Decreased lifespan in female "Munchkin" actors from the cast of the 1939 film version of "*The Wizard of Oz*" does not support the hypothesis linking hypopituitary dwarfism to longevity

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Abstract

In laboratory mice pituitary dwarfism caused by genetic reduction or elimination of the activity of growth hormone (GH) significantly extends lifespan. The effects of congenital pituitary dwarfism on human longevity is not well documented. To analyze the effects of untreated pituitary dwarfism on human lifespan, the longevity of a diverse group of widely-known little people, the 124 adults who played “Munchkins” in the 1939 movie, *The Wizard of Oz* was investigated. Survival of "Munchkin" actors with those of controls defined as cast members of *The Wizard of Oz* and those of other contemporary Academy Award winning Hollywood movies was compared. According to the Kaplan-Meier survival curves, survival of female and male “Munchkin” actors was shorter than cast controls and Hollywood controls of respective sexes. Cox regression analyses showed that female “Munchkin” actors had significantly higher risk ratios compared to both female cast controls (RR: 1.70; 95% CI: 1.05 to 2.77) and female Hollywood controls (RR: 1.52; 95% CI: 1.03 to 2.24). Similar trends were also discernible for men, albeit point estimates were not significant. The lack of lifespan extension in "Munchkin" actors does not support the hypothesis that hereditary GH deficiency regulates longevity in humans.

Introduction

The most reliable and effective genetic intervention to lengthen the life of laboratory mice is to reduce or eliminate the activity of pituitary growth hormone (GH). Long-lived mouse pituitary dwarfs have been created by spontaneous mutations in genes for the transcription factors, Prop1 or Pit1, both of which abolish the development of pituitary GH-, prolactin-, and thyroid stimulating hormone-producing cells, by a spontaneous mutation in the growth hormone releasing hormone (GHRH) receptor, inhibiting GH release by the pituitary, or by targeted disruption of GHRH or the GH receptor [1, 2]. These interventions extend life in both sexes and has been replicated in multiple labs across multiple mouse genotypes. In addition, outbred mice artificially selected for diverse early life growth trajectories displayed a negative correlation between body weight at age 6 months and longevity [3]. By contrast, genetically GH-deficient Lewis rats did not exhibit extended longevity unless GH was administered for 10 weeks in early life [4]. These robust findings in mice, and their apparent contradiction in rats raises the question, which paradigm represents the human impact of reduced GH activity?

Congenital pituitary dwarfism is well-known in humans. Typically, cases are classified as either isolated GH deficiency, due to mutations in GH- or GHRH-producing genes or their receptors or Multiple Pituitary Hormone Deficiency, due to mutations in developmental transcription factor genes such as Prop1 or Pou1F1 (human version of mouse Pit1), which affect multiple pituitary hormones [5]. Despite the large number of individuals affected by these mutations, their longevity impact has been difficult to assess due to the development of therapeutic hormone replacement in the 1960's. What evidence is at hand is mixed. A Swiss cohort with a disabling GH mutation in the 19th and early 20th centuries had reduced longevity compared with unaffected siblings and unrelated contemporaries [6]. Israeli and Ecuadorian populations with GH receptor mutations did not differ in longevity from contemporaries, although they did exhibit lower incidences of cancer and diabetes [7, 8]. However, earlier study of the same Ecuadorian population found higher mortality before age seven in dwarfs compared with normal size siblings [9]. There was also no significant longevity difference in a Brazilian cohort with a GHRH receptor mutation, although that population also exhibited reductions in a number of cancer types [10]. In a Croatian population with a disabling mutation in the Prop1 gene twenty-three untreated heredity dwarfs have been historically identified. Longevity information, however, is only available for nine untreated individuals, including four siblings born in the late 19th century. Of those siblings, the two brothers died at 68 and 77 years of age, fairly typical for that population, but the two sisters lived to 87 and 91 years, provocatively longer than average for contemporary women [11].

Given the sparse information on the longevity of untreated pituitary dwarfs, we have investigated the longevity of a diverse group of widely-known little people, the 124 adults who played "Munchkins" in the 1939 movie, *The Wizard of Oz*. Actors for "Munchkin" roles were recruited by professional agents who scoured the country looking for, in the words of producer Mervyn LeRoy, "little people who were little and cute and looked perfect"[12]. That is, they needed to be small but appropriately proportioned. Headhunters were instructed to weed out achondroplastic dwarfs with their disproportionately short arms and legs. Consequently, only five of the Munchkins were achondroplastic dwarfs and we have deleted them from the following analysis. Therefore, although we do not know the genetic basis of their reduced size, it almost certain signals profoundly reduced GH activity. Median height from a sample of twenty-three known-height "Munchkin" actors was 102 cm, considerably shorter than most of the known genetic hypopituitary dwarfs. For instance, males in the Brazilian cohort with Isolated Growth Hormone Deficiency averaged 129 cm in height, females 117 cm, the Croatian Prop1 cluster had mean height of 125 cm.

Most "Munchkin" actors were recruited from circus and carnival acts, from vaudeville shows, or from a variety of performance venues. They largely came from impoverished, often nightmarish backgrounds, and in some cases had been sold by their parents to passing carnival impresarios. Many had immigrated from Europe, where "little people troupes" were particularly popular in the early part

of the 20th century. They often changed names and possibly birth dates in doing so. Also, as performers who shifted often from job to job, they regularly took on new stage names. All this makes establishing birth year challenging, and for most of the "Munchkin" actors we accepted their self-stated birth year unless other information was available. Ironically, their lot did not improve dramatically while acting in *The Wizard of Oz*, during which as one of them remarked, they were paid less than Toto, the dog. Individual death years were gathered from multiple sources and confirmed with local obituaries whenever possible. In total, we validated age-at-death for 88 little people actors. At the time the movie was filmed, their median age was 32 years, the youngest being 11 years old at the time, the oldest 69 years. We compared survival of "Munchkin" actors with those of controls defined as cast members of *The Wizard of Oz* and those of other contemporary Academy Award winning Hollywood movies.

Methods

Study population and analysis of lifespan data

Data of actors from the movie *"The Wizard of Oz"* (1939) are publicly available (Figure 1). Cases were defined as actors playing Munchkin roles. Only participants with available date of birth and death were included in the study. As for controls, two sets were selected: cast controls and Hollywood controls. Cast controls were defined as other cast members of "*The Wizard of Oz*" movie paired to cases according to sex at a ratio of 1:1. Hollywood controls on the other hand were defined as cast member of movies that won an Academy Award between 1938 and 1940. We decided to include movies from 1938 to 1940 as the production of "*The Wizard of Oz*" began in 1938 thanks to the success of "*Snow White and the Seven Dwarf"* after which filmmaker realized that the adaptation of fairy tales and children's stories can be popular.[13] The movie "*The Wizard of Oz*" was eventually released in 1939 and was awarded an Academy Award for Best Original Music Score in 1940.[14] Movies from which controls were selected are displayed in **Table 1**. Hollywood controls were paired to cases according to sex and age at release date of *"The Wizard of Oz"* (1939) at a 1:3 ratio. Age was matched by conducting age group matching using the following age groups: 10–14, 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, and $\geq$ 50.

To examine the survival of participants, Kaplan-Meier survival curves were plotted, and Cox regression analyses were conducted with follow-up time and total lifespan as underlying time factor comparing "Munchkin" actors to cast controls and Hollywood controls in separate analyses. Outcome was defined as death as a dichotomous variable. Follow-up time was defined as the time between 1939 and death of participants (or 2022 if participants were alive at the time of the present analysis), whereas lifespan was defined as the total number of years lived using the same endpoints. Additionally, Gompertz mortality models were also performed to compare the differences in the age-related changes of age-specific mortality between groups[15]. Each analysis was conducted separately by sex as well. All statistics were carried out with STATA 15 and SPSS 28.0.0. Significance was set at $p<0.05$.

Results

We were able to collect year of birth and death for 98 of them. A total of 9 participants were excluded because either a reliable birth or death year was unavailable. Four participants were excluded because they suffered from achondroplasia and not pituitary dwarfism, resulting in a total of 85 (n=50 male, n=35 female) "Munchkin" actors included in the present analysis.

"Munchkin" actors had similar follow-up times, but shorter total lifespan as opposed to both cast controls and Hollywood controls (Table 2). This is also supported by the Kaplan-Meier survival curves, which show a lower survival for "Munchkin" actors compared to both cast controls and Hollywood controls (Figures 2 and 3, Panels A). Cox regression analyses with follow-up time as underlying time variable showed significantly higher risk ratios for "Munchkin" actors when compared to cast controls [risk ratios (RR): 1.39; 95% confidence interval (95% CI): 1.01–1.91] and

a non-significantly higher point estimate when using Hollywood controls as reference (Figures 2 and 3, Panels B). Similar trends were also observed for Cox regression models with total lifespan as underlying time variable, albeit risk ratios were not significant when compared to cast controls and Hollywood controls (Figures 2 and 3, Panels C). The Gompertz plots showed a significantly steeper increase of age-specific mortality for cast controls (p=0.018), whereas there were no significant differences when using Hollywood controls as reference (Figures 2 and 3, Panels D).

When participants were analysed separately by sex, female cast controls and female Hollywood controls had longer follow-up times and total lifespans than "Munchkin" actors. Among men, cast controls had shorter follow-up time (due to their higher age at the time of shooting), but longer lifespan. Male Hollywood controls exhibited a similar follow-up time and lifespan compared to male "Munchkin" actors (Table 2). According to the Kaplan-Meier survival curves, survival of female and male "Munchkin" actors was mostly shorter than cast controls and Hollywood controls of respective sexes (Figures 4-7, Panels A). When using follow-up time as underlying time variable in the Cox regression analyses, female "Munchkin" actors had significantly higher risk ratios compared to both female cast controls (RR: 1.70; 95% CI: 1.05–2.77) and female Hollywood controls (RR: 1.52; 95% CI: 1.03–2.24). Similar results were also discernible for men, albeit point estimates were not significant (Figure 4–7 Panels B and C). The Gompertz plots revealed a significantly steeper increase of age-specific mortality for male cast controls compared to male "Munchkin" actors ($p<0.001$) and a non-significant difference between female groups (Figure 4, Panel D and Figure 5, Panel D, respectively). Conversely, the Gompertz plots using Hollywood controls as reference showed non-significant differences between males, and a significantly steeper incline for female "Munchkin" actors ($p<0.001$; due the outlier last datapoint) (Figure 6, Panel D and Figure 7, Panel D, respectively).

Discussion

The key finding of this study is that "Munchkin" actors may have lower survival rates than healthy controls. Our data also suggests that lower survival may be more prominent among female "Munchkin" actors. This latter observation was consistent across different Cox proportional regression models. Similar trends were also discernible for male "Munchkin" actors, however, the difference did not reach statistical significance. Gompertz models revealed some inconsistencies for the change in age-specific mortality between comparison groups, but the Gompertz plots with stronger statistical power comprised of participants matched for age and sex at a ratio of 1:3 corroborate the results concerning the sex differences observed in the Cox proportional regression models.

Many disorders can cause short stature, including GH/IGF-1 deficiency, resistance to GH, thyroid hormone deficiency, achondroplasia, malnutrition and others. GH/IGF-1 deficiency and resistance to GH are characterized by proportionate short stature, whereas many genetic skeletal dysplasias are known for disproportionate short stature. The appearance of "Munchkin" actors on the film suggest that most of them had proportionate short stature, likely due to GH/IGF-1 deficiency. In fact, several "Munchkin" actors were known to have been diagnosed with pituitary dwarfism. Examples for "Munchkin" actors with proportionate short stature include Jerry Maren (born Gerard Marenghi; 1920–2018; diagnosed with GH-responsive pituitary dwarfism; **Figure 1**), Jakob Gerlich (born Leo Fuks; 1925 –1960) and Harry Earles (1902 –1985; diagnosed with pituitary dwarfism), who played the Munchkin members of the Lollipop Guild[16], Mickey Carroll (1920-2009, diagnosed with pituitary dwarfism), who played the Town Crier and Olga C. Nardone (1921-2010), who played a member of the Lullaby League. Notably, none of the "Munchkin" actors with diagnosed pituitary dwarfism outlived the longest-lived cast controls. The few "Munchkin" actors who had short-limb short stature, which is known to be caused by achondroplasia, hypochondroplasia, pseudoachondroplasia or multiple epiphyseal dysplasia, were exluded from the analysis.

Our findings accord with the conclusions of previous studies investigating the effects of hereditary GH deficient dwarfism on lifespan[17]. Accordingly, in untreated subjects exhibiting isolated GH deficiency due to a deletion of genomic DNA encompassing the GH-1 gene, median life span is

significantly shorter than that of unaffected brothers and sisters [males, 56 vs. 75 yr ($P < 0.0001$); females, 46 vs. 80 yr ($P < 0.0001$)][17]. Lifespan in patients with congenital GH deficiency caused by a homozygous mutation in the GHRH receptor gene was also reported to be shorter than the general population[18]. Patients with childhood-onset isolated GH deficiency also exhibit a number of health problems and have poor quality of life[19-21]. The finding that disruption of GH/IGF-1 signalling does not extend human lifespan is also supported by survival data obtained in a cohort of rural Ecuadorian indviduals with Laron syndrome[22]. These patients carry mutations in the growth hormone receptor (GHR) gene that lead to resistance to GH and consequential severe IGF-1 deficiency. Similar findings were reported in an Israeli cohort of patients with Laron dwarfism[8]. Of note, the murine model of the Laron syndrome (GHR/BP $^{-/-}$ Laron mice)[23] has a longer life expectancy than wild-type controls[24], highlighting the critical differences between the roles of the GH/IGF-1 axis in regulation of longevity in humans and laboratory animals including mice..

GH and IGF-1 confer multifaceted cytoprotective, growth-promoting and anti-aging effects[25-51]. In addition to short stature, early-onset disruption of GH/IGF-1 signalling compromise health in a myriad of ways. For example, patients with Laron syndrome have poor quality of life, exhibiting cognitive and psychological problems, small genitalia, birth defects, ophthalmological problems, obesity, hyperlipidemia, fatty liver, sleep problems, acromicria, small brain size and cerebrovascular disease[8, 22]. GH/IGF-1 deficiency increases cardiovascular risk[52] and risk for diabetes mellitus[20]. GH replacement therapy in adults with hypopituitary GH deficiency leads to a sustained improvement of adverse serum lipid profile and body composition[20]. The main exception by which disruption of GH/IGF-1 signalling may act to prevent the development of a specific age-related disease is its anti-cancer effect. Epidemiological studies confirm that similar to the findings observed in animal models of early-onset GH/IGF-I deficiency[53-59], patients with congenital GH/IGF-I deficiency have a significantly reduced risk of cancer development[8, 22, 60, 61]. In mice, in which malignancies are a leading cause of death, disruption of GH/IGF-I signaling extends lifespan primarily by inhibiting development of cancer[56, 58, 62-65]. In humans, the deleterious effects of attenuation/disruption of GH/IGF-I signalling on the cardiovascular system and the central nervous system likely overshadow its inhibitory effects on the pathogenesis of malignant diseases[66-68] and thus its net effect may actually shorten lifespan. This is supported by a study performed on humans carrying mutations of the growth hormone receptor gene in which participants seemed to be protected from cancers, while there was an increased cardiac disease risk as a cause of death among these participants[22].

Interestingly, when stratified by sex, the difference between the lifespan of "Munchkin" actors and cast controls persisted only in females, similar to the findings in patients with congenital GH deficiency[18]. Previous preclinical, translational and epidemiological studies demonstrate clear sexually dimorphic actions of the GH/IGF-1 axis[18, 53, 67, 69]. The existing evidence suggest that in mice the sexually dimorphic effects of disruption of GH/IGF-1 signalling on lifespan are due to the sex differences in its anti-cancer actions[53]. In humans the mechanisms contributing to the sexually dimorphic effects of the GH/IGF-1 axis are not well understood and warrant additional studies.

Finally, we must address certain limitations as well, most importantly the lack of information on confounding factors. The socioeconomic status, such as salary and living conditions of “Munchkin” actors, a marginalized group within the population, may be lower than that of actors not affected by this ailment. Other factors that may have biased our results is the possible stigmatization of individuals affected by dwarfism by the general population, which may have predisposed these individuals to riskier behaviours for instance. Judy Garland, who played Dorothy in the film, complained about the drinking problem of “Munchkin” actors in a 1967 interview. Yet, we do not have detailed information whether or not they actually exhibited riskier health behaviour, such as smoking and excessive alcohol consumption more often than members of the control groups. Since these factors may influence mortality, studies examining the longevity of human dwarf cohorts should adjust for their effect for a more precise estimation of differences in mortality between groups.

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Disclosure of Competing Interests

Dr. Anna Csiszar serves as Associate Editor for The Journal of Gerontology, Series A: Biological Sciences and Medical Sciences and GeroScience. Dr. Zoltan Ungvari serves as Editor-in-Chief for GeroScience and as Consulting Editor for The American Journal of Physiology-Heart and Circulatory Physiology. Dr. William E. Sonntag, Dr. Stefano Tarantini and Dr. Andriy Yabluchanskiy serve as Associate Editors for GeroScience.

Disclosure of Financial Interests

The authors declare no competing financial interests.

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REFERENCES

1. Bartke A. Minireview: role of the growth hormone/insulin-like growth factor system in mammalian aging. *Endocrinology*. 2005;146:3718-3723.
2. Sun LY, Spong A, Swindell WR, Fang Y, Hill C, Huber JA, Boehm JD, Westbrook R, Salvatori R and Bartke A. Growth hormone-releasing hormone disruption extends lifespan and regulates response to caloric restriction in mice. *eLife*. 2013;2:e01098.
3. Miller RA, Chrisp C and Atchley W. Differential longevity in mouse stocks selected for early life growth trajectory. *JGerontolA BiolSciMedSci*. 2000;55:B455-B461.
4. Sonntag WE, Carter CS, Ikeno Y, Ekenstedt K, Carlson CS, Loeser RF, Chakrabarty S, Lee S, Bennett C, Ingram R, Moore T and Ramsey M. Adult-onset growth hormone and insulin-like growth factor I deficiency reduces neoplastic disease, modifies age-related pathology, and increases life span. *Endocrinology*. 2005;146:2920-32.
5. Laron Z. Do deficiencies in growth hormone and insulin-like growth factor-1 (IGF-1) shorten or prolong longevity? *Mech Ageing Dev*. 2005;126:305-7.
6. Besson A, Salemi S, Gallati S, Jenal A, Horn R, Mullis PS and Mullis PE. Reduced longevity in untreated patients with isolated growth hormone deficiency. *JClinEndocrinolMetab*. 2003;88:3664-3667.
7. Guevara-Aguirre J, Balasubramanian P, Guevara-Aguirre M, Wei M, Madia F, Cheng CW, Hwang D, Martin-Montalvo A, Saavedra J, Ingles S, de CR, Cohen P and Longo VD. Growth hormone receptor deficiency is associated with a major reduction in pro-aging signaling, cancer, and diabetes in humans. *SciTranslMed*. 2011;3:70ra13.
8. Laron Z, Kauli R, Lapkina L and Werner H. IGF-I deficiency, longevity and cancer protection of patients with Laron syndrome. *Mutat Res Rev Mutat Res*. 2017;772:123-133.
9. Rosenbloom AL, Guevara-Aguirre J, Rosenfeld RG and Francke U. Growth hormone receptor deficiency in Ecuador. *JClinEndocrinolMetab*. 1999;84:4436-4443.
10. Aguiar-Oliveira MH and Bartke A. Growth Hormone Deficiency: Health and Longevity. *Endocrine reviews*. 2019;40:575-601.
11. Krzisnik C, Grguric S, Cvijovic M and Laron Z. Longevity of the hypopituitary patients from the island of Krk: a follow-up study. *Pediatr Endocrinol Rev*. 2010;7:357-362.
12. Weinstock M. “The Wizard of Oz,” the Last Munchkin, and the Little People Left Behind. *New Yorker*. 2018.
13. Harmetz A. *The Making of The Wizard of Oz*: Hyperion; 2004.
14. Kuchan MJ, Jo H and Frangos JA. Role of G proteins in shear stress-mediated nitric oxide production by endothelial cells. *Am J Physiol*. 1994;267:C753-8.
15. de Magalhães JP, Cabral JAS and Magalhães D. The influence of genes on the aging process of mice: a statistical assessment of the genetics of aging. *Genetics*. 2005;169:265-274.
16. "Jerry Maren, Who Sang and Danced as a Munchkin in Oz, Dies at 98". NYTimes.com. June 6, 2018. (accessed on 05/03/2022).
17. Besson A, Salemi S, Gallati S, Jenal A, Horn R, Mullis PS and Mullis PE. Reduced longevity in untreated patients with isolated growth hormone deficiency. *J Clin Endocrinol Metab*. 2003;88:3664-7.
18. Aguiar-Oliveira MH, Oliveira FT, Pereira RM, Oliveira CR, Blackford A, Valenca EH, Santos EG, Gois-Junior MB, Meneguz-Moreno RA, Araujo VP, Oliveira-Neto LA, Almeida RP, Santos MA, Farias NT, Silveira DC, Cabral GW, Calazans FR, Seabra JD, Lopes TF, Rodrigues EO, Porto LA, Oliveira IP, Melo EV, Martari M and Salvatori R. Longevity in untreated congenital growth hormone deficiency

due to a homozygous mutation in the GHRH receptor gene. *J Clin Endocrinol Metab*. 2010;95:714-21.

19. Abs R, Mattsson AF, Bengtsson BA, Feldt-Rasmussen U, Goth MI, Koltowska-Haggstrom M, Monson JP, Verhelst J, Wilton P and Group KS. Isolated growth hormone (GH) deficiency in adult patients: baseline clinical characteristics and responses to GH replacement in comparison with hypopituitary patients. A sub-analysis of the KIMS database. *Growth Horm IGF Res*. 2005;15:349-59.
20. Abs R, Mattsson AF, Thunander M, Verhelst J, Goth MI, Wilton P, Koltowska-Haggstrom M and Luger A. Prevalence of diabetes mellitus in 6050 hypopituitary patients with adult-onset GH deficiency before GH replacement: a KIMS analysis. *Eur J Endocrinol*. 2013;168:297-305.
21. Gaillard RC, Mattsson AF, Akerblad AC, Bengtsson BA, Cara J, Feldt-Rasmussen U, Koltowska-Haggstrom M, Monson JP, Saller B, Wilton P and Abs R. Overall and cause-specific mortality in GH-deficient adults on GH replacement. *Eur J Endocrinol*. 2012;166:1069-77.
22. Guevara-Aguirre J, Balasubramanian P, Guevara-Aguirre M, Wei M, Madia F, Cheng CW, Hwang D, Martin-Montalvo A, Saavedra J, Ingles S, de Cabo R, Cohen P and Longo VD. 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.
23. Zhou Y, Xu BC, Maheshwari HG, He L, Reed M, Lozykowski M, Okada S, Cataldo L, Coschigamo K, Wagner TE, Baumann G and Kopchick JJ. A mammalian model for Laron syndrome produced by targeted disruption of the mouse growth hormone receptor/binding protein gene (the Laron mouse). *Proc Natl Acad Sci U S A*. 1997;94:13215-20.
24. Coschigano KT, Clemmons D, Bellush LL and Kopchick JJ. Assessment of growth parameters and life span of GHR/BP gene-disrupted mice. *Endocrinology*. 2000;141:2608-13.
25. Ashpole NM, Herron JC, Estep PN, Logan S, Hodges EL, Yabluchanskiy A, Humphrey MB and Sonntag WE. Differential effects of IGF-1 deficiency during the life span on structural and biomechanical properties in the tibia of aged mice. *Age (Dordr)*. 2016;38:38.
26. Ashpole NM, Herron JC, Mitschelen MC, Farley JA, Logan S, Yan H, Ungvari Z, Hodges EL, Csiszar A, Ikeno Y, Humphrey MB and Sonntag WE. IGF-1 Regulates Vertebral Bone Aging Through Sex-Specific and Time-Dependent Mechanisms. *J Bone Miner Res*. 2015.
27. Bailey-Downs LC, Mitschelen M, Sosnowska D, Toth P, Pinto JT, Ballabh P, Valcarcel-Ares MN, Farley J, Koller A, Henthorn JC, Bass C, Sonntag WE, Ungvari Z and Csiszar A. Liver-specific knockdown of IGF-1 decreases vascular oxidative stress resistance by impairing the Nrf2-dependent antioxidant response: a novel model of vascular aging. *J Gerontol A Biol Sci Med Sci*. 2012;67:313-29.
28. Bailey-Downs LC, Sosnowska D, Toth P, Mitschelen M, Gautam T, Henthorn JC, Ballabh P, Koller A, Farley JA, Sonntag WE, Csiszar A and Ungvari Z. Growth Hormone and IGF-1 Deficiency Exacerbate High-Fat Diet-Induced Endothelial Impairment in Obese Lewis Dwarf Rats: Implications for Vascular Aging. *J Gerontol A Biol Sci Med Sci*. 2012;67:553-64.
29. D'Costa AP, Xu X, Ingram RL and Sonntag WE. Insulin-like growth factor-1 stimulation of protein synthesis is attenuated in cerebral cortex of aging rats. *Neuroscience*. 1995;65:805-13.
30. Deak F and Sonntag WE. Aging, synaptic dysfunction, and insulin-like growth factor (IGF)-1. *J Gerontol A Biol Sci Med Sci*. 2012;67:611-25.
31. Farias Quipildor GE, Mao K, Hu Z, Novaj A, Cui MH, Gulinello M, Branch CA, Gubbi S, Patel K, Moellering DR, Tarantini S, Kiss T, Yabluchanskiy A, Ungvari Z, Sonntag WE and Huffman DM. Central IGF-1 protects against features of cognitive and sensorimotor decline with aging in male mice. *Geroscience*. 2019;41:185-208.
32. Grill JD, Sonntag WE and Riddle DR. Dendritic stability in a model of adult-onset IGF-I deficiency. *Growth Horm IGF Res*. 2005;15:337-48.

33. Groban L, Lin M, Kassik KA, Ingram RL and Sonntag WE. Early-onset growth hormone deficiency results in diastolic dysfunction in adult-life and is prevented by growth hormone supplementation. *Growth Horm IGF Res*. 2011;21:81-8.
34. Hua K, Forbes ME, Lichtenwalner RJ, Sonntag WE and Riddle DR. Adult-onset deficiency in growth hormone and insulin-like growth factor-I alters oligodendrocyte turnover in the corpus callosum. *Glia*. 2009;57:1062-71.
35. Khan AS, Lynch CD, Sane DC, Willingham MC and Sonntag WE. Growth hormone increases regional coronary blood flow and capillary density in aged rats. *J Gerontol A Biol Sci Med Sci*. 2001;56:B364-71.
36. Lichtenwalner RJ, Forbes ME, Bennett SA, Lynch CD, Sonntag WE and Riddle DR. Intracerebroventricular infusion of insulin-like growth factor-I ameliorates the age-related decline in hippocampal neurogenesis. *Neuroscience*. 2001;107:603-13.
37. Lichtenwalner RJ, Forbes ME, Sonntag WE and Riddle DR. Adult-onset deficiency in growth hormone and insulin-like growth factor-I decreases survival of dentate granule neurons: insights into the regulation of adult hippocampal neurogenesis. *J Neurosci Res*. 2006;83:199-210.
38. Logan S, Pharaoh GA, Marlin MC, Masser DR, Matsuzaki S, Wronowski B, Yeganeh A, Parks EE, Premkumar P, Farley JA, Owen DB, Humphries KM, Kinter M, Freeman WM, Szweda LI, Van Remmen H and Sonntag WE. Insulin-like growth factor receptor signaling regulates working memory, mitochondrial metabolism, and amyloid-beta uptake in astrocytes. *Mol Metab*. 2018;9:141-155.
39. Miller LR, Tarantini S, Nyul-Toth A, Johnston MP, Martin T, Bullen EC, Bickel MA, Sonntag WE, Yabluchanskiy A, Csiszar A, Ungvari ZI, Elliott MH and Conley SM. Increased Susceptibility to Cerebral Microhemorrhages Is Associated With Imaging Signs of Microvascular Degeneration in the Retina in an Insulin-Like Growth Factor 1 Deficient Mouse Model of Accelerated Aging. *Front Aging Neurosci*. 2022;14:788296.
40. Mitschelen M, Yan H, Farley JA, Warrington JP, Han S, Herenu CB, Csiszar A, Ungvari Z, Bailey-Downs LC, Bass CE and Sonntag WE. Long-term deficiency of circulating and hippocampal insulin-like growth factor I induces depressive behavior in adult mice: a potential model of geriatric depression. *Neuroscience*. 2011;185:50-60.
41. Nieves-Martinez E, Sonntag WE, Wilson A, Donahue A, Molina DP, Brunso-Bechtold J and Nicolle MM. Early-onset GH deficiency results in spatial memory impairment in mid-life and is prevented by GH supplementation. *J Endocrinol*. 2010;204:31-6.
42. Poe BH, Linville C, Riddle DR, Sonntag WE and Brunso-Bechtold JK. Effects of age and insulin-like growth factor-1 on neuron and synapse numbers in area CA3 of hippocampus. *Neuroscience*. 2001;107:231-8.
43. Ramsey MM, Weiner JL, Moore TP, Carter CS and Sonntag WE. Growth hormone treatment attenuates age-related changes in hippocampal short-term plasticity and spatial learning. *Neuroscience*. 2004;129:119-27.
44. Shi L, Linville MC, Tucker EW, Sonntag WE and Brunso-Bechtold JK. Differential effects of aging and insulin-like growth factor-1 on synapses in CA1 of rat hippocampus. *Cereb Cortex*. 2005;15:571-7.
45. Sonntag WE, Csiszar A, deCabo R, Ferrucci L and Ungvari Z. Diverse roles of growth hormone and insulin-like growth factor-1 in mammalian aging: progress and controversies. *J Gerontol A Biol Sci Med Sci*. 2012;67:587-98.
46. Sonntag WE, Deak F, Ashpole N, Toth P, Csiszar A, Freeman W and Ungvari Z. Insulin-like growth factor-1 in CNS and cerebrovascular aging. *Front Aging Neurosci*. 2013;5:27.
47. Tarantini S, Balasubramanian P, Yabluchanskiy A, Ashpole NM, Logan S, Kiss T, Ungvari A, Nyul-Toth A, Schwartzman ML, Benyo Z, Sonntag WE, Csiszar A and Ungvari Z. IGF1R signaling

regulates astrocyte-mediated neurovascular coupling in mice: implications for brain aging. *Geroscience*. 2021;43:901-911.

48. Tarantini S, Nyul-Toth A, Yabluchanskiy A, Csipo T, Mukli P, Balasubramanian P, Ungvari A, Toth P, Benyo Z, Sonntag WE, Ungvari Z and Csiszar A. Endothelial deficiency of insulin-like growth factor-1 receptor (IGF1R) impairs neurovascular coupling responses in mice, mimicking aspects of the brain aging phenotype. *Geroscience*. 2021;43:2387-2394.

49. Tarantini S, Valcarcel-Ares NM, Yabluchanskiy A, Springo Z, Fulop GA, Ashpole N, Gautam T, Giles CB, Wren JD, Sonntag WE, Csiszar A and Ungvari Z. Insulin-like growth factor 1 deficiency exacerbates hypertension-induced cerebral microhemorrhages in mice, mimicking the aging phenotype. *Aging Cell*. 2017;16:469-479.

50. Toth P, Tarantini S, Ashpole NM, Tucsek Z, Milne GL, Valcarcel-Ares NM, Menyhart A, Farkas E, Sonntag WE, Csiszar A and Ungvari Z. IGF-1 deficiency impairs neurovascular coupling in mice: implications for cerebromicrovascular aging. *Aging Cell*. 2015;14:1034-44.

51. Toth P, Tucsek Z, Tarantini S, Sosnowska D, Gautam T, Mitschelen M, Koller A, Sonntag WE, Csiszar A and Ungvari Z. IGF-1 deficiency impairs cerebral myogenic autoregulation in hypertensive mice. *J Cereb Blood Flow Metab*. 2014;34:1887-97.

52. Abs R, Feldt-Rasmussen U, Mattsson AF, Monson JP, Bengtsson BA, Goth MI, Wilton P and Koltowska-Haggstrom M. Determinants of cardiovascular risk in 2589 hypopituitary GH-deficient adults - a KIMS database analysis. *Eur J Endocrinol*. 2006;155:79-90.

53. Ashpole NM, Logan S, Yabluchanskiy A, Mitschelen MC, Yan H, Farley JA, Hodges EL, Ungvari Z, Csiszar A, Chen S, Georgescu C, Hubbard GB, Ikeno Y and Sonntag WE. IGF-1 has sexually dimorphic, pleiotropic, and time-dependent effects on healthspan, pathology, and lifespan. *Geroscience*. 2017;39:129-145.

54. Podlutsky A, Valcarcel-Ares MN, Yancey K, Podlutskaya V, Nagykaldi E, Gautam T, Miller RA, Sonntag WE, Csiszar A and Ungvari Z. The GH/IGF-1 axis in a critical period early in life determines cellular DNA repair capacity by altering transcriptional regulation of DNA repair-related genes: implications for the developmental origins of cancer. *Geroscience*. 2017;39:147-160.

55. Ramsey MM, Ingram RL, Cashion AB, Ng AH, Cline JM, Parlow AF and Sonntag WE. Growth hormone-deficient dwarf animals are resistant to dimethylbenzanthracine (DMBA)-induced mammary carcinogenesis. *Endocrinology*. 2002;143:4139-42.

56. Garcia AM, Busuttil RA, Calder RB, Dolle ME, Diaz V, McMahan CA, Bartke A, Nelson J, Reddick R and Vijg J. Effect of Ames dwarfism and caloric restriction on spontaneous DNA mutation frequency in different mouse tissues. *Mech Ageing Dev*. 2008;129:528-33.

57. Sun LY, Fang Y, Patki A, Koopman JJ, Allison DB, Hill CM, Masternak MM, Darcy J, Wang J, McFadden S and Bartke A. Longevity is impacted by growth hormone action during early postnatal period. *Elife*. 2017;6.

58. Ikeno Y, Bronson RT, Hubbard GB, Lee S and Bartke A. Delayed occurrence of fatal neoplastic diseases in ames dwarf mice: correlation to extended longevity. *J Gerontol A Biol Sci Med Sci*. 2003;58:291-6.

59. Panici JA, Harper JM, Miller RA, Bartke A, Spong A and Masternak MM. Early life growth hormone treatment shortens longevity and decreases cellular stress resistance in long-lived mutant mice. *FASEB J*. 2010;24:1-7.

60. Shevah O and Laron Z. Patients with congenital deficiency of IGF-I seem protected from the development of malignancies: a preliminary report. *Growth Horm IGF Res*. 2007;17:54-7.

61. Steuerman R, Shevah O and Laron Z. Congenital IGF1 deficiency tends to confer protection against post-natal development of malignancies. *Eur J Endocrinol*. 2011;164:485-9.

62. Bartke A, Sun LY and Longo V. Somatotropic signaling: trade-offs between growth, reproductive development, and longevity. *Physiol Rev*. 2013;93:571-98.

63. Gesing A, Wiesenborn D, Do A, Menon V, Schneider A, Victoria B, Stout MB, Kopchick JJ, Bartke A and Masternak MM. A Long-lived Mouse Lacking Both Growth Hormone and Growth Hormone Receptor: A New Animal Model for Aging Studies. *J Gerontol A Biol Sci Med Sci*. 2016.
64. Ikeno Y, Hubbard GB, Lee S, Cortez LA, Lew CM, Webb CR, Berryman DE, List EO, Kopchick JJ and Bartke A. Reduced incidence and delayed occurrence of fatal neoplastic diseases in growth hormone receptor/binding protein knockout mice. *J Gerontol A Biol Sci Med Sci*. 2009;64:522-9.
65. Bartke A and Brown-Borg H. Life extension in the dwarf mouse. *Curr Top Dev Biol*. 2004;63:189-225.
66. Zhang WB, Ye K, Barzilai N and Milman S. The antagonistic pleiotropy of insulin-like growth factor 1. *Aging Cell*. 2021;20:e13443.
67. Milman S, Atzmon G, Huffman DM, Wan J, Crandall JP, Cohen P and Barzilai N. Low insulin-like growth factor-1 level predicts survival in humans with exceptional longevity. *Aging Cell*. 2014;13:769-71.
68. Zhang WB, Aleksic S, Gao T, Weiss EF, Demetriou E, Verghese J, Holtzer R, Barzilai N and Milman S. Insulin-like Growth Factor-1 and IGF Binding Proteins Predict All-Cause Mortality and Morbidity in Older Adults. *Cells*. 2020;9.
69. Mao K, Quipildor GF, Tabrizian T, Novaj A, Guan F, Walters RO, Delahaye F, Hubbard GB, Ikeno Y, Ejima K, Li P, Allison DB, Salimi-Moosavi H, Beltran PJ, Cohen P, Barzilai N and Huffman DM. Late-life targeting of the IGF-1 receptor improves healthspan and lifespan in female mice. *Nat Commun*. 2018;9:2394.

Table 1. Academy Award winning movies of Hollywood controls

Movie	Award	Year
The Adventures of Robin Hood	Best Art Direction, Best Film Editing, Best Original Music Score	1938
The Great Waltz	Best Cinematography	1938
You Can't Take It with You	Best Picture, Best Director	1938
Jezebel	Best Actress in a Leading Role, Best Actress in a Supporting Role	1938
Snow White and the Seven Dwarfs	Best Music Score/Honorary Award	1938/1939
Gone with the Wind	Best Picture, Best Director, Best Actress in a Leading Role, Best Actress in a Supporting Role, Best Screenplay Writing, Best Colour Cinematography, Best Art Direction, Best Screenplay Writing	1939
Wuthering Heights	Best Black-and-White Cinematography	1939
Stagecoach	Best Actress in a Supporting Role, Best Music Score	1939
Goodbye, Mr. Chips	Best Actor in a Leading Role	1939
Sons of Liberty	Best Short Subject (Two-reel)	1939
When Tomorrow Comes	Best Sound Recording	1939
Busy Little Bears	Best Short Subject (One-reel)	1940
Mr. Smith Goes to Washington	Best Writing, Original Story	1940
Ugly Duckling	Best Short Subject (Cartoons)	1940
The Rains Came	Best Special Effects	1940

Table 2. Median follow-up time (IQR), age at shooting (IQR) and total lifespan (IQR) of "Munchkin" actors, cast controls amd Hollywoods controls

	"Munchkin" actors		
	Age at shooting	**Follow-up time**	**Total lifespan**
	Median (IQR)	Median (IQR)	Median (IQR)
Female (n=35)	33.0 (23.0–39.0)	41.0 (30.0–56.0)	75.0 (63.0–84.0)
Male (n=50)	30.0 (22.0–37.0)	41.0 (20.8–54.5)	73.0 (56.5–84.0)
Total (n=85)	31.0 (22.0–37.5)	41.0 (26.5–55.5)	74.0 (60.5–83.5)
	Cast controls		
	Age at shooting	**Follow-up time**	**Total lifespan**
	Median (IQR)	Median (IQR)	Median (IQR)
Female (n=35)	31.0 (22.0–38.0)	52.0 (33.0–63.0)	83.0 (76.0–86.0)
Male (n=50)	41.0 (35.8–49.3)	30.0 (17.0–46.0)	78.5 (64.0–86.0)
Total (n=85)	37.0 (30.5–47.0)	39.0 (23.5–54.5)	81.0 (69.0–86.0)
	Hollywood controls		
	Age at shooting	**Follow-up time**	**Total lifespan**
	Median (IQR)	Median (IQR)	Median (IQR)
Female (n=105)	32.0 (23.0–38.0)	48.0 (33.0–57.5)	81.0 (69.0–90.0)
Male (n=150)	31.0 (22.8–38.0	41.5 (28.0–61.3)	75.0 (65.0–86.0)
Total (n=255)	31.0 (23.0–38.0)	45.0 (30.0–58.0)	78.0 (67.0–87.0)

*Abbreviations: IQR: interquartile range

Table 3. Results of the Cox regression analysis with follow-up and age as underlying time variable

	"Munchkin" actors vs. Cast controls		"Munchkin" actors vs. Hollywood controls	
	Follow-up time*	**Lifespan***	**Follow-up time***	**Lifespan***
	aRR (95% CI)	**aRR (95% CI)**	**aRR (95% CI)**	**aRR (95% CI)**
Female	1.70 (1.05–2.77)*	1.64 (1.01–2.67)*	1.52 (1.03–2.24)*	1.47 (1.00–2.17)*
Male	1.14 (0.74–1.74)	1.12 (0.73–1.70)	1.05 (0.76–1.45)	1.05 (0.76–1.45)
Total	1.39 (1.01–1.91)*	1.34 (0.98–1.85)	1.24 (0.97–1.59)	1.23 (0.96–1.57)
Age at shooting	1.09 (1.07–1.10)*	1.01 (1.00–1.02)	1.10 (1.09–1.12)*	1.03 (1.02–1.04)*

Abbreviations: aRR: adjusted risk ratio; IQR: interquartile range

*Follow-up of subjects began from their age at shooting and ended with their death. Cast controls were chosen as reference. Risk ratios were adjusted for age at shooting, sex, and disease status by sex interaction.

Figure legends

Figure 1. Four surviving "Munchkin" actors in 1998. From left to right, Jerry Maren, the longest-lived of all the Munchkins (1920-2018 who played the green-garbed member of the "Lillipop Guild" who handed a lollipop to Dorothy. Karl Slover (1918-2011, among the smallest of the Munchkin men at 91 cm (36 inches) in height at the time of the movie. Both men were formally diagnosed with pituitary dwarfism. Clarence Swensen (1917-2009) at 131 cm (52 inches) was among the tallest of the Munchkins played a soldier. Margaret Pellegrini (1923-2013) played the "Flowerpot Munchkin". (Image is in the public domain and was taken from: https://en.wikipedia.org/wiki/Jerry_Maren#/media/File:WIKI_MUNCHKIN_1.jpg) The copyrighted image of Jerry Maren and the other members of the "Lollipop Gang" with proportionate dwarfism from the 1939 film can be found here: https://www.nytimes.com/2018/06/06/arts/jerry-maren-dead-wizard-of-oz-munchkin.html

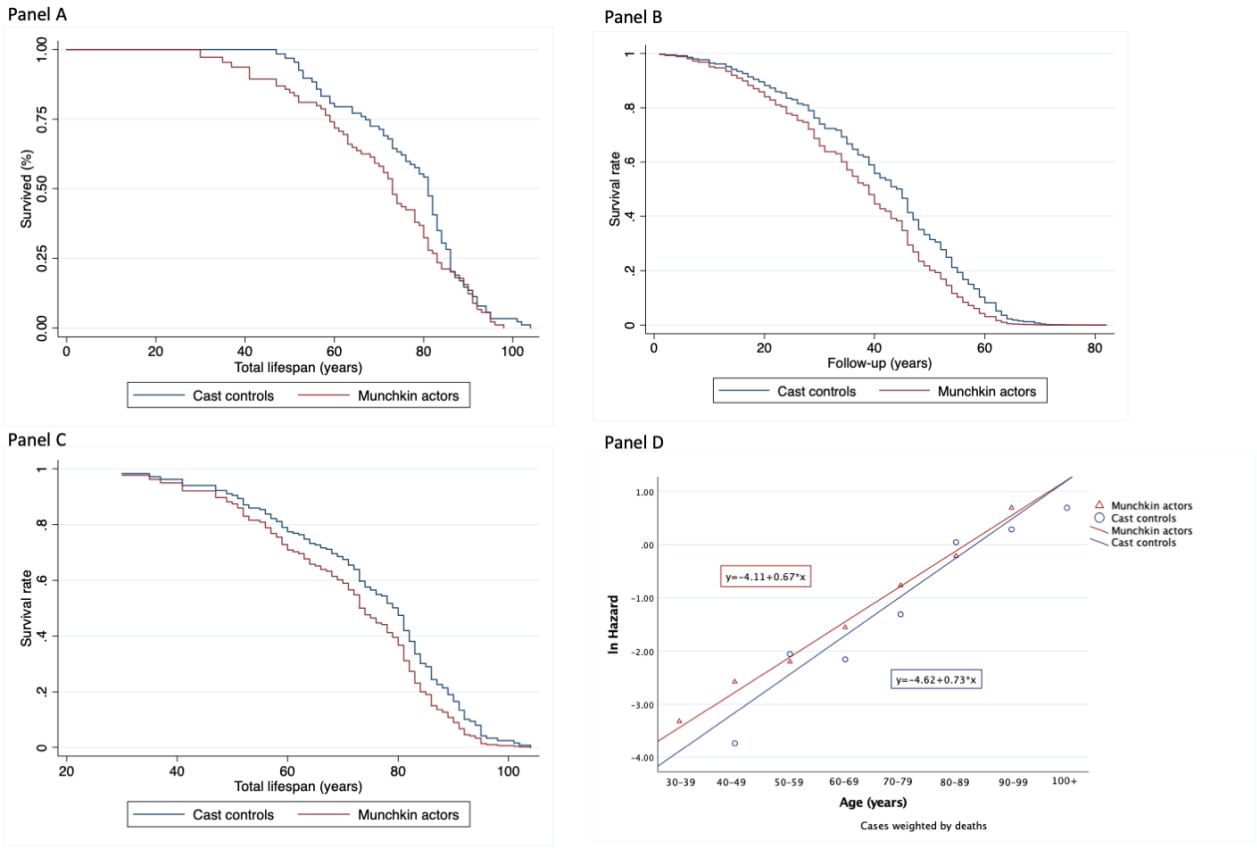

Figure 2. Kaplan-Meier survival curve (Panel A), survival plots for Cox regression analyses with follow-up (Panel B) and total lifespan (Panel C) as underlying time variable, age-specific mortality (Panel D) for "Munchkin" actors vs. cast controls

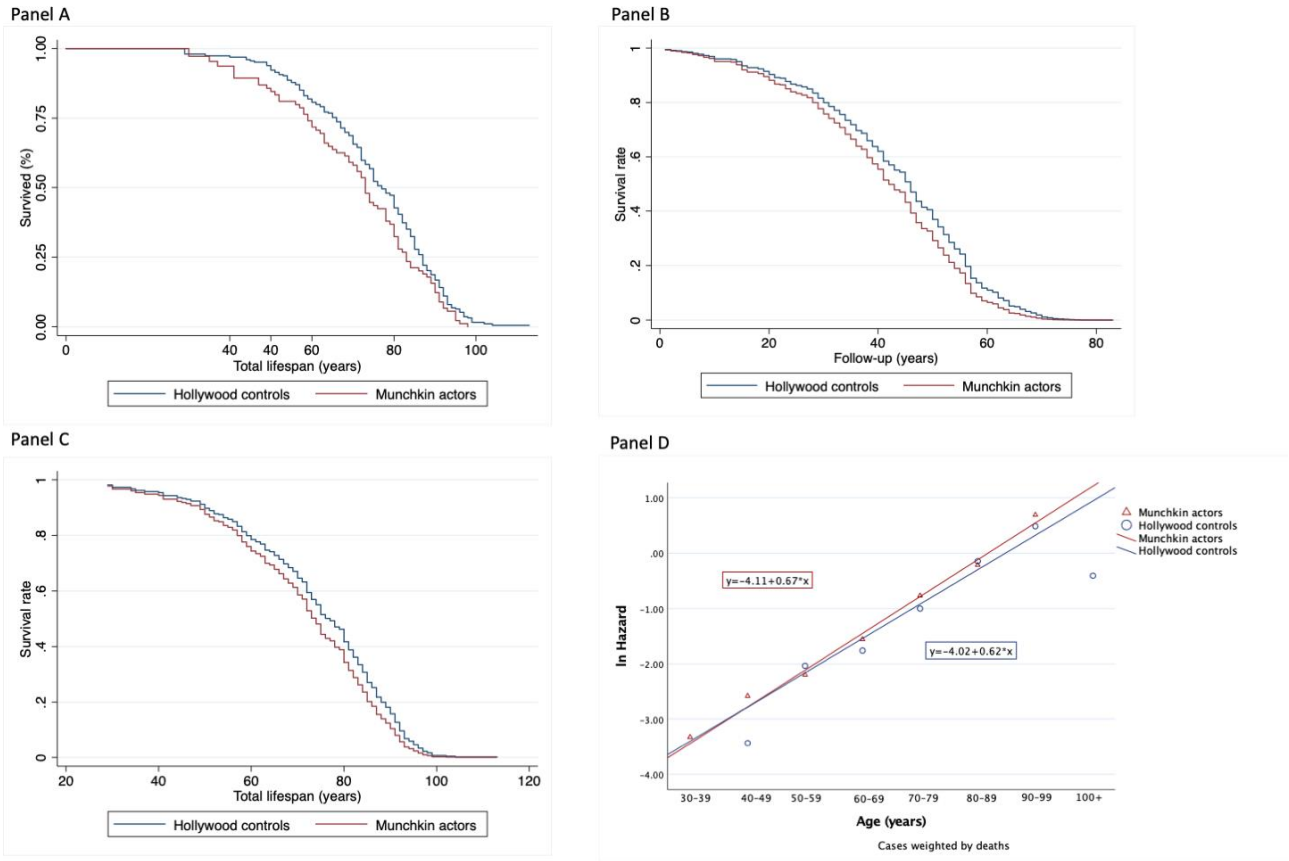

Figure 3. Kaplan-Meier survival curve (Panel A), survival plots for Cox regression analyses with follow-up (Panel B) and total lifespan (Panel C) as underlying time variable, and age-specific mortality (Panel D) for "Munchkin" actors vs. Hollywood controls

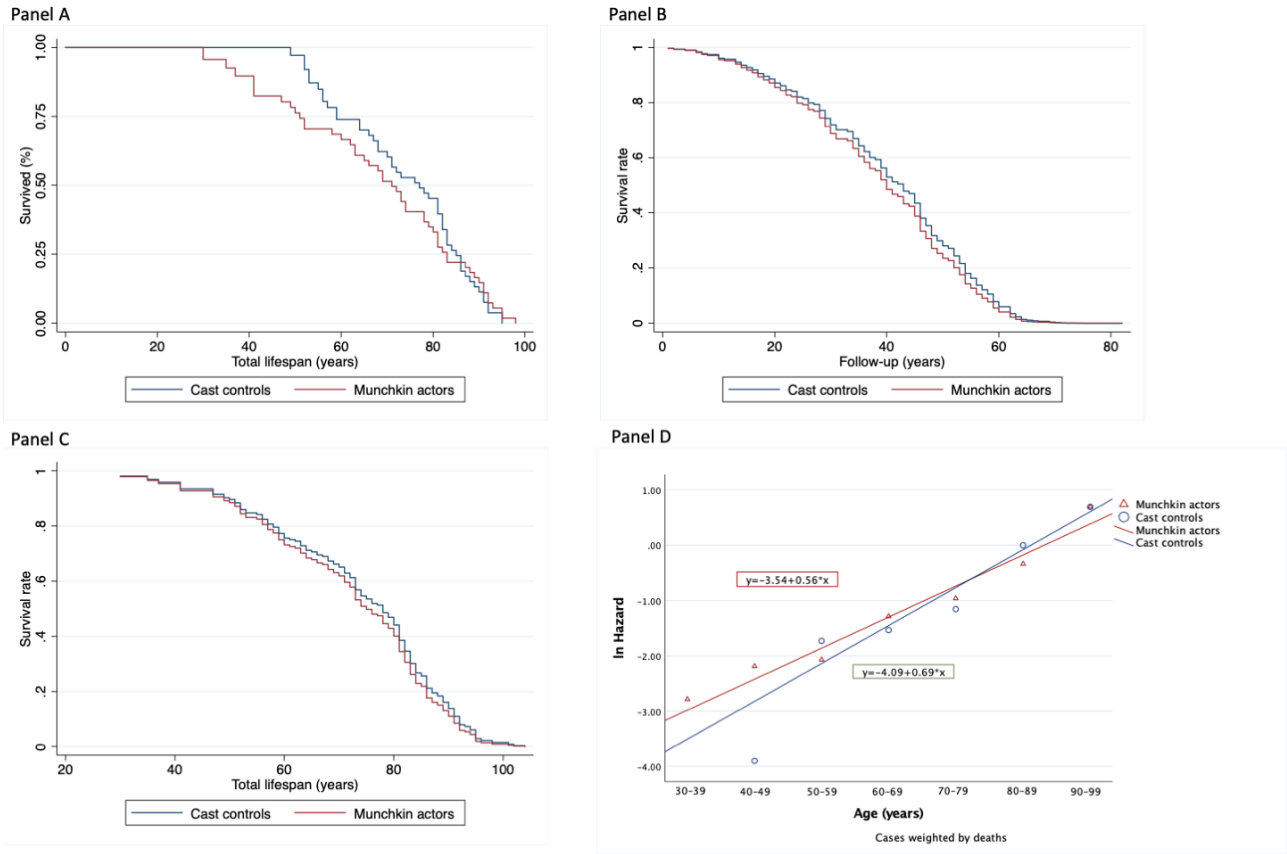

Figure 4. Kaplan-Meier survival curve (Panel A), survival plots for Cox regression analyses with follow-up (Panel B) and total lifespan (Panel C) as underlying time variable, and age-specific mortality (Panel D) for male "Munchkin" actors vs. male cast controls

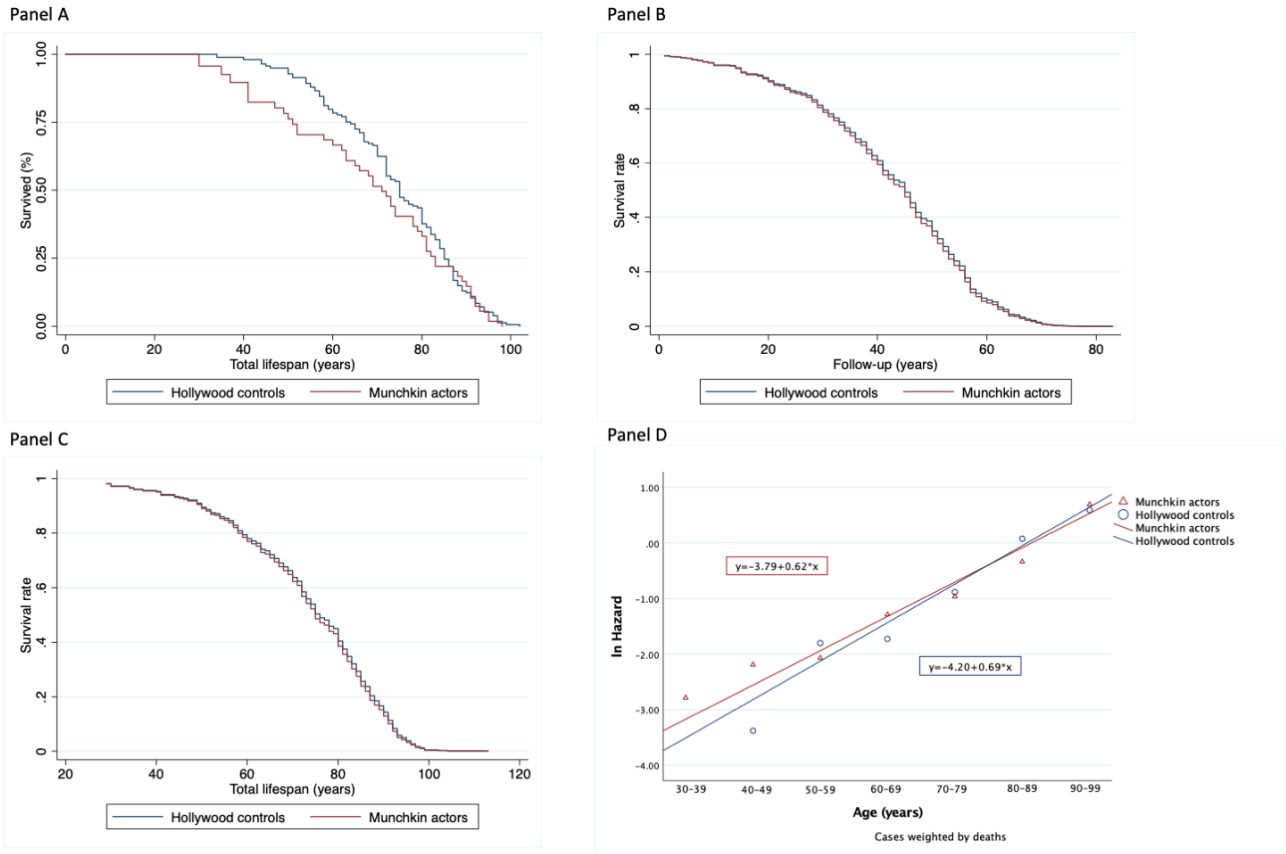

Figure 5. Kaplan-Meier survival curve (Panel A), survival plots for Cox regression analyses with follow-up (Panel B) and total lifespan (Panel C) as underlying time variable, and age-specific mortality (Panel D) for male "Munchkin" actors vs. male Hollywood controls

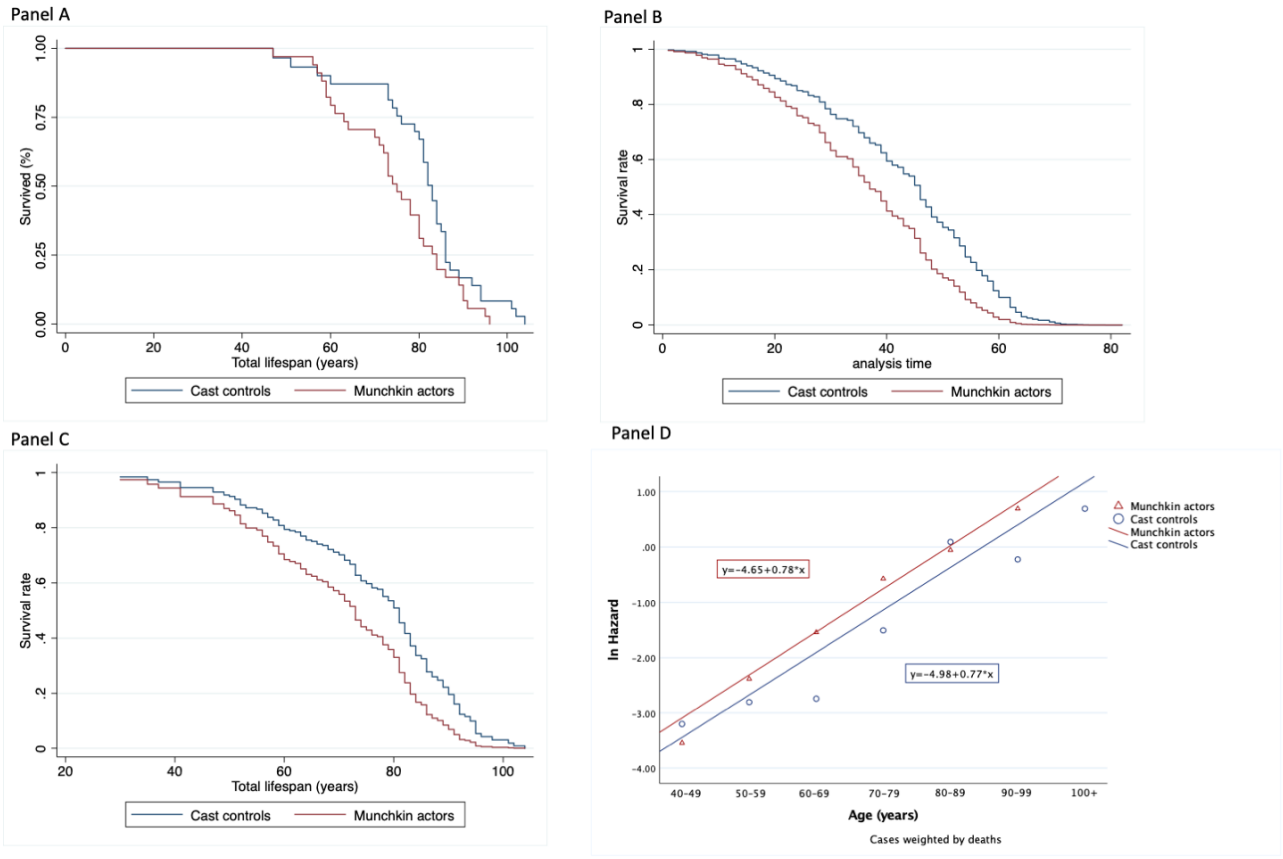

Figure 6. Kaplan-Meier survival curve (Panel A), survival plots for Cox regression analyses with follow-up (Panel B) and total lifespan (Panel C) as underlying time variable, and age-specific mortality (Panel D) for female "Munchkin" actors vs. female cast controls

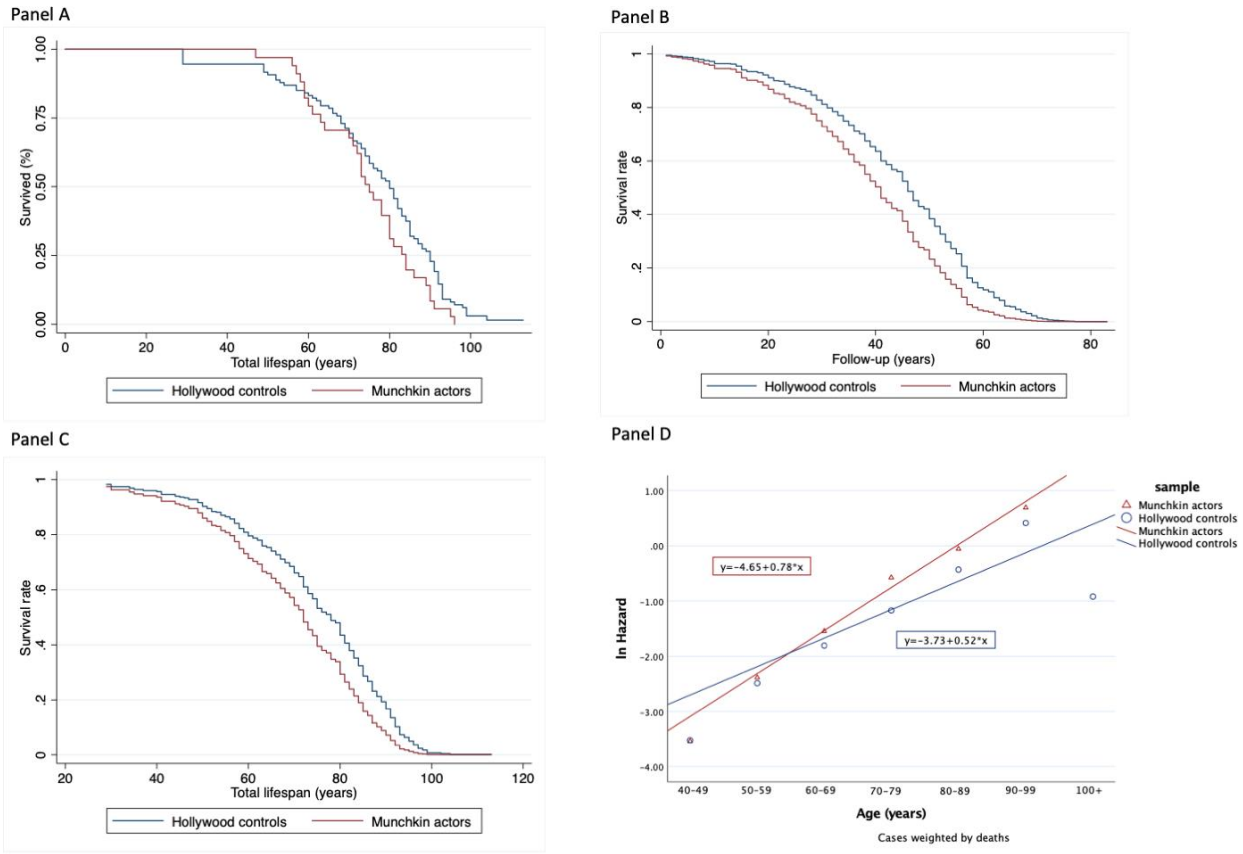

Figure 7. Kaplan-Meier survival curve (Panel A), survival plots for Cox regression analyses with follow-up (Panel B) and total lifespan (Panel C) as underlying time variable, and age-specific mortality (Panel D) for female "Munchkin" actors vs. female Hollywood controls