people. Others include the Amish and Ashkenazi Jews (AJ), a larger population (Barzilai et al. 2003; Atzmon et al. 2008; Suh et al. 2008; Atzmon et al. 2009b; Atzmon et al. 2010). The advantage of studying a genetically homogeneous population was exemplified by a recent study which demonstrated that the addition of each Ashkenazi Jewish subject contributed 20 times more genetic variability to the cohort as compared to adding a European subject to a cohort of European origin of identical sample size (Carmi et al. 2014).

There are several ways in which genetically similar populations can contribute to genetic and biological discovery. One is if the population has a higher frequency of carriers of a particular genotype and its associated phenotype due to the founder effect, as is the case with breast cancer caused by mutations in the *BRCA* genes among Ashkenazi Jewish women. Another is that single nucleotide polymorphisms (SNPs) that are novel or rare in the general population will occur at higher frequencies in a homogenous population. This will result in the associated rare phenotype, such as longevity, to be more amenable to withstand the rigorous statistical analysis that is performed on genetic data. Third is that many SNPs that are statistically significant, but below the threshold for GWAS, may still be relevant. Lastly, it is possible that numerous SNPs contribute in combination to the phenotype. Indeed, Sebastiani et. al have identified 281 SNPs that can distinguish centenarians from controls (Sebastiani et al. 2012).

Although discovery of longevity-associated genes has been met with several challenges, many genes have been identified that are associated with risk for CVD, AD, T2DM and other age related diseases. One attractive hypothesis had been that centenarians lack these disease-associated genes; thus, being protected by a more “perfect genome”. However, it has become clear from GWAS studies that centenarians harbor as many disease-associated genotypes as controls. Furthermore, a whole genome sequence analysis of 44 centenarians revealed that this group carried a total of 227 autosomal and 7 X-chromosome coding single nucleotide variants (SNVs) that are likely to cause disease according to the ClinVar database (Freudenberg-Hua et al. 2014). Among these are variants associated with Parkinson’s disease, AD, neurodegenerative diseases, neoplastic, and cardiac diseases. Despite more than 95 years of exposure to these risky genotypes none of the centenarians exhibited any of the diseases for which they were genetic carriers. These observations lead to the conclusion that there are longevity-associated protective genotypes in centenarians that delay aging or specifically protect against the manifestation of age-related diseases.

Although the GWAS approach did not prove to be particularly helpful in identifying longevity genes, some success stories have emerged through the application of the candidate gene approach. Several genes were selected for investigation because they were previously implicated in aging and SNPs within these genes were suggested to be linked with longevity. These included *PON1* (Bonafe et al. 2002; Rea et al. 2004; Franceschi et al. 2005; Marchegiani et al. 2006; Tan et al. 2006), *IGF-1* (Bonafe et al. 2003; Kojima et al. 2004; van Heemst et al. 2005), *PAPR-1*, cytokine genes, genes that code for enzymatic

antioxidants such as superoxide dismutases (Andersen et al. 1998; Mecocci et al. 2000), and components of lipid metabolism (Barzilai et al. 2006; Vergani et al. 2006). Other genes that have been implicated in human aging, and not only longevity, are updated on http://genomics.senescence.info/genes/.

However, not all discoveries resulted in improved understanding of the biology of aging. One of the most notable discoveries of a longevity-associated gene, which has been validated by numerous research groups, is the FOXO3a genotype. As summarized by Kahn (Kahn 2014), the FOXO3a genotypes are rather common, the identified SNPs within the gene localize to intronic or non-coding regions, and despite sequencing of the whole gene by several groups, no functional mutations have thus far been identified in the regions of the gene that would predict altered protein function. Furthermore, assays of cells with the FOXO3a genotype variants also have not been, thus far, associated with functional changes. Finally, no identifiable phenotype has yet been linked with these FOXO3a genotypes and they have not been related to risk or protection from disease. In fact, a panel of experts did not agree on whether a drug that displaces FOXO3a from the nucleus to the cytoplasm would induce longevity or shorten the lifespan (Monsalve and Olmos 2011). The example of FOXO3a demonstrates that even a validated genotype does not always translate into better understanding of the biology of longevity.

There are also other challenges that face researchers studying longevity. In addition to the usual problems and pitfalls of association studies, particularly in the new age of ‘big data’ brought on by whole genome sequencing (Lawrence et al. 2005), there is another problem that is particular to longevity studies, that of identifying appropriate controls for a cohort of exceptionally long lived individuals. This has been a challenge because the ideal controls, individuals of the same birth cohort as the centenarians but who have not achieved exceptional longevity, are all deceased. One approach to overcome this challenge has been to rely on the innovative experimental design in which the progeny of centenarians, who have inherited about half of their genome from the centenarian parent, are compared to their spouses who do not have a parental history of longevity and thus can serve as matched controls (Barzilai et al. 2001).

4. Genomic discoveries and mechanisms for exceptional longevity

The Longevity Genes Project (LGP) and LonGenity are studies that include families of AJs with exceptional longevity. Since longevity carries a substantial genetic component, these studies conduct genomic and detailed phenotype analyses in the families with exceptional longevity in an effort to determine the functions of genes of interest. Using the candidate gene approach in this AJ cohort, several favorable homozygous genotypes were identified in multiple genes, which were associated with unique biological phenotypes.

The cholesterol ester transfer protein (*CETP*) gene codon 405 isoleucine to valine variant was associated with low levels of plasma CETP, high levels of HDL cholesterol and large lipoprotein particle size. This genotype was also shown to be protective against cognitive decline and AD in an independent diverse population (Sanders et al. 2010). This same genotype was validated by another research group in an Italian population (Vergani et al.

2006). Three other genotypes in the *CETP* gene were also found to be significantly associated with longevity in the Long Life Family Study (LLFS). Although none of the other studies have confirmed these findings, it is important to keep in mind that a particular SNP may not exhibit a similar phenotype in all populations. Therefore, the biological phenotype itself should be tested for association with longevity rather than a particular SNP that may have differential expression in varying populations. Further complicating matters is the possibility that the gene with the significant action may be in linkage disequilibrium with the SNP and that there may be genetic variations at that associated locus.

Another lipid-related genotype, homozygosity for the apolipoprotein C-3 (*APOC-3*) −641 C allele was also associated with exceptional longevity in AJs (Atzmon et al. 2006). It too exhibited a unique lipid phenotype and low levels of plasma APOC-3 (Atzmon et al. 2006). In a striking example of validation, carriers of a different *APOC3* genotype in a homogenous Pennsylvania Amish population also exhibited low APOC-3 levels, a favorable lipid phenotype, better arterial health score, and enhanced longevity (Pollin et al. 2008). These findings demonstrate the power of discovery in selected genetically homogeneous populations. The *APOC-3* genotype was also identified to be related to exceptional longevity in the LLFS but the phenotype associated with this SNP has not yet been revealed.

ADIPOQ is another longevity associated genotype. Adiponectin is a fat derived peptide with powerful effects on lipids and metabolism. A deletion at +2019 in the adiponectin (*ADIPOQ*) gene was associated in the AJ cohorts with longevity, which was also related to a phenotype of high adiponectin level, independent of fat mass (Atzmon et al. 2008).

A longevity-associated genotype whose discovery has already made an impact on clinical practice is that of the thyroid stimulating hormone receptor (*TSHR*) (Atzmon et al. 2009a; Atzmon et al. 2009b). The metabolic rate theory of aging suggests that in nature there exists an inverse relationship between basal metabolic rate and aging, with several hypothyroid mammalian models exhibiting longer lifespan. Centenarians have higher plasma TSH levels, although they are not hypothyroid, and their offspring also exhibit this phenotype with significant hereditability (Atzmon et al. 2009a; Rozing et al. 2010). These clinical features have been supported by a National Health and Nutrition Examination Survey (NHANES III) conducted across US and led to the recommendation to not supplement older adults with mild elevations in TSH with thyroid hormone (Tabatabaie and Surks 2013).

In nature, disruption of the growth hormone/insulin-like growth factor-1 (GH/IGF-1) action has led to extension of life-span. Spontaneous and experimentally induced partial disruptions of the GH/IGF-1 pathway, including genetic alterations, are associated with a small body size (dwarfism) across species (Brown-Borg et al. 1996). Thus, small dogs have longer lifespans than large dogs (Samaras and Elrick 2002). Models of IGF-1 deficiency demonstrate numerous indices of delayed aging, including enhanced stress resistance and a major increase in lifespan (Kenyon et al. 1993; Brown-Borg et al. 1996). On the other hand, reduced levels of IGF-1 in humans, while protective against cancer, have been linked with higher risk for cardiovascular disease and diabetes (Sandhu et al. 2002; Burgers et al. 2011), suggesting a more complex physiological role for IGF-1 in humans. Several SNPs in genes within the insulin/IGF-1 signaling pathway have been associated with and validated in

exceptional longevity, but for the most part no specific phenotype related to these SNPs has been identified (Pawlikowska et al. 2009). An exception to this has been the identification of a functional IGF-1 receptor (*IGF1R*) gene mutation discovered after sequencing the *IGF1* and *IGF1R* genes of centenarians (Suh et al. 2008). Heterozygous mutations in the *IGF1R* gene have been overrepresented among centenarians compared to the controls without familial longevity and have been associated with high serum IGF-1 level in the setting of reduced activity of the *IGF1R,* as measured in transformed lymphocytes (Tazearslan et al. 2011). Partial IGF-1 resistance conferred by these longevity-associated *IGF1R* genotypes was confirmed in a study conducted on wild-type cells transformed with the mutant genes (Tazearslan et al. 2011). A particular *IGF1R* genotype was also associated with longevity in the LLFS; however, its associated phenotype has not yet been defined.

Another example that highlights the importance of GH/IGF-1 signaling in extended healthspan comes from a population of Laron Dwarfs, who are carriers of a rare mutation in the GH receptor (*GHR*) gene that results in GHR deficiency. A group with this genotype was studied in Ecuador and appears to have a negligible prevalence of Type 2 diabetes mellitus and cancer (Guevara-Aguirre et al. 2011). Although they did not live long, clearly they have been protected from major age-related diseases.

Finally, among females with exceptional longevity, those with IGF-1 levels below the median exhibited significantly longer survival compared to those with levels above the median, (Figure 2) (Milman et al. 2014). However, this relationship between IGF-1 levels and survival was not observed in males with exceptional longevity. On the other hand, among males and females who achieved longevity and had a history of cancer, lower IGF-1 levels predicted longer survival (Milman et al. 2014). Thus, low IGF-1 levels predict life expectancy in exceptionally long-lived individuals, supporting the role of the GH/IGF-1 pathway in exceptional longevity.

Interest in telomeres and their association with aging led to significant research efforts aimed at identifying the role of telomere length in exceptional longevity. Telomere length or mass assessment showed that centenarians have longer telomeres, that this length is inherited in their offspring, and is associated with decreased incidence of the metabolic syndrome (MS), T2DM, and cognitive decline (Atzmon et al. 2010). This longevity-associated telomere phenotype has also been related to a genetic ‘fingerprint’ in the telomerase genes in centenarians (Atzmon et al. 2010).

Other genomic mechanisms, no doubt, also contribute to aging, including epigenomic variations. Sirtuins, resveratrol and other specific activators have been used to induce histone deacetylation and activation of the *SIRT1* gene, thereby resulting in longevity in a variety of animal models and in high-fat fed mice. However, no significant association between *SIRT1* genotypes and longevity have been reported in humans thus far (Han et al. 2014). Methylation patterns have been noted to change with aging and may affect the transcribed DNA. Initial studies have shown significant differences in methylation patterns between centenarians and younger controls, with several groups currently pursuing this line of research. Finally, longevity-associated microRNAs have been identified, but their effects still need to be determined (Gombar et al. 2012).

5. Exceptional longevity leading to age-delaying drugs

The goal of longevity research is to identify pathways that are relevant to human aging and to develop drugs that will delay aging by targeting these pathways. Longevity and extension of healthy lifespan have been achieved in models via a variety of genetic manipulations, drugs, and environmental influences, thereby providing the preclinical foundation needed to proceed to drug development. The main obstacle facing the development of drugs for the treatment of aging is the fact that the FDA does not consider aging as a preventable condition. Even if there would be a popular demand for drugs that delay aging, the pharmaceutical industry would not develop drugs that will not be reimbursed by health insurance companies. The same was true for hypertension, until studies demonstrated that lowering blood pressure prevented cardiovascular diseases (CVD), including strokes.

The pharmaceutical industry has relied on genetic discoveries made in longevity studies, as well as other studies, to identify individuals who have naturally occurring genetic variants or mutations that confer desirable phenotypes. The goals for pharmaceutical development is to create drugs whose actions would mimic those of the favorable genetic variants. Observing the carriers of these genetic variants for any detrimental health effects informs drug makers of any potential side effects that may arise from a drug that targets the desired pathway. For example, the observation that centenarians are enriched with a unique *CETP* genotype that exposes them to a life-time of lower CETP levels that is also associated with high HDL level and large lipoprotein particle size, suggests that decreased CETP function is safe (Barzilai et al. 2003). In fact, a CETP inhibitor is currently being tested in a phase 3 trial by a leading pharmaceutical company (Cannon et al. 2010). Similar observations were made about the APOC-3 protein and an APOC-3 inhibitor is also being tested in a phase 3 trial by another pharmaceutical company (Graham et al. 2013; Lee et al. 2013).

Another class of agents whose actions on aging may be predicted through longevity research are monoclonal antibodies directed against the IGF-1 receptor. These were initially developed by several pharmaceutical industries as anti-neoplastic therapies; however, they were not successful at treating cancer due a significant degree of mutagenesis within cancer cells that eventually made them resistant to these drugs. Nonetheless, these compounds are available for pre-clinical testing in aging research. Similarly, the GH/IGF-1 pathway, which may be important for human aging, can be targeted by the GH receptor antagonist that is currently in clinical use for the treatment of acromegaly, a condition of GH excess (Kopchick 2003). Although the above mentioned therapeutics are not presently being developed for longevity, these drugs may be tested in the future for the indication of delaying aging and age-associated diseases.

Other drugs may target aging more specifically, although they are in clinical use for other indications. One example is a class of drugs that inhibit the mammalian target of rapamycin (mTOR) enzyme. These drugs are primarily used as immune modulators post organ transplantation, but recently also have been shown to increase the immune response to vaccinations in the elderly (Mannick et al. 2014), thereby demonstrating their potential utility in the treatment of health conditions associated with aging.

Another drug of interest is metformin, the first line drug treatment for T2DM. Several research groups tested the effect of metformin on aging and demonstrated that it caused extension in lifespan and healthspan in many rodent models (Anisimov et al. 2008; Anisimov et al. 2010; Smith et al. 2010; Anisimov et al. 2011; Martin-Montalvo et al. 2013). Metformin also extended the lifespan of nematodes (Cabreiro et al. 2013), suggesting that its action is mediated via an evolutionary conserved mechanism. Numerous investigators looked at the potential anti-aging effects of this drug in populations treated with metformin for T2DM. The large United Kingdom Prospective Diabetes Study (UKPDS) convincingly demonstrated that metformin reduced the incidence of CVD (Holman et al. 2008; Anfossi et al. 2010). This finding has been validated and reproduced by other studies and meta analysis (Johnson et al. 2005; Lamanna et al. 2011; Roumie et al. 2012; Hong et al. 2013; Whittington et al. 2013). In addition, a number of studies suggested that metformin use is associated with a decreased incidence of cancer (Libby et al. 2009; Landman et al. 2010; Lee et al. 2011; Monami et al. 2011; Tseng 2012), with many animal and cell models demonstrating the inhibitory effects of metformin on tumorigenesis (Seibel et al. 2008; Tosca et al. 2010; Liu et al. 2011; Salani et al. 2012; Anisimov and Bartke 2013; Karnevi et al. 2013; Quinn et al. 2013). The proposed mechanisms of action for metformin's effect on inhibiting tumorigenesis include decrease in insulin production and its action, decrease in IGF-1 signaling, and AMPK activation.

In the future, other compounds discovered to be important for longevity may be developed into drugs. For example, the level of humanin, a mitochondrial derived peptide, decreases with aging but has been shown to be up to 3-fold increased in the offspring of centenarians (Muzumdar et al. 2009), thus making it an attractive candidate for drug development.

Concluding Remarks

This chapter demonstrates that via the use of biologic and genetic experimental methods scientists can determine why some people age more slowly or more rapidly than others. Such discoveries in humans, as opposed to those in other animal models, have the advantage of being directly relevant to human longevity and can be relied upon by pharmaceutical developers looking to establish the safety of drugs whose actions mimic the function of the genetic variants found in centenarians. Thus it follows that if functional mutations or SNPs that are more common in centenarians are also deemed safe in that population, then drugs that mimic the desired actions are worth developing. This kind of drug development should result in unique drugs that target not only specific diseases but also aging. The barrier for development of drugs that target aging is that at present aging is not an indication for treatment by the FDA. There is an urgent need to change this paradigm in order to accelerate drug development and realize the longevity dividend.

Acknowledgments

SM is supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number KL2TR001071. NB is supported by grants from the National Institutes of Health (P01AG021654), The Nathan Shock Center of Excellence for the Biology of Aging (P30AG038072, the Glenn Center for the Biology of Human Aging (Paul Glenn Foundation for Medical Research), NIH R37 AG18381 (Barzilai Merit Award), NIH/NIA 1 R01AG044829. The content is solely the responsibility of the authors and does not necessary represent the official views of the National Institutes of Health.

References

Centers for Disease Control and Prevention. http://www.cdc.gov/nchs/hus.htm

Adams ER, Nolan VG, Andersen SL, Perls TT, Terry DF. Centenarian offspring: start healthier and stay healthier. J Am Geriatr Soc. 2008; 56:2089–2092. [PubMed: 18811609]

Ailshire JA, Beltran-Sanchez H, Crimmins EM. Becoming centenarians: disease and functioning trajectories of older US Adults as they survive to 100. J Gerontol A Biol Sci Med Sci. 2015; 70:193–201. [PubMed: 25136001]

Altmann-Schneider I, van der Grond J, Slagboom PE, Westendorp RG, Maier AB, van Buchem MA, de Craen AJ. Lower Susceptibility to Cerebral Small Vessel Disease in Human Familial Longevity: The Leiden Longevity Study. Stroke. 2012

Andersen HR, Jeune B, Nybo H, Nielsen JB, Andersen-Ranberg K, Grandjean P. Low activity of superoxide dismutase and high activity of glutathione reductase in erythrocytes from centenarians. Age Ageing. 1998; 27:643–648. [PubMed: 12675104]

Andersen SL, Sebastiani P, Dworkis DA, Feldman L, Perls TT. Health span approximates life span among many supercentenarians: compression of morbidity at the approximate limit of life span. J Gerontol A Biol Sci Med Sci. 2012; 67:395–405. [PubMed: 22219514]

Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. Am Heart J. 1991; 121:293–298. [PubMed: 1985385]

Anfossi G, Russo I, Bonomo K, Trovati M. The cardiovascular effects of metformin: further reasons to consider an old drug as a cornerstone in the therapy of type 2 diabetes mellitus. Curr Vasc Pharmacol. 2010; 8:327–337. [PubMed: 19485923]

Anisimov VN, Bartke A. The key role of growth hormone-insulin-IGF-1 signaling in aging and cancer. Crit Rev Oncol Hematol. 2013; 87:201–223. [PubMed: 23434537]

Anisimov VN, Berstein LM, Egormin PA, Piskunova TS, Popovich IG, Zabezhinski MA, Tyndyk ML, Yurova MV, Kovalenko IG, Poroshina TE, et al. Metformin slows down aging and extends life span of female SHR mice. Cell Cycle. 2008; 7:2769–2773. [PubMed: 18728386]

Anisimov VN, Berstein LM, Popovich IG, Zabezhinski MA, Egormin PA, Piskunova TS, Semenchenko AV, Tyndyk ML, Yurova MN, Kovalenko IG, et al. If started early in life, metformin treatment increases life span and postpones tumors in female SHR mice. Aging (Albany NY). 2011; 3:148–157. [PubMed: 21386129]

Anisimov VN, Egormin PA, Piskunova TS, Popovich IG, Tyndyk ML, Yurova MN, Zabezhinski MA, Anikin IV, Karkach AS, Romanyukha AA. Metformin extends life span of HER-2/neu transgenic mice and in combination with melatonin inhibits growth of transplantable tumors in vivo. Cell Cycle. 2010; 9:188–197. [PubMed: 20016287]

Atzmon G, Barzilai N, Hollowell JG, Surks MI, Gabriely I. Extreme longevity is associated with increased serum thyrotropin. J Clin Endocrinol Metab. 2009a; 94:1251–1254. [PubMed: 19158193]

Atzmon G, Barzilai N, Surks MI, Gabriely I. Genetic predisposition to elevated serum thyrotropin is associated with exceptional longevity. J Clin Endocrinol Metab. 2009b; 94:4768–4775. [PubMed: 19837933]

Atzmon G, Cho M, Cawthon RM, Budagov T, Katz M, Yang X, Siegel G, Bergman A, Huffman DM, Schechter CB, et al. Evolution in health and medicine Sackler colloquium: Genetic variation in human telomerase is associated with telomere length in Ashkenazi centenarians. Proc Natl Acad Sci U S A. 2010; 107(Suppl 1):1710–1717. [PubMed: 19915151]

Atzmon G, Pollin TI, Crandall J, Tanner K, Schechter CB, Scherer PE, Rincon M, Siegel G, Katz M, Lipton RB, et al. Adiponectin levels and genotype: a potential regulator of life span in humans. J Gerontol A Biol Sci Med Sci. 2008; 63:447–453. [PubMed: 18511746]

Atzmon G, Rincon M, Schechter CB, Shuldiner AR, Lipton RB, Bergman A, Barzilai N. Lipoprotein genotype and conserved pathway for exceptional longevity in humans. PLoS Biol. 2006; 4:e113. [PubMed: 16602826]

Atzmon G, Schechter C, Greiner W, Davidson D, Rennert G, Barzilai N. Clinical phenotype of families with longevity. J Am Geriatr Soc. 2004; 52:274–277. [PubMed: 14728640]

Barzilai N, Atzmon G, Derby CA, Bauman JM, Lipton RB. A genotype of exceptional longevity is associated with preservation of cognitive function. Neurology. 2006; 67:2170–2175. [PubMed: 17190939]

Barzilai N, Atzmon G, Schechter C, Schaefer EJ, Cupples AL, Lipton R, Cheng S, Shuldiner AR. Unique lipoprotein phenotype and genotype associated with exceptional longevity. Jama. 2003; 290:2030–2040. [PubMed: 14559957]

Barzilai N, Gabriely I, Gabriely M, Iankowitz N, Sorkin JD. Offspring of centenarians have a favorable lipid profile. J Am Geriatr Soc. 2001; 49:76–79. [PubMed: 11207846]

Beekman M, Nederstigt C, Suchiman HE, Kremer D, van der Breggen R, Lakenberg N, Alemayehu WG, de Craen AJ, Westendorp RG, Boomsma DI, et al. Genome-wide association study (GWAS)-identified disease risk alleles do not compromise human longevity. Proc Natl Acad Sci U S A. 2010; 107:18046–18049. [PubMed: 20921414]

Bonafe M, Barbieri M, Marchegiani F, Olivieri F, Ragno E, Giampieri C, Mugianesi E, Centurelli M, Franceschi C, Paolisso G. Polymorphic variants of insulin-like growth factor I (IGF-I) receptor and phosphoinositide 3-kinase genes affect IGF-I plasma levels and human longevity: cues for an evolutionarily conserved mechanism of life span control. J Clin Endocrinol Metab. 2003; 88:3299–3304. [PubMed: 12843179]

Bonafe M, Marchegiani F, Cardelli M, Olivieri F, Cavallone L, Giovagnetti S, Pieri C, Marra M, Antonicelli R, Troiano L, et al. Genetic analysis of Paraoxonase (PON1) locus reveals an increased frequency of Arg192 allele in centenarians. Eur J Hum Genet. 2002; 10:292–296. [PubMed: 12082503]

Brown-Borg HM, Borg KE, Meliska CJ, Bartke A. Dwarf mice and the ageing process. Nature. 1996; 384:33. [PubMed: 8900272]

Burgers AM, Biermasz NR, Schoones JW, Pereira AM, Renehan AG, Zwahlen M, Egger M, Dekkers OM. Meta-analysis and dose-response metaregression: circulating insulin-like growth factor I (IGF-I) and mortality. J Clin Endocrinol Metab. 2011; 96:2912–2920. [PubMed: 21795450]

Cabreiro F, Au C, Leung KY, Vergara-Irigaray N, Cocheme HM, Noori T, Weinkove D, Schuster E, Greene ND, Gems D. Metformin retards aging in C. elegans by altering microbial folate and methionine metabolism. Cell. 2013; 153:228–239. [PubMed: 23540700]

Cannon CP, Shah S, Dansky HM, Davidson M, Brinton EA, Gotto AM, Stepanavage M, Liu SX, Gibbons P, Ashraf TB, et al. Safety of anacetrapib in patients with or at high risk for coronary heart disease. N Engl J Med. 2010; 363:2406–2415. [PubMed: 21082868]

Carmi S, Hui KY, Kochav E, Liu X, Xue J, Grady F, Guha S, Upadhyay K, Ben-Avraham D, Mukherjee S, et al. Sequencing an Ashkenazi reference panel supports population-targeted personal genomics and illuminates Jewish and European origins. Nat Commun. 2014; 5:4835. [PubMed: 25203624]

Evans CJ, Ho Y, Daveson BA, Hall S, Higginson IJ, Gao W. Place and cause of death in centenarians: a population-based observational study in England, 2001 to 2010. PLoS Med. 2014; 11:e1001653. [PubMed: 24892645]

Florez H, Ma Y, Crandall JP, Perreault L, Marcovina SM, Bray GA, Saudek CD, Barrett-Connor E, Knowler WC. Parental longevity and diabetes risk in the Diabetes Prevention Program. J Gerontol A Biol Sci Med Sci. 2011; 66:1211–1217. [PubMed: 21852284]

Franceschi C, Olivieri F, Marchegiani F, Cardelli M, Cavallone L, Capri M, Salvioli S, Valensin S, De Benedictis G, Di Iorio A, et al. Genes involved in immune response/inflammation, IGF1/insulin pathway and response to oxidative stress play a major role in the genetics of human longevity: the lesson of centenarians. Mech Ageing Dev. 2005; 126:351–361. [PubMed: 15621218]

Freudenberg-Hua Y, Freudenberg J, Vacic V, Abhyankar A, Emde AK, Ben-Avraham D, Barzilai N, Oschwald D, Christen E, Koppel J, et al. Disease Variants in Genomes of 44 Centenarians. Molecular Genetics & Genomic Medicine. 2014 **in press**.

Gavrilov L, Gavrilova N, Semyonova V, Evdokushkina G. Parental age effects on human longevity. Annual meeting of the Gerontological Society of America. 2001

Goldman DP, Cutler D, Rowe JW, Michaud PC, Sullivan J, Peneva D, Olshansky SJ. Substantial health and economic returns from delayed aging may warrant a new focus for medical research. Health Aff (Millwood). 2013; 32:1698–1705. [PubMed: 24101058]

Gombar S, Jung HJ, Dong F, Calder B, Atzmon G, Barzilai N, Tian XL, Pothof J, Hoeijmakers JH, Campisi J, et al. Comprehensive microRNA profiling in B-cells of human centenarians by massively parallel sequencing. BMC Genomics. 2012; 13:353. [PubMed: 22846614]

Graham MJ, Lee RG, Bell TA 3rd, Fu W, Mullick AE, Alexander VJ, Singleton W, Viney N, Geary R, Su J, et al. Antisense oligonucleotide inhibition of apolipoprotein C-III reduces plasma triglycerides in rodents, nonhuman primates, and humans. Circ Res. 2013; 112:1479–1490. [PubMed: 23542898]

Guevara-Aguirre J, Balasubramanian P, Guevara-Aguirre M, Wei M, Madia F, Cheng CW, Hwang D, Martin-Montalvo A, Saavedra J, Ingles S, et al. Growth hormone receptor deficiency is associated with a major reduction in pro-aging signaling, cancer, and diabetes in humans. Sci Transl Med. 2011; 3:70ra13.

Han J, Atzmon G, Barzilai N, Suh Y. Genetic variation in Sirtuin 1 (SIRT1) is associated with lipid profiles but not with longevity in Ashkenazi Jews. Transl Res. 2014

Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008; 359:1577–1589. [PubMed: 18784090]

Hong J, Zhang Y, Lai S, Lv A, Su Q, Dong Y, Zhou Z, Tang W, Zhao J, Cui L, et al. Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease. Diabetes Care. 2013; 36:1304–1311. [PubMed: 23230096]

Ismail KNL, Sebastiani P, Milman S, Perls TT, Barzilai N. Individuals with Exceptional Longevity Exhibit Increased Health Span and Delayed Onset of Age-Related Diseases. Presidential Poster Session of the American Geriatrics Society Annual Meeting. 2014

Johnson JA, Simpson SH, Toth EL, Majumdar SR. Reduced cardiovascular morbidity and mortality associated with metformin use in subjects with Type 2 diabetes. Diabet Med. 2005; 22:497–502. [PubMed: 15787679]

Kahn AJ. FOXO3 and Related Transcription Factors in Development, Aging, and Exceptional Longevity. J Gerontol A Biol Sci Med Sci. 2014

Karnevi E, Said K, Andersson R, Rosendahl AH. Metformin-mediated growth inhibition involves suppression of the IGF-I receptor signalling pathway in human pancreatic cancer cells. BMC Cancer. 2013; 13:235. [PubMed: 23663483]

Kenyon C, Chang J, Gensch E, Rudner A, Tabtiang R. A C. elegans mutant that lives twice as long as wild type. Nature. 1993; 366:461–464. [PubMed: 8247153]

Kojima T, Kamei H, Aizu T, Arai Y, Takayama M, Nakazawa S, Ebihara Y, Inagaki H, Masui Y, Gondo Y, et al. Association analysis between longevity in the Japanese population and polymorphic variants of genes involved in insulin and insulin-like growth factor 1 signaling pathways. Exp Gerontol. 2004; 39:1595–1598. [PubMed: 15582274]

Kopchick JJ. Discovery and mechanism of action of pegvisomant. Eur J Endocrinol. 2003; 148(Suppl 2):S21–S25. [PubMed: 12670297]

Lamanna C, Monami M, Marchionni N, Mannucci E. Effect of metformin on cardiovascular events and mortality: a meta-analysis of randomized clinical trials. Diabetes Obes Metab. 2011; 13:221–228. [PubMed: 21205121]

Landman GW, Kleefstra N, van Hateren KJ, Groenier KH, Gans RO, Bilo HJ. Metformin associated with lower cancer mortality in type 2 diabetes: ZODIAC-16. Diabetes Care. 2010; 33:322–326. [PubMed: 19918015]

Lawrence RW, Evans DM, Cardon LR. Prospects and pitfalls in whole genome association studies. Philos Trans R Soc Lond B Biol Sci. 2005; 360:1589–1595. [PubMed: 16096108]

Lee MS, Hsu CC, Wahlqvist ML, Tsai HN, Chang YH, Huang YC. Type 2 diabetes increases and metformin reduces total, colorectal, liver and pancreatic cancer incidences in Taiwanese: a representative population prospective cohort study of 800,000 individuals. BMC Cancer. 2011; 11:20. [PubMed: 21241523]

Lee RG, Crosby J, Baker BF, Graham MJ, Crooke RM. Antisense technology: an emerging platform for cardiovascular disease therapeutics. J Cardiovasc Transl Res. 2013; 6:969–980. [PubMed: 23856914]

Libby G, Donnelly LA, Donnan PT, Alessi DR, Morris AD, Evans JM. New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes. Diabetes Care. 2009; 32:1620–1625. [PubMed: 19564453]

Lipton RB, Hirsch J, Katz MJ, Wang C, Sanders AE, Verghese J, Barzilai N, Derby CA. Exceptional parental longevity associated with lower risk of Alzheimer's disease and memory decline. J Am Geriatr Soc. 2010; 58:1043–1049. [PubMed: 20487085]

Liu B, Fan Z, Edgerton SM, Yang X, Lind SE, Thor AD. Potent anti-proliferative effects of metformin on trastuzumab-resistant breast cancer cells via inhibition of erbB2/IGF-1 receptor interactions. Cell Cycle. 2011; 10:2959–2966. [PubMed: 21862872]

Mannick JB, Del Giudice G, Lattanzi M, Valiante NM, Praestgaard J, Huang B, Lonetto MA, Maecker HT, Kovarik J, Carson S, et al. mTOR inhibition improves immune function in the elderly. Sci Transl Med. 2014; 6:268ra179.

Marchegiani F, Marra M, Spazzafumo L, James RW, Boemi M, Olivieri F, Cardelli M, Cavallone L, Bonfigli AR, Franceschi C. Paraoxonase activity and genotype predispose to successful aging. J Gerontol A Biol Sci Med Sci. 2006; 61:541–546. [PubMed: 16799134]

Martin GM. Genetic modulation of senescent phenotypes in Homo sapiens. Cell. 2005; 120:523–532. [PubMed: 15734684]

Martin-Montalvo A, Mercken EM, Mitchell SJ, Palacios HH, Mote PL, Scheibye-Knudsen M, Gomes AP, Ward TM, Minor RK, Blouin MJ, et al. Metformin improves healthspan and lifespan in mice. Nat Commun. 2013; 4:2192. [PubMed: 23900241]

Mecocci P, Polidori MC, Troiano L, Cherubini A, Cecchetti R, Pini G, Straatman M, Monti D, Stahl W, Sies H, et al. Plasma antioxidants and longevity: a study on healthy centenarians. Free Radic Biol Med. 2000; 28:1243–1248. [PubMed: 10889454]

Milman S, Atzmon G, Huffman DM, Wan J, Crandall JP, Cohen P, Barzilai N. Low insulin-like growth factor-1 level predicts survival in humans with exceptional longevity. Aging Cell. 2014

Monami M, Colombi C, Balzi D, Dicembrini I, Giannini S, Melani C, Vitale V, Romano D, Barchielli A, Marchionni N, et al. Metformin and cancer occurrence in insulin-treated type 2 diabetic patients. Diabetes Care. 2011; 34:129–131. [PubMed: 20980415]

Monsalve M, Olmos Y. The complex biology of FOXO. Curr Drug Targets. 2011; 12:1322–1350. [PubMed: 21443460]

Muzumdar RH, Huffman DM, Atzmon G, Buettner C, Cobb LJ, Fishman S, Budagov T, Cui L, Einstein FH, Poduval A, et al. Humanin: a novel central regulator of peripheral insulin action. PLoS One. 2009; 4:e6334. [PubMed: 19623253]

Nebel A, Kleindorp R, Caliebe A, Nothnagel M, Blanche H, Junge O, Wittig M, Ellinghaus D, Flachsbart F, Wichmann HE, et al. A genome-wide association study confirms APOE as the major gene influencing survival in long-lived individuals. Mech Ageing Dev. 2011; 132:324–330. [PubMed: 21740922]

Pawlikowska L, Hu D, Huntsman S, Sung A, Chu C, Chen J, Joyner AH, Schork NJ, Hsueh WC, Reiner AP, et al. Association of common genetic variation in the insulin/IGF1 signaling pathway with human longevity. Aging Cell. 2009; 8:460–472. [PubMed: 19489743]

Perls TT, Bubrick E, Wager CG, Vijg J, Kruglyak L. Siblings of centenarians live longer. Lancet. 1998; 351:1560. [PubMed: 10326548]

Perls TT, Wilmoth J, Levenson R, Drinkwater M, Cohen M, Bogan H, Joyce E, Brewster S, Kunkel L, Puca A. Life-long sustained mortality advantage of siblings of centenarians. Proc Natl Acad Sci U S A. 2002; 99:8442–8447. [PubMed: 12060785]

Pollin TI, Damcott CM, Shen H, Ott SH, Shelton J, Horenstein RB, Post W, McLenithan JC, Bielak LF, Peyser PA, et al. A null mutation in human APOC3 confers a favorable plasma lipid profile and apparent cardioprotection. Science. 2008; 322:1702–1705. [PubMed: 19074352]

Quinn BJ, Dallos M, Kitagawa H, Kunnumakkara AB, Memmott RM, Hollander MC, Gills JJ, Dennis PA. Inhibition of lung tumorigenesis by metformin is associated with decreased plasma IGF-I and diminished receptor tyrosine kinase signaling. Cancer Prev Res (Phila). 2013; 6:801–810. [PubMed: 23771523]

Rajpathak SN, Liu Y, Ben-David O, Reddy S, Atzmon G, Crandall J, Barzilai N. Lifestyle factors of people with exceptional longevity. J Am Geriatr Soc. 2011; 59:1509–1512. [PubMed: 21812767]

Rea IM, McKeown PP, McMaster D, Young IS, Patterson C, Savage MJ, Belton C, Marchegiani F, Olivieri F, Bonafe M, et al. Paraoxonase polymorphisms PON1 192 and 55 and longevity in Italian centenarians and Irish nonagenarians. A pooled analysis. Exp Gerontol. 2004; 39:629–635. [PubMed: 15050299]

Roumie CL, Hung AM, Greevy RA, Grijalva CG, Liu X, Murff HJ, Elasy TA, Griffin MR. Comparative effectiveness of sulfonylurea and metformin monotherapy on cardiovascular events in type 2 diabetes mellitus: a cohort study. Ann Intern Med. 2012; 157:601–610. [PubMed: 23128859]

Rozing MP, Houwing-Duistermaat JJ, Slagboom PE, Beekman M, Frolich M, de Craen AJ, Westendorp RG, van Heemst D. Familial longevity is associated with decreased thyroid function. J Clin Endocrinol Metab. 2010; 95:4979–4984. [PubMed: 20739380]

Salani B, Maffioli S, Hamoudane M, Parodi A, Ravera S, Passalacqua M, Alama A, Nhiri M, Cordera R, Maggi D. Caveolin-1 is essential for metformin inhibitory effect on IGF1 action in non-small-cell lung cancer cells. Faseb J. 2012; 26:788–798. [PubMed: 22038047]

Samaras TT, Elrick H. Height, body size, and longevity: is smaller better for the human body? West J Med. 2002; 176:206–208. [PubMed: 12016250]

Sanders AE, Wang C, Katz M, Derby CA, Barzilai N, Ozelius L, Lipton RB. Association of a functional polymorphism in the cholesteryl ester transfer protein (CETP) gene with memory decline and incidence of dementia. Jama. 2010; 303:150–158. [PubMed: 20068209]

Sandhu MS, Heald AH, Gibson JM, Cruickshank JK, Dunger DB, Wareham NJ. Circulating concentrations of insulin-like growth factor-I and development of glucose intolerance: a prospective observational study. Lancet. 2002; 359:1740–1745. [PubMed: 12049864]

Schoenmaker M, de Craen AJ, de Meijer PH, Beekman M, Blauw GJ, Slagboom PE, Westendorp RG. Evidence of genetic enrichment for exceptional survival using a family approach: the Leiden Longevity Study. Eur J Hum Genet. 2006; 14:79–84. [PubMed: 16251894]

Sebastiani P, Solovieff N, Dewan AT, Walsh KM, Puca A, Hartley SW, Melista E, Andersen S, Dworkis DA, Wilk JB, et al. Genetic signatures of exceptional longevity in humans. PLoS One. 2012; 7:e29848. [PubMed: 22279548]

Sebastiani P, Sun FX, Andersen SL, Lee JH, Wojczynski MK, Sanders JL, Yashin A, Newman AB, Perls TT. Families Enriched for Exceptional Longevity also have Increased Health-Span: Findings from the Long Life Family Study. Front Public Health. 2013; 1:38. [PubMed: 24350207]

Seibel SA, Chou KH, Capp E, Spritzer PM, von Eye Corleta H. Effect of metformin on IGF-1 and IGFBP-1 levels in obese patients with polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol. 2008; 138:122–124. [PubMed: 17350746]

Smith DL Jr, Elam CF Jr, Mattison JA, Lane MA, Roth GS, Ingram DK, Allison DB. Metformin supplementation and life span in Fischer-344 rats. J Gerontol A Biol Sci Med Sci. 2010; 65:468–474. [PubMed: 20304770]

Suh Y, Atzmon G, Cho MO, Hwang D, Liu B, Leahy DJ, Barzilai N, Cohen P. Functionally significant insulin-like growth factor I receptor mutations in centenarians. Proc Natl Acad Sci U S A. 2008; 105:3438–3442. [PubMed: 18316725]

Tabatabaie V, Surks MI. The aging thyroid. Curr Opin Endocrinol Diabetes Obes. 2013; 20:455–459. [PubMed: 23974775]

Tan Q, Christiansen L, Bathum L, Li S, Kruse TA, Christensen K. Genetic association analysis of human longevity in cohort studies of elderly subjects: an example of the PON1 gene in the Danish 1905 birth cohort. Genetics. 2006; 172:1821–1828. [PubMed: 16387878]

Tazearslan C, Huang J, Barzilai N, Suh Y. Impaired IGF1R signaling in cells expressing longevity-associated human IGF1R alleles. Aging Cell. 2011; 10:551–554. [PubMed: 21388493]

Tosca L, Rame C, Chabrolle C, Tesseraud S, Dupont J. Metformin decreases IGF1-induced cell proliferation and protein synthesis through AMP-activated protein kinase in cultured bovine granulosa cells. Reproduction. 2010; 139:409–418. [PubMed: 19906888]

Tseng CH. Diabetes, metformin use, and colon cancer: a population-based cohort study in Taiwan. Eur J Endocrinol. 2012; 167:409–416. [PubMed: 22778198]

van Heemst D, Beekman M, Mooijaart SP, Heijmans BT, Brandt BW, Zwaan BJ, Slagboom PE, Westendorp RG. Reduced insulin/IGF-1 signalling and human longevity. Aging Cell. 2005; 4:79–85. [PubMed: 15771611]

Vergani C, Lucchi T, Caloni M, Ceconi I, Calabresi C, Scurati S, Arosio B. I405V polymorphism of the cholesteryl ester transfer protein (CETP) gene in young and very old people. Arch Gerontol Geriatr. 2006; 43:213–221. [PubMed: 16384616]

Westendorp RG, van Heemst D, Rozing MP, Frolich M, Mooijaart SP, Blauw GJ, Beekman M, Heijmans BT, de Craen AJ, Slagboom PE. Nonagenarian siblings and their offspring display lower risk of mortality and morbidity than sporadic nonagenarians: The Leiden Longevity Study. J Am Geriatr Soc. 2009; 57:1634–1637. [PubMed: 19682117]

Whittington HJ, Hall AR, McLaughlin CP, Hausenloy DJ, Yellon DM, Mocanu MM. Chronic metformin associated cardioprotection against infarction: not just a glucose lowering phenomenon. Cardiovasc Drugs Ther. 2013; 27:5–16. [PubMed: 23192487]

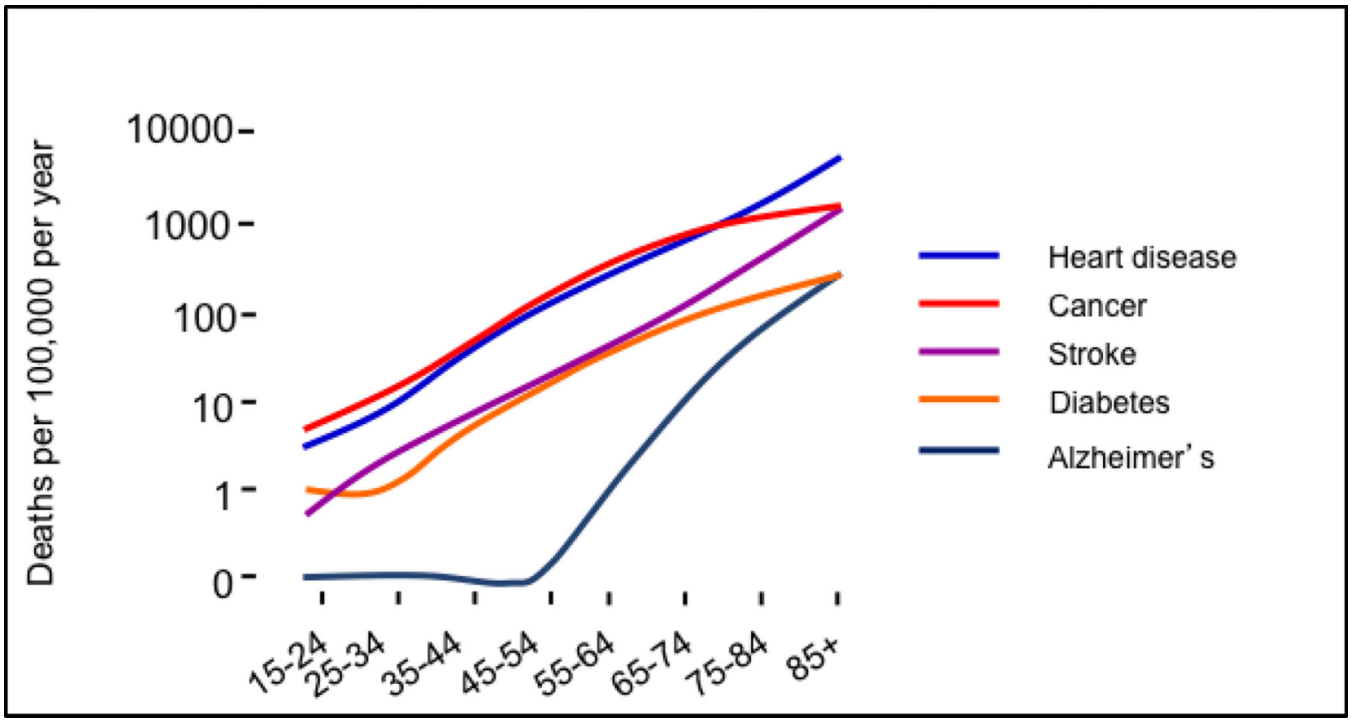

Figure 1.
Rate of death per 100,000 people per year for age-related diseases, stratified by age groups.

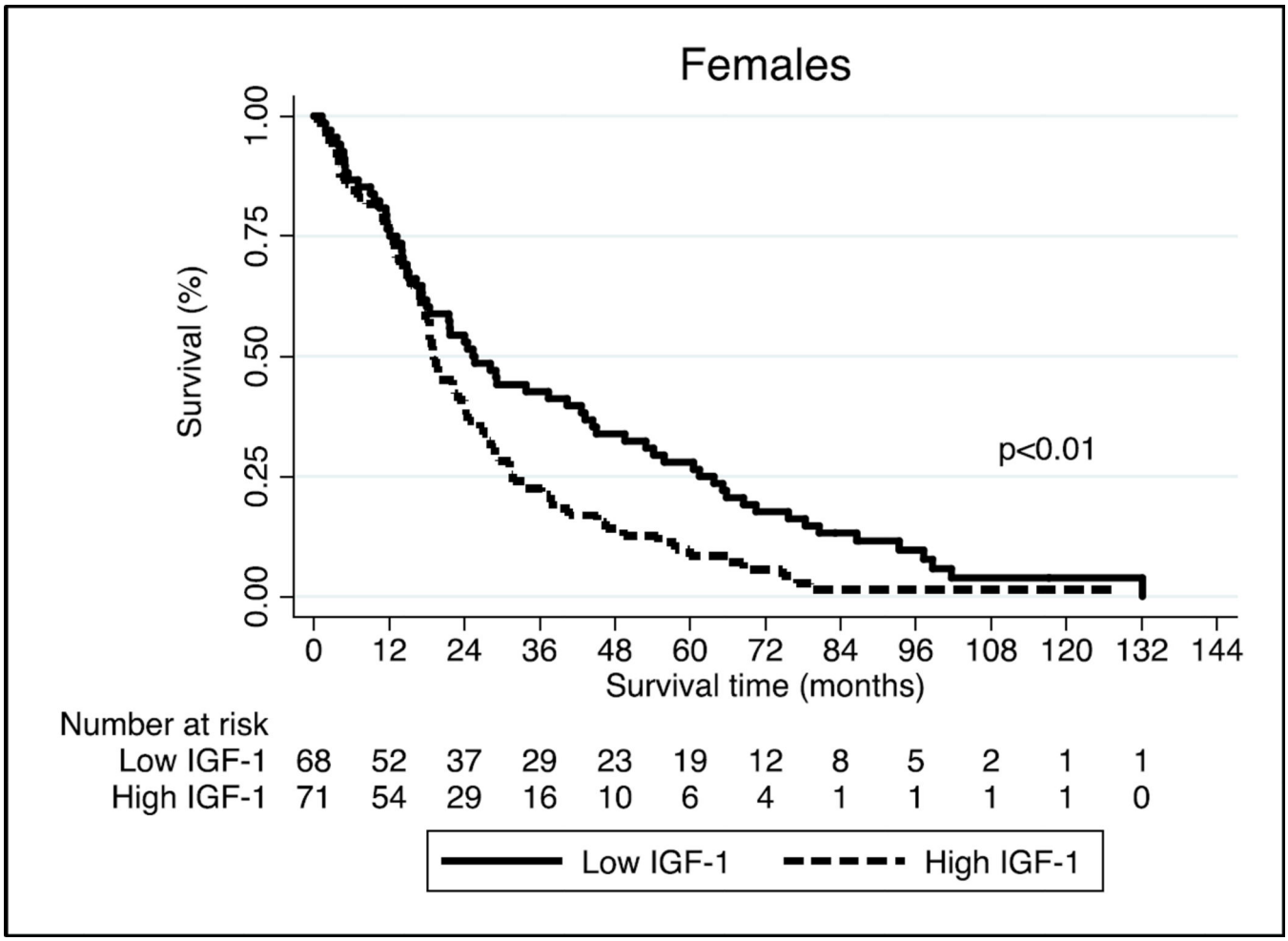

Figure 2.
Kaplan-Meier survival curves for females with IGF-1 levels above and below the median. Adapted from Milman et al. Aging Cell 2014.