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Fasting blood glucose as a predictor of mortality: Lost in translation

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SUMMARY

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AUTHOR CONTRIBUTIONS

D.L.P., E.J.S., and J.K.N. conducted data analysis. E.J.S. wrote codes for data analysis. D.L.P., E.J.S., N.L.P., M.B., L.F., and R.d.C. interpreted data. D.L.P. and E.J.S. wrote original draft of manuscript. D.L.P., E.J.S., N.L.P., M.B., S.C., E.D., and C.V.L.T. contributed to SLAM study supervision. K.L.V. and J.A.M. curated the data from the NIA nonhuman primate studies. R.J.C. and R.M.A. curated the data from the WIS nonhuman primate studies. A.D., R.K., L.L.P., and G.A.C. conducted JAX mouse studies. S.L.D., K.E., and D.B.A. independently analyzed all data. E.J.S., D.B.A., and L.J.L. contributed to establishing epidemiological and statistical methods. E.M.S., C.W.C., and J.E. facilitated BLSA metabolic data collection, analysis, and curation. L.F. and R.d.C. conceived and supervised the studies. All authors read and contributed to editing the manuscript.

SUPPLEMENTAL INFORMATION

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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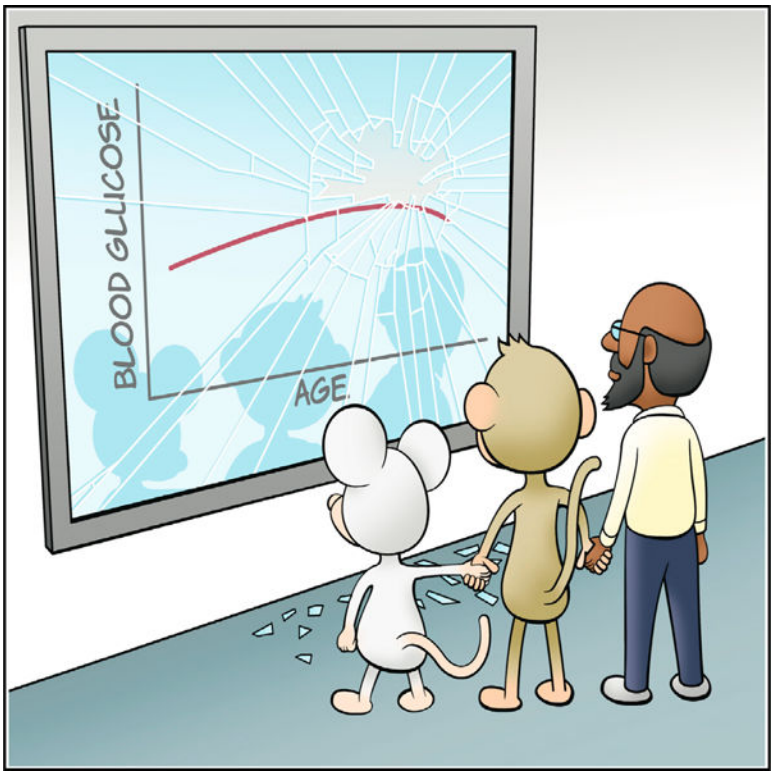
Aging leads to profound changes in glucose homeostasis, weight, and adiposity, which are considered good predictors of health and survival in humans. Direct evidence that these age-associated metabolic alterations are recapitulated in animal models is lacking, impeding progress to develop and test interventions that delay the onset of metabolic dysfunction and promote healthy aging and longevity. We compared longitudinal trajectories, rates of change, and mortality risks of fasting blood glucose, body weight, and fat mass in mice, nonhuman primates, and humans throughout their lifespans and found similar trajectories of body weight and fat in the three species. In contrast, fasting blood glucose decreased late in life in mice but increased over the lifespan of nonhuman primates and humans. Higher glucose was associated with lower mortality in mice but higher mortality in nonhuman primates and humans, providing a cautionary tale for translating age-associated metabolic changes from mice to humans.

Graphical Abstract



In brief

Fasting blood glucose is widely used to measure metabolic health, and mice are used to model age-associated metabolic diseases in humans. Here, Palliyaguru and Shiroma et al. reveal that fasting blood glucose trajectories and mortality risk associations differ between species—a cautionary tale for using mice to model perturbations in age-associated glucoregulation.

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INTRODUCTION

Human life expectancy is increasing globally (Beard et al., 2016; Christensen et al., 2009), leading to an expansion of the proportion of individuals afflicted with chronic diseases and disabilities (Berry et al., 2012). The development of chronic diseases, such as obesity, type 2 diabetes, and cardiovascular disease, begins as early as gestation and continues dynamically through life (Bjerregaard and Baker, 2018; Burton et al., 2016). Studying this progression in humans is time and resource intensive and poses several challenges (Mody et al., 2008). Therefore, mice and nonhuman primates (NHPs) are often used as model organisms to study human diseases and aging processes (Ackert-Bicknell et al., 2015; Kenyon, 2010; Mattison and Vaughan, 2017). Mice are readily available, convenient to house and handle, genetically malleable, and have short lifespans. Hence, mice have been successfully used to dissect biological mechanisms and understand the pathophysiology of diseases and test pharmacological interventions (Mitchell et al., 2015; Perlman, 2016). Studies conducted in NHPs are substantially more costly, ethically challenging, and less amenable to genetic manipulation than those conducted in mice. However, NHPs are evolutionarily closer to humans, and there is consensus that findings of these studies are more directly relevant to humans (Mattison et al., 2017). Translation of results from animal models to humans hinges on the assumption that the underlying biological mechanisms that sustain life and cause diseases are similar across species. Broadly speaking, whereas many essential biological elements are conserved across species, overlooking physiological differences between model organisms and humans may lead to translational inferences from scientific findings that are not valid and may result in the eventual failure of lengthy and costly research efforts (Kleinert et al., 2018; Moore et al., 2018; Perel et al., 2007).

Metabolic measures, such as blood glucose (fasting or after ingestion of a standard glucose load), body weight, and body composition, are routinely assessed in clinical practice for disease risk assessment and tracking the efficacy of interventions. Therefore, these indices can serve as physiological biomarkers to study complex links between weight, adiposity, and glucose homeostasis as they pertain to disease development as people age (Kahn et al., 2006). Body fat mass gradually increases until ~70 years in most individuals (Hughes et al., 2002), and fasting glucose increases progressively from adult to old age even in people who never develop type 2 diabetes (Chia et al., 2018; Danaei et al., 2011). Elevated fasting glucose, body mass, and fat content generally correlate with higher rate of mortality (Gerstein and Yusuf, 1996; Global BMI Mortality Collaboration et al., 2016; Rao Kondapally Seshasai et al., 2011), but losing body weight and adiposity in older people could also be detrimental to survival (Chapman, 2010), indicating the important effect of aging on these metabolic health indices.

Despite mice and NHPs being used to model aspects of human metabolism, how these metabolic variables change over their lifespans and affect longevity is poorly understood. Many studies that have examined age-associated metabolic changes in wild-type mice thus far have been cross-sectional with small sample sizes and did not examine incremental and nonlinear changes across the entire lifespan (Azzu and Valencak, 2017). To provide a better understanding of normative mouse aging, the Study of Longitudinal Aging in Mice (SLAM) was initiated to assess longitudinal changes in functional and molecular characteristics of

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aging in two different strains of mice (C57BL/6 and HET3) of both sexes (Palliyaguru et al., 2020). Furthermore, mouse metabolic aging has not been directly compared with human metabolic aging using the same standardized methodology. To address this gap in knowledge, we examined data from SLAM with NHP aging studies at the National Institute on Aging (NIA) and Wisconsin National Primate Research Center (referred to as WIS), as well as with humans from the Baltimore Longitudinal Study of Aging (BLSA). Therein, we compared longitudinal trajectories and associated mortality risks of three well-established human biomarkers of metabolic health (fasting blood glucose, body weight, and body fat) among mice, NHPs, and humans.

RESULTS

Species-specific population and lifespan characteristics are shown in Figure 1. Details of populations and specific criteria are listed in the STAR Methods section. Using an a priori methodological choice, 50%, 75%, and 90% of median life expectancy of each species was used to categorize specific life stages (midlife, late life, and oldest in life) based on the distribution of life expectancy of each population. In SLAM mice, there were 776 natural deaths (62.5% of total population of 1,241 animals, number of deaths were equally distributed by sex and strain), resulting in a median life expectancy (IQR) of 115.0 (98.0, 129.0) weeks; midlife, late life, and oldest in life were then defined as 57.5, 86.3, and 103.5 weeks, respectively. It is noteworthy that the SLAM study design includes planned euthanasia of randomized mice at various time points, which would not be considered natural deaths (Palliyaguru et al., 2020). In NHPs, there were 87 deaths (34.3% of total population of 254 animals; 57% of the 87 deaths were NIA and 43% were WIS; 43% of the 87 deaths were females and 57% were males), leading to a median life expectancy (IQR) of 26.7 (23.1, 30.3) years; midlife, late life, and oldest in life were therefore defined as 13.4 years, 20.1 years, and 24.1 years, respectively. In BLSA human participants, there were 1,193 participant deaths as of 2019 (39.5% of total population of 3,023; 34% of 1,193 deaths were females and 66% were males), with a median life expectancy (IQR) of 86.0 (79.0, 91.0) years; midlife, late life, and oldest in life were thus 43.0, 64.5, and 77.4 years, respectively. Sex and strain/site-specific characteristics are shown in Figure S1 and Table S1.

Due to the large differences in life expectancy across species, a time variable that is comparable between species was established to estimate the rate of change across species. 5% of the median life expectancy was chosen, as it was a short time interval that would allow for rates of change to be modeled linearly to facilitate interpretability. Species-specific 5% of median life expectancies used for this estimation of rates of change corresponded to 6 weeks (SLAM mice), 1 year (NHPs), and 4 years (BLSA humans).

Pearson correlation analysis showed that glucose, weight, and body fat were positively correlated with each other to varying degrees in all 3 species. Weight and body fat showed the strongest correlations, whereas glucose was less strongly correlated with body weight and body fat across life stages in all 3 species (Table S2). Next, age-associated trajectories of change in metabolic indices were explored in the 3 species by sex and strain/site. Given that the metabolic indices changed substantially throughout the lifespan and in a nonlinear fashion, rates of change were also examined per increase in 5% median life expectancy.

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Subgroup-specific trajectories and rates of change were modeled to account for differences by sex and mouse strain/NHP site.

Fasting blood glucose

In SLAM mice, glucose levels remained stable until mid to late life, then significantly decreased at a rate of –3.08% every 6 weeks ($p < 0.0001$) (Table 1). In NHPs and humans, glucose increased throughout life (0.48% per year and 0.70% per 4 years, respectively, $p < 0.0001$) (Table 1).

The overall shapes of the trajectories were similar between subgroups, but differences were apparent in both absolute values and when metabolic indices peaked (Figures 2 and S2). Male HET3 mice exhibited the highest glucose levels, followed by male B6 and female HET3, whereas female B6 mice showed the lowest levels. Interestingly, the age at which the peak glucose occurred was earlier for HET3 mice (male, ~36 weeks; female, ~40.7 weeks) compared with B6 mice (male, ~76.4; female, ~81.4 weeks). In addition, the rate of glucose decline post-peak was highest for male B6 mice (4.38% decrease every 6 weeks) and was lowest for female HET3 mice (1.02% decrease every 6 weeks).

WIS NHPs appeared to have higher blood glucose whose levels increased more dramatically with advancing age than NIA animals. Additionally, the reduction in blood glucose observed in the extremely long-lived female monkeys in the NIA study were not observed in the WIS monkeys. The peak of glucose occurred the latest for NIA male monkeys (~39 years) and the earliest for NIA female monkeys (~26 years).

Looking at BLSA data, the analysis was carried out by sex only as there were insufficient data to conduct an analysis by race. Blood glucose in BLSA females peaked at ~69 years, whereas males peaked at ~67 years. The pre-peak rate was 0.75% increase every 4 years among males and 0.65% increase every 4 years in females.

Since status of diabetes has important implications for the outcomes being examined here, NHP and human data were stratified by diabetes status (Figure S3). Diabetes status was not applicable to mice. Age-associated trajectories were similar between the diabetic and nondiabetic groups, but the diabetic groups sustained clearly higher absolute values of metabolic indices through the lifespan, as well as earlier ages at which the metabolic indices peaked. A comprehensive listing of drugs administered to diabetic participants was not available and, therefore, could not be included as a covariate; however, diabetic participants routinely begin standard glucose-lowering drug regimens upon first diagnosis.

Data were also analyzed by groups of subjects that survived up to various time points to explore the effect of potential survivorship bias. All groups of subjects, independent of how long they lived, followed the same general trajectory as the full population. To examine any site-specific events that may lead to differential trajectories of glucose between mice and humans, SLAM and BLSA fasting glucose data were compared with data from two independent studies. The decreasing glucose across lifespan was recapitulated in a large cohort of Diversity Outbred mice from an independent study at The Jackson Laboratory (Churchill et al., 2012) (Figure S4). Data from National Health and Nutrition Examination

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Survey (NHANES) participants showed similar increasing trends across the lifespan to that of BLSA, although BLSA participants had lower absolute values of circulating glucose (Figure S4).

Weight and body fat

Weight and body fat followed the same general trend in all 3 species during the life course, where peaks were observed between mid and late life. Weight markedly increased from early to midlife and decreased later in life in mice (increase, 0.65% [$p < 0.0001$]; decrease, –0.67% [$p < 0.0001$]; every 6 weeks), NHPs (increase, 0.28% [$p < 0.0001$]; decrease, –0.05% [$p < 0.0001$]; annually), and humans (increase, 0.81% [$p < 0.0001$]; decrease, –1.35% [$p < 0.0001$]; every 4 years) (Table 1). Subgroup analyses revealed some differences (Figures 2 and S2; Table 1). In mice, HET3 mice were heavier than B6 mice and males were heavier than females. The peak weight occurred about 13 weeks later in females (females, ~84–85 weeks; males, 68–74 weeks). Similarly, in NHPs, males were heavier than females, and NHPs at WIS were heavier than those at the NIA. Once again, the peak weight was later for females (18.4–19.3 years) compared with males (16.5–16.6 years). As observed in both mice and NHPs, BLSA females were lighter than males and peaked at ~61 years compared with ~52 years in males.

In all three species, body fat increased significantly until midlife and decreased thereafter: mice (increase, 0.36% [$p < 0.05$]; decrease, –0.36% [$p < 0.0001$]; every 6 weeks), NHPs (increase, 0.17% [$p < 0.0001$]; decrease, –0.03% [$p < 0.0001$]; annually), and humans (increase, 0.88% [$p < 0.0001$]; decrease, –0.55% [$p < 0.0001$]; every 4 years) (Table 1). Subgroup analyses showed some differences (Figures 2 and S2; Table 1). In mice, males showed overall higher adiposity compared with females, and HET3 mice had higher adiposity than B6. Female adiposity peaked later than male mice (~81–88 weeks versus 66–67 weeks, respectively), reminiscent of peak weight. In NHPs, WIS males showed highest adiposity whereas NIA females showed the lowest, with body fat peaking earlier in females than males. The trajectory of adiposity was more stable and showed a double peak in NIA male monkeys. In BLSA humans, female waist circumference was lower than males, but the age at peak appeared similar between females and males.

Mortality risk—fasting blood glucose

To determine whether subgroups can be combined for the survival analysis to increase power and facilitate comparisons across species, statistical interactions were tested by sex and strain/site (Table S3). Model fit was evaluated using a nested likelihood ratio test to compare the addition of an interaction term by sex or strain. The testing clearly showed that almost all interactions in our survival model are insignificant (except SLAM, body fat—oldest in life and strain, which could be driven by spurious effects). Based on this analysis, there was insufficient evidence to support adding an interaction of strain to the survival models. Although no significant interaction was observed, sex-specific estimates were calculated according to a priori research questions.

Specific life stages were categorized using 50%, 75%, and 90% of median life expectancy of each species (midlife, late life, and oldest in life, respectively) based on the distribution of

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life expectancy and the clinical significance of these life stages. Data were divided into sex-specific quartiles at these time points, and Kaplan-Meier survival curves and age-adjusted mortality hazard ratios were calculated, comparing individuals above the highest and below the lowest quartiles of metabolic indices. At midlife, individuals in the highest quartile of glucose levels compared with the lowest did not have a significantly different risk of mortality in any of the three species (Figure 3). At late life, no statistically significant association between glucose and mortality was observed in mice. In contrast, in NHPs and humans, the highest glucose quartile experienced a significantly higher mortality rate compared with the lowest quartile (NHPs, HR = 2.46 [1.12, 5.38], p = 0.025; humans, HR = 1.40 [1.05, 1.86], p = 0.028; Figure 3). At oldest in life, mice with higher glucose levels had a significantly lower mortality rate (HR = 0.76 [0.59, 0.97], p = 0.025), whereas the opposite association was observed in NHPs (HR = 2.74 [1.24, 6.04], p = 0.012) and humans (HR = 1.32 [1.06, 1.65], p = 0.026) (Figure 3). Examination of sex-specific, age-adjusted mortality hazard ratios showed that high glucose was more protective in female than male mice at oldest in life (Table 2). Further adjustment for body fat did not markedly alter the results (Table 2).

Mortality risk—weight and body fat

Higher weight in mice did not predict mortality at midlife but was associated with lower mortality rates at late life (HR = 0.78 [0.63,0.97], p = 0.023) and oldest in life (HR = 0.61 [0.48, 0.77], p < 0.0001) (Figure S5). In NHPs, the highest weight quartile was associated with over twice the mortality rate compared with the lowest quartile at midlife and late life (HR = 2.04 [1.00, 4.15], p = 0.049; HR = 2.23 [1.10, 4.49], p = 0.026), respectively. However, at oldest in life, there was no association between weight and mortality. In humans, weight was not associated with mortality in the BLSA population. Higher body fat was associated with significantly better survival at late and oldest in life in mice, whereas in NHPs, the opposite effect was observed at mid and late life (Figure S6). In BLSA participants, body fat neither significantly reduced nor elevated risk of death.

DISCUSSION

This study comparing longitudinal trajectories of fasting blood glucose, body weight, and adiposity among mice, NHPs, and humans reveals that the impact of age on circulating glucose levels is similar in NHPs and humans, where a gradual increase was detected over the lifespan for both species. In contrast, glucose levels significantly decreased after midlife in mice. Among NHPs and humans, individuals with higher glucose levels had higher mortality rates than those with lower glucose at later stages of life. On the contrary, mice with higher glucose had an ~24% lower mortality rate compared with the lower glucose group. Marked sex differences were seen in all three species in terms of absolute values, age at which indices peaked, and mortality risks. The low levels and delayed peaks of metabolic measures in females seen here may propagate a survival advantage in some groups (Cheng et al., 2019), but these observations need to be explored further (Zore et al., 2018). Strain- and site-specific differences were also observed in life-course trends in metabolic indices. Adjusting for body fat did not substantially alter the association of high glucose with low mortality rate in mice. However, the relationship between glucose and specific fat depots in

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mice needs to be further explored, especially within the context of aging-associated insulin resistance (Fink et al., 1983).

In contrast to glucose trajectories, longitudinal changes in body weight and adiposity in the 3 species were similar, increasing until midlife, and then decreasing through oldest in life. Weight and adiposity were prominent correlative determinants of mortality after midlife. Strikingly, higher weight and body fat were associated with lower mortality rates in mice, whereas in NHPs, the risk of death was greater for heavier animals and those with high adiposity, with most prominent associations around midlife (Ejima et al., 2016). This protective effect of adiposity on longevity of mice agrees with previous reports (Liao et al., 2011). However, we and others have previously shown that mice on caloric restriction that have much lower body fat lived longer (Mitchell et al., 2016), indicating the complex associations between fat and longevity. It is also noteworthy that earlier studies have shown that adipose function plays an important role in health (Miller et al., 2017), which was not examined here. In the BLSA population, no significant mortality associations with weight and body fat were seen. Although this is in contrast to some prior observations (Pischon et al., 2008), it may be consistent with the so-called obesity paradox where being overweight is not associated with increased mortality, whereas being obese is (Global BMI Mortality Collaboration et al., 2016). The absence of association between weight/adiposity and mortality risk may be explained by the grouping of overweight and obese participants in the highest quartile in our dataset and thus inadvertently attenuating the association of obesity on mortality. Although retention of weight and body fat provides a survival advantage in older persons with illness (Childers and Allison, 2010), we were unable to statistically validate this within the BLSA, a population that is generally healthy. Previous studies have shown a slightly earlier inflection point in human body composition changes (Westerterp, 2018) compared with what we observed here (~70 years), suggesting population-specific characteristics. Waist circumference was used as a proxy for adiposity as more comprehensive measures, such as body composition scans, were unavailable when the BLSA was first initiated. Future studies should examine other proxies for adiposity, including waist-to-hip ratio, if these measures are available.

Glucose homeostasis becomes impaired with aging over the human lifespan, and the rate of dysregulation in this system has been proposed as a strong candidate biomarker of aging and a risk factor for mortality in humans (Heianza et al., 2012; Yashin et al., 2009). High fasting blood glucose is a correlate of insulin resistance, visceral fat accumulation, sarcopenia, and other manifestations of metabolic dysfunction in older adults (Barzilai and Ferrucci, 2012). Similarly, there is evidence from epidemiological studies that the accumulation of fat, especially in the visceral compartment, is associated with insulin resistance and higher levels of fasting glucose (Chia et al., 2018). Data availability on crosstalk between metabolic markers and their role in spontaneous disease in mice is limited. However, small studies using only a single strain of mice and one sex show that blood glucose levels appear to go down and glucose tolerance to increase with age (Ko et al., 2017; Leiter et al., 1988; Oh et al., 2016). These data support our observations using longitudinal measures from both sexes and two strains (C57BL/6 and HET3). This finding was further validated with data from the Diversity Outbred strain of mice from The Jackson Laboratory. Although

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age-associated changes in fasting glucose in mice have been widely assumed to be similar to that of humans, our large longitudinal study using diverse animal species and strains from multiple testing sites has revisited this concept, and the results clearly indicate that mice are not equivalent to NHPs and humans in the context of age-associated glucose homeostasis patterns. This observation has critical implications for translational studies that focus on improving aging-related outcomes by modulating glucose homeostasis.

Targeting imbalances in metabolism with glucoregulatory drugs has been proposed as a way to mitigate age-related chronic diseases and extend lifespan (Curtis et al., 2005). Mouse models serve as essential tools to study these phenomena; however, our data reveal a potential challenge in using mice to study the impact of aging, specifically on glucoregulatory function. Thus, interventions in mice focused on correcting age-related metabolic dysfunction, particularly lowering blood glucose, may not necessarily translate to NHPs and humans. Moreover, strategies that are effective at lowering blood glucose in mice could show minimal or detrimental effects on mouse lifespan and yet be valuable for their potential to improve health, preserve function, and perhaps, increase lifespan in humans. Indeed, some drugs that are primarily known for their glucose-lowering action, such as acarbose and canagliflozin, have shown lifespan extension in select groups of mice (Harrison et al., 2019; Miller et al., 2020). Longitudinal, life-course levels of fasting glucose were not reported in these studies, but interestingly, neither of these drugs lowered HbA1c levels, indicating that perhaps the lifespan extension effects of such drugs might occur independently of glucose modulation. Future studies should, therefore, carefully investigate how glucoregulatory drugs can be used for lifespan and healthspan extension. Importantly, our study suggests that strategies to ‘‘correct elevated glucose’’ would not be relevant for mouse aging. A central corollary is that other glucose-lowering drugs that are ineffective in extending lifespan in mice might still have potential for humans and NHPs, where elevated glucose is an outcome of advanced age. This important finding has not been previously reported and is currently not recognized in the aging field.

This study has several strengths. Examining metabolic indices longitudinally across the lifespan in 1,241 mice (both sexes and 2 strains), 254 NHPs (both sexes and 2 study sites), and 3,023 humans (both sexes), as well as comparing these indices with those from external mouse and human cohorts provides evidence of the generalizability of these findings. The robustness of these findings is supported by the consistency in findings across sexes, strains, and study sites. The prospective study design reduces potential bias of reverse causation (or more precisely, confounding by preexisting illness). The use of standardized, common metabolic indices that are noninvasive and convenient to measure allows for comparison with prior and future studies as well.

Standard models and methods that are commonly used in biomedical and epidemiological research were employed here. It is noteworthy that some of these standard methodologies need to be reconsidered to improve the strength of translational aging research and the aging field as a whole. For example, there have been extensive discussions about how laboratory conditions can contribute to comparative biology studies where reproductive status and housing temperatures may play a role in how model organisms age. However, as the primary goal of this work was to compare between commonly used models of aging

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and human populations, the most studied conditions for mouse studies were examined (i.e., virgin animals, sub-thermoneutral housing conditions, and the inclusion of C57BL/6 mice). Environmental exposures could significantly affect aging and survival outcomes–whether it is housing temperature in laboratory animals (Speakman and Keijer, 2012) or exposure to environmental toxicants in humans (Lelieveld et al., 2020). Several other confounders are specific to human populations that could lead to larger heterogeneity (e.g., variations in diet, smoking status, socioeconomic status, height, and birthweight) that may have effects on the outcomes examined here. However, since the purpose of this study was to compare across species, such confounders could not be meaningfully considered within the context of laboratory animals. Yet we surmise that having multiple variables such as strain and NHP study sites (the diets at the two sites were markedly different, as previously published; Mattison et al., 2017) recapitulates partially the variability expected in the human population. Interestingly, our data also show that animal models display a high degree of heterogeneity on par with what is observed in the human population, despite being subjected to a smaller number of genetic and environmental confounders. Examining how observations made in this study compared with studies that account for these modifications could be the focus of future studies that are more refined to address these issues.

Limitations of study

Due to the complexity, cost, enrollment methodology, and duration of NHP and human life-course studies, there were lower numbers of NHP and humans compared with SLAM, particularly for humans in the younger age groups. This may have reduced our statistical power in some of the subgroup analyses. Examining other measures of glucose homeostasis (e.g., insulin levels, HOMA-IR as an index for insulin resistance) should be the focus of future studies, where the volume of blood that can be obtained from mice would be a central consideration. It is postulated that older mice may respond differently to fasting, which could lead to alterations in biological responses, indicating that fasting time could be a driver of the observations made here. However, we have noted that age-associated non-fasted blood glucose also decreases in a randomly selected subset of SLAM mice (unpublished observation). As the technology to measure lean mass was not available at the early phases of BLSA, lean mass was not examined in the present analysis. Future studies should examine, where possible, the effect of lean mass on mortality, given evidence in humans (Wang et al., 2019). Additionally, this study did not attempt to untangle the separate contributions of stature (height/length) and obesity to weight changes that were observed, although a separate analysis of body fat was performed. As stature has previously been shown to impact risk of important age-related diseases in human populations, future work should look more directly at the impact of stature on mortality risk across species (e.g., tail to tip of nose measurement as an equivalent for stature in mice).

Although some differences in life-course trajectories were observed across mouse strain and NHP sites, we did not observe differences when examining their effects on survival, allowing for the subgroups to be pooled for the survival analyses. Future studies should be designed with sufficient power so that potential subgroup differences, however minor, could be examined in depth within the context of survival. Future studies should also examine how survivorship bias contributes to these findings, as long-lived subjects may exhibit specific

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phenotypes that are not representative of the general population. additionally, as the age of enrollment into BLSA and NHP studies varied, this study was not able to directly address how trajectories of change at earlier ages in metabolic parameters impacted mortality risk across species. To examine differences between individuals, we conducted a mixed model analysis and observed that the individual baseline (random effect) was not significant, and accounting for the individual variability does not substantially change the estimated hazard ratios for glucose, age, sex, or strain. Lastly, this analysis was not intended to examine specific biological mechanisms of metabolic and glucoregulatory action as a function of age (Amisten et al., 2017; Chandrasekera and Pippin, 2014; Dolenšek et al., 2015; Rorsman and Ashcroft, 2018; Wentworth et al., 1986) and, thus, cannot explain the species-specific differences reported. This will be the goal of ongoing follow-up studies.

In conclusion, mice are widely used to model human metabolism due to considerable genetic and physiological overlap and our ability to control variables in experimental design–including genetics, environment, diet, and husbandry. Moreover, most of the core machinery regulating glucose homeostasis is conserved between mice and humans (Chandrasekera and Pippin, 2014). Therefore, mice are without a doubt a valuable tool for identifying factors that lower blood glucose within the context of diabetes mellitus and other metabolic conditions. In the context of aging, our finding that longitudinal trajectories of glucose and associations with mortality rates are markedly different between mice and humans holds critical bearing, particularly in the context of interventions for health span and lifespan, since several dietary interventions and metabolically active compounds regulate blood glucose, weight, and body fat (caloric restriction, rapamycin, metformin, resveratrol, disulfiram, etc.). Our data also highlight the importance of conducting longitudinal measurements of established parameters to fully understand the translational value of animal models and to define which markers truly recapitulate disease onset, progression, and mortality predictors of the aging process in humans and which ones are solely relevant for understanding the underlying biology of the aging mouse.

STAR☆METHODS

RESOURCE AVAILABILITY

Lead contact—Further information and requests for resources and reagents should be directed to and will be fulfilled by the Lead Contact, Rafael de Cabo (decabora@mail.nih.gov).

Materials availability—This study did not generate new unique reagents.

Data and code availability

- The human data used in this paper are from the Baltimore Longitudinal Study of Aging (BLSA). Specific language included in the BLSA consent form does not allow publication in public domain. However, BLSA data are available upon request from the BLSA website [https://www.blsa.nih.gov/] pending approval of the IRB of the National Institutes of Health, the IRB overseeing the BLSA. All requests submitted through the website are routed to the BLSA Data Sharing

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Proposal Review Committee that oversee all data requests/releases. All murine and nonhuman primate data have been deposited at Zenodo (https://zenodo.org/) and will be publicly available as of the date of publication. The DOI is listed in the key resources table.

- All original code has been deposited at Zenodo and will be publicly available as of the date of publication. The DOI is listed in the key resources table.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

Study of longitudinal aging in mice (SLAM)—SLAM is an ongoing, longitudinal cohort-based assessment of normative aging in mice conducted at the National Institute on Aging (NIA) (Palliyaguru et al., 2020). Mice were born at The Jackson Laboratory (Bar Harbor, ME), shipped to the NIA animal facility (Baltimore, MD) under a special breeding contract in cohorts of ~200 12-week-old mice every 3 months, and followed longitudinally thereafter. Mice are inbred C57BL/6 (stock number: 000664) and outbred HET3 (stock number: 409673) of both sexes. For the current analysis, data collected from 1241 mice (cohorts 1 to 6; ~50% female, ~50% HET3) between 2015–2019 were included. Mice were grouped housed (4 mice per cage) and fed NIH-31 diet ad libitum and had free access to acidified water. Mice were housed in rooms that were maintained at 22.2 ± 1 °C and 30–70% humidity. Routine tests are performed to ensure that mice are pathogen-free and sentinel cages are maintained and tested according to American Association for Accreditation of Laboratory Animal Care (AAALAC) criteria. This study was approved by the Animal Care and Use Committee of the NIA in Baltimore, MD under Animal Study Protocol number TGB-458–2021.

Nonhuman primates: NIA & Wisconsin National Primate Research Center (WNPRC;WIS)—Rhesus monkey (*Macaca mulatta*) data were pooled from control animals in multiple studies conducted at the NIA (Indian and Chinese origin) and Wisconsin National Primate Research Center (WIS, WNPRC) (Indian origin) primate colonies. The current analysis consisted of data collected from 254 monkeys (44% female, 85% NIA) between 1987–2018. Housing, husbandry, and diet conditions are in some cases different between the two study sites and have been previously published (Mattison et al., 2017). For example, NIA monkeys were fed a natural ingredient diet containing 17.3% protein and 5% fat and WIS monkeys were fed a semi-purified, nutritionally fortified, low-fat diet containing 15% protein and 10% fat. All animal rooms were maintained at ~21 C and 50–65% humidity. All animals were maintained in accordance with recommendations in the ‘‘Guide for the Care and Use of Laboratory Animals’’ (NIH publication No. 85–23) (National Research Council et al., 2011). All procedures were approved by the Institutional Animal Care and Use Committees (IACUC) and conducted as per applicable guidelines and regulations.

Baltimore longitudinal study of aging (BLSA)—BLSA is a long-running (1958 to present), continuous-enrollment longitudinal cohort study of healthy aging in community-

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dwelling men and women residing primarily in the Baltimore/Washington area (Ferrucci, 2008). At enrollment, participants were at least 20 years old and free from functional limitations, cognitive impairment, and chronic disease. For the current analysis, data from 3023 adults (47% women, 22% non-White) collected between 1958–2019 were included. All participants provided written consent and study protocols were approved by the Institutional Review Board at the National Institute of Environmental Health Sciences (AG000015–60).

METHOD DETAILS

Study of longitudinal aging in mice (SLAM)—Blood glucose was measured every 12 weeks from submandibular blood after a 6-hour fast in all mice. All mice were weighed every other week and underwent NMR spectroscopy without anesthesia for absolute body fat quantifications every 12 weeks. Inclusion criteria were that mice belonged to cohorts 1 through 6. As per the study design of SLAM, most mice were followed until their natural death, but subsets of randomly selected mice undergo planned euthanasia throughout the course of the study. While these selections were not based on any of the data collected as part of the study, animals whose cage-mates had died during the course of the study were preferentially selected for euthanasia to minimize impact of individual housing on longitudinal measurements. Mortality, defined as a natural death, was reported by daily cage checks and veterinary inspection.

Nonhuman primates: NIA & Wisconsin National Primate Research Center (WNPRC;WIS)—Fasting blood glucose was measured under anesthesia after an overnight fast at least bi-annually. Body weight and absolute body fat (by DEXA) were assessed at least annually. Only NHPs with both body weight and body fat data obtained at the time of DEXA were used. The exact frequency of measurements was dependent on each NHP colony and their study protocol. For some groups, more measurements were available for glucose than for weight and body fat at earlier and later stages, in part due to the development of kyphosis in aged NHPs, which prevented assessment of body composition by DEXA. Inclusion criteria were having lived past 10 years, not being removed from the studies due to health reasons and having at least one valid glucose, body weight, or body fat measurement. At both sites, NHPs were assessed daily and euthanized when clinically indicated and the animal was approaching the end of its life.

Baltimore longitudinal study of aging (BLSA)—Fasting blood glucose, body weight, and waist circumference (as an indirect measure of body fat) were collected at each visit. Inclusion criteria was having at least one valid glucose, body weight, or waist circumference measurement. Mortality was assessed by attempted participant contact, medical records, obituaries, and the National Death Index.

QUANTIFICATION AND STATISTICAL ANALYSIS

Kaplan-Meier survival curves were constructed for each population using those who died to determine median (with interquartile range, IQR) and maximum life expectancy. Midlife, late life and oldest in life were defined as 50%, 75% and 90% of median life expectancy, respectively. This was an a priori methodological choice based on the distribution of life

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expectancy and the clinical significance of the life stages that allowed for comparison between species. Trajectories over the lifespan for each metabolic index were plotted against age with a LOESS smoothed trend curve for all three species by subgroup (sex and strain/site). It is important to note that dots in the trajectory plots represent repeated assessments on individual animals at different time points, showing differences in absolute values at different ages. This approach was necessary because participants of nonhuman primate and BLSA studies are not enrolled into the study at the same age, unlike SLAM mice. Additionally, presenting data as absolute measures allowed for generalizability and interpretability with regard to other studies that are most frequently conducted in a cross-sectional fashion.

Next, the mean age corresponding to the highest values for each metabolic index (denoted as the peak; based on pre-and post-values) along with 95% confidence intervals were identified using the highest peak based on general additive model-predicted values at each age for each species subgroup. Pre-peak period was defined as 25% of median life expectancy to age at peak value and post-peak period was defined as age at peak to 125% median life expectancy. Secondary, minor peaks although present were not examined during this analysis. Mean pre- and post-peak rates and corresponding 95% confidence intervals were modeled linearly per 5% increase in median life expectancy. One sample Student's t test was used to test whether means were significantly different from zero. Missing values were imputed with last observed value carried forward when possible. Statistical significance was set at $p < 0.05$ (2-tailed). All analyses were conducted in R (version 1.2.1335).

Mortality risk analysis—To determine mortality risk associated with life course trajectories of fasting blood glucose, body weight and fat, Kaplan-Meier survival curves were plotted comparing the mortality rates of subjects above the highest and below the lowest quartile (Altman and Bland, 1994) of each metabolic index. Statistical interactions of the association of the trajectory and mortality by sex and strain/site were tested using a nested log-likelihood model comparison with and without the interaction term. This testing clearly showed that while most subgroups do show differences in absolute values of the lifespan trajectory, this did not translate to the association of the trajectory on mortality, allowing for pooling by sex and strain/site for the survival analysis. Sex-specific hazard ratios are also presented according to an a priori research question. Subjects alive in each study at the beginning of three time points: midlife, late life and oldest in life were used for this analysis. As such, sex-specific quartiles were used to dichotomize the continuous variables (glucose, body weight, adiposity) so that they were appropriate for group-wise comparison. Since Cox regression is a multivariable form of semi-parametric regression, it allows for regression using both indicator and continuous confounders with fewer statistical distribution assumptions. In standard output of these regressions for group-wise comparison, a log-rank test with the null hypothesis that the hazard ratio is not different from zero was used (Clark et al., 2003). Therein, hazard ratios (95% confidence intervals) were calculated using Cox proportional hazard models, adjusting for age and additionally for sex and/or body fat. The proportion hazards assumption was tested and met. Subjects that did not undergo a natural death, were alive at the time point of interest and those lost to follow-up were censored in the mortality analysis, where they were included in the population ‘‘at

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risk'' for an event (in this case, death) until the date of their removal from the study (*e.g.*, due to a planned euthanasia).

Assessment of generalizability to external studies—Life course trends of glucose of SLAM mouse cohort were compared to an independent cohort of Diversity Outbred (DO) mice (n=597, 53% female) from The Jackson Laboratory, which had 3 longitudinal assessments of blood glucose. Similarly, BLSA glucose data were compared to data from the National Health and Nutrition Examination Survey (NHANES, 1999–2016), a cross-sectional, US population-based study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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Highlights

- Age-associated fasting blood glucose trends differ between mice and monkeys/humans
- Mice, monkeys, and humans have similar body weight trajectories with age
- The association of glucose with survival is inverse for mice versus monkeys/humans
- Mice do not fully recapitulate aging-related glucose metabolism changes of primates

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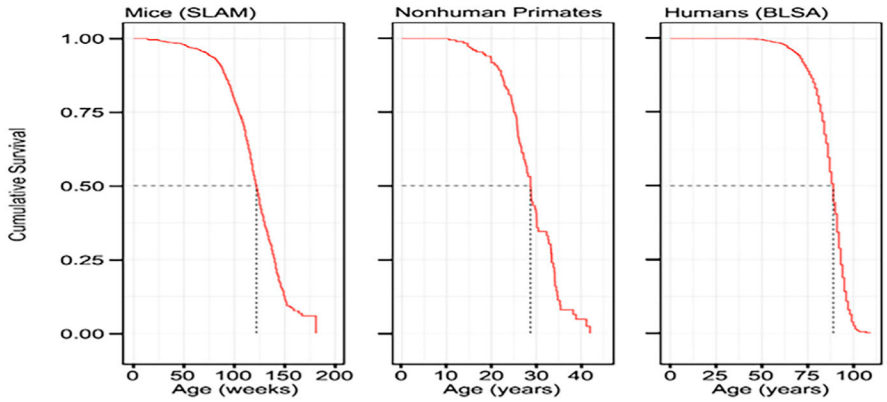

Metric	Mice (SLAM)	Nonhuman Primates	Humans (BLSA)
N Total	1241	254	3023
N Dead	776	87	1193
Median Life Expectancy (IQR)	115.00 (98.00, 129.00)	26.74 (23.09, 30.30)	86.00 (79.00, 91.00)
Maximum Life Expectancy	181	42.03	109
Midlife	57.50	13.37	43.00
Late Life	86.25	20.06	64.50
Oldest in Life	103.50	24.07	77.40

Figure 1. Species-specific population and lifespan characteristics

Kaplan-Meier survival curves (top panel) and population characteristics (bottom panel) for mice, NHPs, and humans involved in this study. Life expectancy values are in weeks for mice and years for nonhuman primates and humans. SLAM, Study of Longitudinal Aging in Mice; BLSA, Baltimore Longitudinal Study of Aging; IQR, interquartile range.

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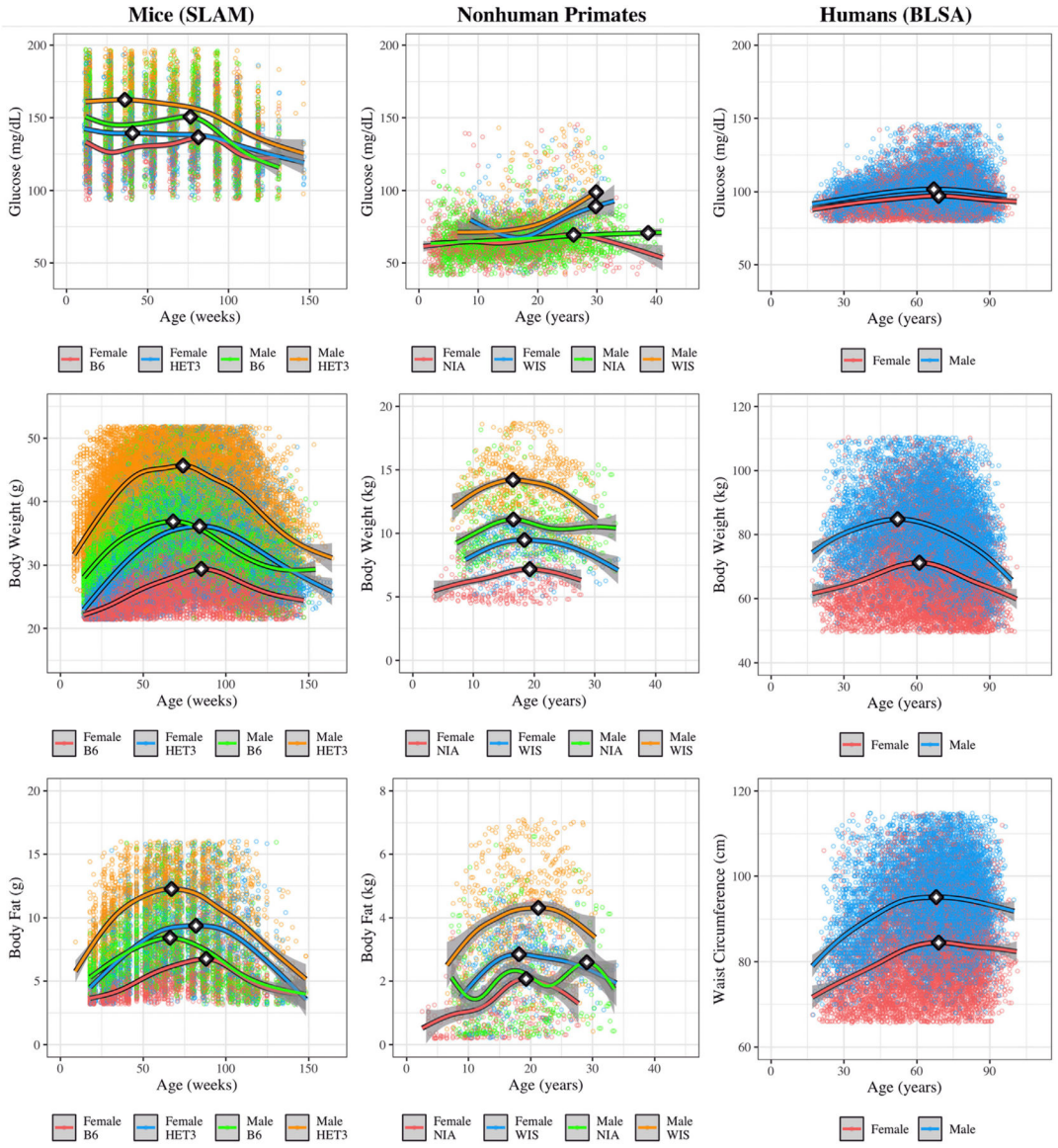

Figure 2. Trends in metabolic indices over the lifespan across species by sex and strain/site

Life-course trajectories for fasting blood glucose (top panels), weight (middle panels), and body fat (bottom panels) in mice (left), NHPs (middle), and humans (right). Age is listed in weeks for mice and years for NHPs and humans. Fasting blood glucose is measured in mg/dL in all three species, whereas weight and body fat are measured in grams (g) in mice and kilograms (kg) in NHPs. In humans, weight is measured in kg and body fat is measured by waist circumference (cm). Diamonds represent age at peak index value between 25% and 125% of median life expectancy. SLAM B6 females (n = 310), B6 males (n = 313), HET3 females (n = 311), HET3 males (n = 307), NHP female NIA (n = 96), NHP male NIA (n = 120), NHP female WIS (n = 15), NHP male WIS (n = 23), BLSA females (n = 1,410), and BLSA males (n = 1,613). SLAM, Study of Longitudinal Aging in Mice; BLSA, Baltimore Longitudinal Study of Aging.

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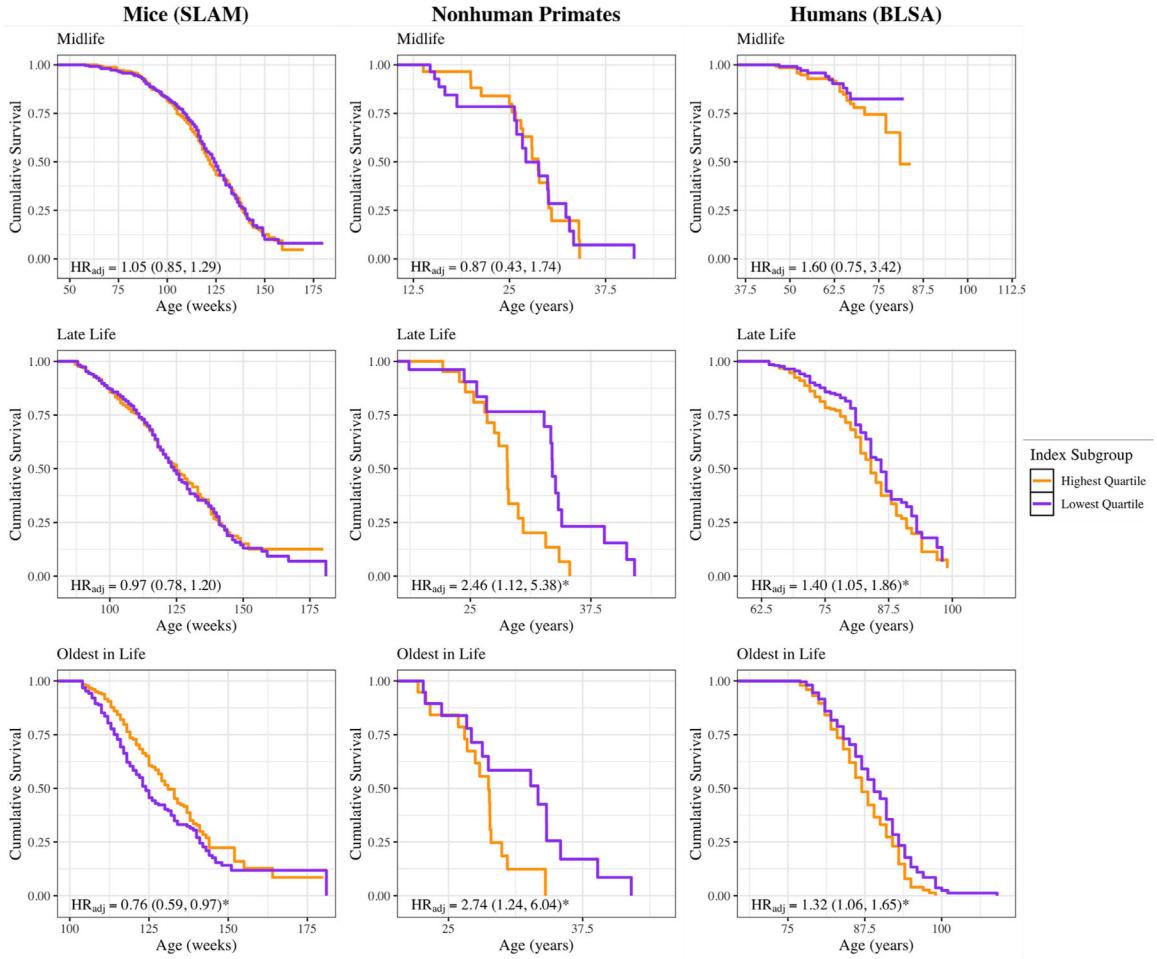

Figure 3. Mortality analysis based on metabolic stratification

Kaplan-Meier survival curves and age-adjusted mortality hazard ratios (HR_{adj}, 95% confidence intervals) comparing individuals above the highest (orange) and below the lowest (purple) quartiles of fasting glucose at midlife (50% median life expectancy, top panels), late life (75% median life expectancy, middle panels), and oldest in life (90% median life expectancy, bottom panels) across in mice (left), NHPs (middle), and humans (right). Age is listed in weeks for mice and years for NHPs and humans. *$p < 0.05$ was considered statistically significant. SLAM mice (n = 776); NHPs (n = 87); BLSA (n = 1,193). SLAM, Study of Longitudinal Aging in Mice; BLSA, Baltimore Longitudinal Study of Aging.

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Table 1.

Rate of percent change in metabolic indices during pre- and post-peak phases across species by subgroup

		Nonhuman primates				Humans (BLSA)						
Metabolic index	**Subgroup**	**Peak age[a] (weeks)**	**Pre-peak[b,c] rate (per 6 weeks)**	**Post-peak[b,c] rate (per 6 weeks)**	**Subgroup**	**Peak age[a] (years)**	**Pre-peak[b,c] rate (per year)**	**Post-peak[b,c] rate (per year)**	**Subgroup**	**Peak age[a] (years)**	**Pre-peak[b,c] rate (per 4 years)**	**Post-peak[b,c] rate (per 4 years)**
Glucose	All	78.29 (67.43, 92.00)	0.11% (0.10, 0.13)*	−3.08% (−3.12, −3.04)*	all	26.89 (24.25, 31.25)	0.48% (0.47, 0.49)*	−0.68% (−0.71, −0.64)*	all	69.00 (63.00, 75.00)	0.70% (0.69, 0.70)*	−0.64% (−0.64, −0.63)*
	female B6	81.43 (67.43, 103.43)	1.02% (0.99, 1.05)*	−2.95% (−3.17, −2.74)*	female NIA	26.08 (22.00, 30.58)	0.26% (0.24, 0.28)*	−0.64% (−0.70, −0.58)*	female	69.00 (61.00, 76.00)	0.65% (0.65, 0.66)*	−0.58% (−0.58, −0.57)*
	female HET3	40.71 (35.00, 92.00)	0.11% (0.11, 0.12)*	−1.02% (−1.07, −0.96)*	female WIS	29.79 (18.46, 29.82)	0.66% (0.48, 0.84)*	peak at 125% MLE	male	67.00 (58.00, 75.00)	0.75% (0.74, 0.76)*	−0.57% (−0.58, −0.57)*
	male B6	76.43 (54.29, 92.00)	0.96% (0.94, 0.98)*	−4.38% (−4.45, −4.30)*	male NIA	38.58 (29.25, 38.83)	0.23% (0.23, 0.23)*	peak at 125% MLE	–	–	–	–
	male HET3	36.00 (36.00, 63.43)	Peak at 25% MLE	−1.89% (−1.96, −1.82)*	male WIS	29.86 (22.96, 30.44)	1.25% (1.16, 1.33)*	2.54% (2.54, 2.54)*	–	–	–	–
Body weight	All	77.43 (71.00, 84.14)	0.65% (0.65, 0.66)*	−0.67% (−0.67, −0.67)*	all	17.00 (13.50, 33.42)	0.28% (0.27, 0.29)*	−0.05% (−0.06, −0.05)*	all	60.00 (52.00, 66.00)	0.81% (0.80, 0.82)*	−1.35% (−1.36, −1.34)*
	female B6	85.14 (80.14, 91.00)	0.65% (0.65, 0.65)*	−0.61% (−0.61, −0.60)*	female NIA	19.25 (14.50, 27.75)	0.11% (0.11, 0.11)*	−0.10% (−0.11, −0.09)*	female	61.00 (54.00, 67.00)	1.03% (1.02, 1.03)*	−1.22% (−1.22, −1.21)*
	female HET3	84.14 (74.14, 94.14)	0.94% (0.93, 0.95)*	−0.81% (−0.82, −0.80)*	female WIS	18.39 (8.72, 29.82)	0.15% (0.14, 0.16)*	−0.10% (−0.11, −0.09)*	male	52.00 (44.00, 59.00)	0.96% (0.94, 0.98)*	−1.42% (−1.43, −1.41)*
	male B6	68.00 (60.14, 75.00)	0.70% (0.69, 0.71)*	−0.80% (−0.80, −0.79)*	male NIA	16.58 (12.50, 21.50)	0.21% (0.20, 0.22)*	−0.03% (−0.04, −0.02)*	–	–	–	–
	male HET3	74.00 (66.14, 79.86)	0.78% (0.76, 0.79)*	−1.09% (−1.10, −1.08)*	male WIS	16.52 (6.63, 30.44)	0.20% (0.19, 0.21)*	−0.19% (−0.20, −0.18)*	–	–	–	–

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		Nonhuman primates						Humans (BLSA)				
Metabolic index	**Subgroup**	**Peak age[a] (weeks)**	**Pre-peak[b,c] rate (per 6 weeks)**	**Post-peak[b,c] rate (per 6 weeks)**	**Subgroup**	**Peak age[a] (years)**	**Pre-peak[b,c] rate (per year)**	**Post-peak[b,c] rate (per year)**	**Subgroup**	**Peak age[a] (years)**	**Pre-peak[b,c] rate (per 4 years)**	**Post-peak[b,c] rate (per 4 years)**
Body fat	all	71.14 (61.86, 83.86)	0.36% (0.35, 0.36)*	−0.36% (−0.37, −0.36)*	all	17.84 (15.50, 33.42)	0.17% (0.17, 0.18)*	−0.03% (−0.04, −0.03)*	all	73.00 (65.00, 80.00)	0.88% (0.87, 0.88)*	−0.55% (−0.56, −0.54)*
	female B6	88.14 (77.43, 95.29)	0.31% (0.31, 0.32)*	−0.41% (−0.43, −0.40)*	female NIA	19.25 (15.75, 27.75)	0.11% (0.10, 0.12)*	−0.08% (−0.09, −0.08)*	female	69.00 (61.00, 78.00)	1.00% (0.99, 1.01)*	−0.28% (−0.28, −0.28)*
	female HET3	81.86 (63.29, 100.14)	0.40% (0.38, 0.41)*	−0.48% (−0.50, −0.46)*	female WIS	18.11 (8.72, 29.82)	0.14% (0.13, 0.15)*	−0.04% (−0.04, −0.04)*	male	68.00 (57.00, 78.00)	1.01% (0.99, 1.03)*	−0.36% (−0.36, −0.35)*
	male B6	66.14 (57.43, 77.00)	0.35% (0.34, 0.36)*	−0.43% (−0.43, −0.42)*	male NIA	29.08 (23.58, 33.50)	0.04% (0.03, 0.04)*	−0.20% (−0.23, −0.18)*	–	–	–	–
	male HET3	67.00 (54.43, 80.14)	0.44% (0.42, 0.45)*	−0.50% (−0.51, −0.49)*	male WIS	21.22 (6.63, 30.44)	0.10% (0.09, 0.11)*	−0.09% (−0.10, −0.09)*	–	–	–	–

Entire population and subgroup-specific values are both listed. SLAM, Study of Longitudinal Aging in Mice; BLSA, Baltimore Longitudinal Study of Aging. One sample Student's t test was used to test whether the means are significantly different from zero.

*$p < 0.05$ was considered statistically significant.

[a]Mean (range of ages at similar values) of age at peak index value

[b]Mean (95% confidence interval) rate of percent change

[c]Pre-peak is defined as 25% life expectancy to age at peak value; post-peak is defined as peak to 125% life expectancy

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Table 2.

Mortality hazard ratios of highest and lowest glucose quartiles at varying time points across species by subgroup

		Mice (SLAM)		Nonhuman primates		Humans (BLSA)	
Group	**Time point**[b,c]	**HR11**	**HR22**	**HR11**	**HR22**	**HR11**	**HR22**
All	midlife	1.05 (0.85, 1.29)	1.02 (0.82, 1.28)	0.88 (0.43, 1.80)	0.46 (0.21, 0.97)[a]	1.60 (0.75, 3.42)	1.42 (0.64, 3.15)
	late life	0.97 (0.78, 1.20)	1.09 (0.87, 1.38)	2.50 (1.15, 5.46)[a]	1.82 (0.71, 4.65)	1.40 (1.05, 1.86)[a]	1.36 (1.00, 1.83)[a]
	oldest in life	0.76 (0.59, 0.97)[a]	0.96 (0.74, 1.25)	3.00 (1.34, 6.70)[a]	2.32 (0.87, 6.17)	1.32 (1.06, 1.65)[a]	1.09 (0.76, 1.58)
Female	midlife	1.04 (0.78, 1.40)	1.06 (0.78, 1.45)	0.31 (0.09, 1.08)	0.23 (0.07, 0.83)[a]	1.11 (0.38, 3.26)	0.99 (0.33, 3.00)
	late life	0.95 (0.69, 1.29)	1.08 (0.78, 1.50)	0.99 (0.27, 3.65)	1.44 (0.29, 7.08)	1.24 (0.76, 2.02)	1.45 (0.86, 2.42)
	oldest in life	0.63 (0.44, 0.90)[a]	0.74 (0.51, 1.08)	1.68 (0.50, 5.63)	1.03 (0.28, 3.80)	1.40 (0.95, 2.05)	1.40 (0.95, 2.08)
Male	midlife	1.05 (0.79, 1.41)	0.98 (0.71, 1.34)	1.62 (0.61, 4.30)	0.70 (0.24, 2.02)	1.84 (0.62, 5.42)	1.56 (0.50, 4.87)
	late life	1.01 (0.74, 1.37)	1.09 (0.79, 1.52)	4.21 (1.42, 12.48)[a]	2.26 (0.64, 7.93)	1.39 (0.98, 1.97)	1.26 (0.87, 1.82)
	oldest in life	0.90 (0.64, 1.26)	1.31 (0.90, 1.92)	12.79 (3.43, 47.72)[a]	10.67 (2.61, 43.65)[a]	1.29 (0.98, 1.70)	1.28 (0.96, 1.71)

Entire population and subgroup-specific values are both listed. SLAM, Study of Longitudinal Aging in Mice; BLSA, Baltimore Longitudinal Study of Aging. The numbers in parentheses are 95% CI.

[a] $p < 0.05$ was considered statistically significant

[b] Midlife, 50% median life expectancy; late life, 75% median life expectancy; oldest in life, 90% median life expectancy

[c] Hazard ratios are (1) adjusted for age and sex and (2) additionally adjusted for body fat

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KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
Murine and nonhuman primate data	This study	https://doi.org/10.5281/zenodo.5167639
Human data	BLSA study	Available upon request/approval
All original codes	This study	https://doi.org/10.5281/zenodo.5167639
Experimental models: Organisms/strains		
Female and male C57BL/6J mice	The Jackson Laboratory	000664
Female and male HET3 mice	The Jackson Laboratory	409673
Nonhuman primates (Indian and Chinese origin)	National Institute on Aging	N/A
Nonhuman primates (Indian origin)	Wisconsin National Primate Research Center	N/A
Software and algorithms		
R	The Comprehensive R Archive Network (CRAN)	https://cran.r-project.org/
Microsoft Excel 2019	Microsoft	https://www.microsoft.com/en-gb/; RRID: SCR_016137
SAS	Statistical Analysis System (SAS)	https://www.sas.com/
Other		
Minispec LF90	Bruker Optics	https://www.bruker.com/products/mr/td-nmr/minispec-lf-series.html
Contour Next EZ Glucometer and strips	Bayer	https://www.contournext.com/products/contour-next-ez/