Ageing Research Reviews 112 (2025) 102873

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review Article

L-deprenyl extends lifespan across mammalian species: A meta-analysis of 22 longevity experiments

Michael R. Bene

Department of Medicine, Division of Geriatric Medicine and Gerontology, The Johns Hopkins University School of Medicine, Baltimore, MD, United States of America

ARTICLE INFO

Keywords:
Geroscience
Interventions
Animal model
Anti-aging

ABSTRACT

Identifying interventions that reproducibly extend lifespan is a central aim in geroscience, with hopes of translating these findings to enhance the health and longevity of older adults. L-deprenyl, an FDA approved medication, has been investigated for its role in aging for over three decades. To evaluate the effect of L-deprenyl on lifespan in mammals we performed a random-effects meta-analysis on 22 rodent lifespan experiments. The results indicate L-deprenyl significantly increases average lifespan with moderate effect size (SMD = 0.6773, $p = 0.0002$). We identified no significant evidence of publication bias in the examined studies, but did observe substantial heterogeneity. Accounting for experimental factors revealed significant effects of dose ($p = 0.0233$) and age at initiation ($p < 0.0001$), with higher doses and older age associated with larger effects. Assessment of treatment effects by mean lifespan of controls suggests short-lived controls are not responsible for the observed effects. In addition to the meta-analysis, we reanalyzed a dog survival study by Ruehl et al. When accounting for age at enrollment and sex, the study no longer displayed a significant effect on survival, though power was limited by small sample size. Together, this analysis of 23 L-deprenyl lifespan experiments spans 27 years of research in 6 countries, 8 strains of rodents, 4 species, 6 doses, and 2 delivery methods, providing some of the most comprehensive data supporting the effect of a compound on lifespan in mammals. Future clinical studies examining L-deprenyls effects on health outcomes in older adults will be critical to determine the translatability of these findings.

1. Introduction

As the field of geroscience has grown, a substantial amount of putative geroprotectors have been identified. One of the most widely accepted criteria for geroprotectors is the extension of lifespan in model organisms. As such, hundreds of reports have been published on the extension of lifespan in naturally aging model organisms (Barardo et al., 2017; Berkel and Cacan, 2021). Reproducibility, robustness, and translatability all act as significant challenges to the development of such therapeutics towards clinical applications, with key issues in each area (Bene and Salmon, 2023; Kirkland, 2016; Lucanic et al., 2017; Pabis et al., 2024). The identification of interventions which show consistent effects across studies and diverse mammalian species may therefore provide promising candidates for clinical translation.

L-deprenyl (also known as Selegiline) is an FDA approved drug used in treatment of Parkinson's disease and major depressive disorder (Miklya, 2016). It is a selective irreversible inhibitor of Monoamine Oxidase B (MAO-B) with widely described neuroprotective properties. In addition to its mainstream medical usage, L-deprenyl has also been extensively studied for its effects on aging and longevity, with research initially performed by Joseph Knoll starting in the 1980's and extensive studies later conducted by Kenichi Kitani (Kitani et al., 2002; Knoll et al., 1989). Despite the reduction of interest in L-deprenyl in aging and longevity research in recent decades, it remains one of the most studied pharmacological interventions for lifespan in mammals. We therefore sought to perform a comprehensive meta-analysis of lifespan studies using L-deprenyl to evaluate the current evidence that it may be a geroprotector.

2. Methods

2.1. Data collection

An initial data search was performed using pubmed and google scholar with combinations of keywords: "L-Deprenyl", "Selegiline", "lifespan", "survival", and "mortality". Only studies utilizing non-disease models were considered. Studies found using this search were then examined for references to other studies not already identified for

E-mail address: mbene1@jh.edu.

https://doi.org/10.1016/j.arr.2025.102873
Received 23 May 2025; Received in revised form 21 July 2025; Accepted 12 August 2025
Available online 13 August 2025

potential inclusion. In total 18 papers reporting the effects of L-Deprenyl on survival in non-disease model mammals were identified (Archer and Harrison, 1996; Bickford et al., 1997; Carrillo et al., 2000; Dallo, 2001; Gallagher et al., 1998; Ingram et al., 1993; Kitani et al., 1992, 1998, 2005; Knoll et al., 1989, 1994; Knoll and Miklya, 2016; Malgram' Norton et al., 1990; Piantanelli et al., 1994; Ruehl et al., 1997; Stoll et al., 1997; Yen et al., 1990; Yen and Knoll, 1992). Of these studies, 2 did not report sufficient information for determination of average lifespan and a measure of variability (Carrillo et al., 2000; Gallagher et al., 1998). In particular, both the Carrillo and Gallagher study described only the number or percent of animals alive after the total study period, with no information about the age at death for any individual animals or experimental group averages. For some studies, summary statistics were not provided nor raw data and therefore an online tool (plotdigitizer.com) was used to estimate values based on presented survival curves (Bickford et al., 1997; Ingram et al., 1993; Knoll et al., 1994; Yen and Knoll, 1992). All data used for this analysis are provided as a Supplemental file.

2.2. Analysis

All analyses were performed using R (version 4.4.1) in RStudio (2024.09.0 + 375 "Cranberry Hibiscus"). Briefly, effect sizes were computed by calculating standard deviations from standard errors and sample sizes and deriving the mean difference between treatment and control group lifespans in days. The "meta" package's "metacont" function was employed to perform a basic random-effects meta-analysis of standardized mean differences using Hedges' correction, and potential publication bias was assessed via funnel plots and the "metabias" function. Subgroup effects for sex, species, strain, dose, delivery method, and censorship status were estimated by updating the meta-analysis with grouping variables using the "update" function from meta. Meta-regression analyses were conducted using the package "metafor", applying the "metareg" function to model effect sizes against multiple moderators (e.g., age, sex, species/strain, method, dose, and their interactions). To test for potential non-linearity of age and dose effects, three additional models were compared to the linear model with polynomial terms added for age, dose, or both with likelihood-ratio tests suggesting no significant improvement with inclusion of these terms (age: $p = 0.055$, dose: $p = 0.14$, both: $p = 0.15$). Subsequent predictions were generated over a grid of age and dose values by combining estimated coefficients from the full model, with predictions restricted to the convex hull of the observed data using functions from the "geometry" and "sp" packages. Forest plots were generated and visualized with "ggplot2" and "cowplot". An additional sensitivity analysis was also performed omitting all studies derived from estimated data with a SMD of 0.76[0.25,1.27] and $I^2 = 92.5$ % [89.2 %,94.7 %], indicating inclusion of these estimated data did not substantially alter the estimated effects or between study heterogeneity. Lastly, the relationship between mean lifespan of control groups with treatment effect was assessed using Pearsons r and weighted correlation using the "weights" package.

For the analysis of the dog survival data Kaplan–Meier analysis was performed by defining time variable as time in study and using the "survfit" function from the "survival" package to estimate the survival function stratified by treatment groups. A power analysis was performed using the "pwr" package. The "survminer" package's "ggsurvplot" function was used to generate the figure. A log-rank test was executed using "surv_pvalue". The Cox proportional hazards model was fitted using "coxph", adjusting for covariates including age at study entry and sex. Adjusted survival curves were derived from the Cox model via the "survfit" function. Finally, to characterize the instantaneous risk of mortality, an analysis of the hazard rate by age was conducted. For each treatment group, the "bshazard" function was utilized to compute a non-parametric estimate of the hazard function over age. The individual hazard estimates were collated and visualized using "ggplot2". All code used in analysis is provided as a supplemental file.

3. Results

3.1. Meta-analysis

A literature search identified 18 studies which reported the effects of L-deprenyl on lifespan in naturally aging mammals. Of these studies, two did not provide sufficient information for the determination of average lifespan and an estimate of variability and thus were excluded from the analysis (Carrillo et al., 2000; Gallagher et al., 1998). Additionally, one study in dogs reported large differences in age at enrollment and was therefore not included in the meta-analysis but was reassessed independently (Ruehl et al., 1997). The results of the random-effects meta-analysis of the remaining 15 studies are presented in Fig. 1. The pooled effect of L-deprenyl on lifespan was significant ($p = 0.0002$) and of a moderate effect size (SMD = 0.6773[0.3209, 1.0337]). Subgroup analysis was then performed using separate random-effects models for sex, species, strain, delivery method, dose, and whether the study was right-censored. A Q-test was utilized to determine if there were significant differences in any subgroups, with both sex ($p = 0.0326$, $p_{adj} = 0.116$) and strain ($p = 0.0463$, $p_{adj} = 0.116$) showing significant effects, though in both cases these results lost significance with correction for multiple comparisons.

To test for publication bias a funnel plot analysis was performed (Fig. 2). A linear regression test of funnel plot asymmetry suggested no evidence of publication bias with a bias estimate of 0.1851 (SE = 3.4612, p-value = 0.9579). Notably, however, the studies displayed significant heterogeneity ($Q(21) = 199.79$, $p < 0.0001$), with an estimated between-study variance (tau^2) of 0.6497 and an I^2 of 89.5 %.

Next, we performed a meta-regression to evaluate the impact of various experimental factors on treatment effect. Accounting for sex, species, strain, delivery method, dose, age and dose:age interaction accounted for a substantial portion of between-study heterogeneity (R^2 = 79.59 %). Despite the significant moderation by these experimental factors ($QM = 65.8$, $p < 0.0001$), there was still a substantial degree of residual heterogeneity suggesting unaccounted for experimental differences (I^2=64.13 %). Both dose (estimate = 6.466[0.88,12.05], $p = 0.0233$) and age (estimate = 0.0049[0.0027,0.0072], $p < 0.0001$) showed significant effect estimates suggesting higher doses and treatment started at older ages resulted in a larger increase to mean lifespan (Fig. 3).

Lastly, there is strong evidence that effects of interventions may be exaggerated by short-lived controls (Pabis et al., 2024). To test for this effect in L-deprenyl treated rodents we analyzed the relationship between mean control lifespan and treatment effect across studies (Fig. 4). We found evidence of a positive correlation across all studies ($r = 0.53$ at $p = 0.0111$, and weighted $r = 0.501$ at $p = 0.0175$), while a sub-analysis suggested a non-significant negative correlation in mice ($r = -0.2$ at $p = 0.63$, and weighted $r = -0.25$ at $p = 0.55$) and a positive correlation in rats ($r = 0.7$ at $p = 0.01$, and weighted $r = 0.66$ at $p = 0.02$).

3.2. Dog lifespan re-analysis

As discussed above, a lifespan study in dogs by Ruehl et al. reported significant improvement in the survival of aged dogs treated with L-deprenyl (results reproduced in Fig. 5a) (Ruehl et al., 1997). However, the dogs showed significant variation in age at enrollment-ranging from 10.2 to 14.7 years at the start of the study. To address this confounder, we reanalyzed the survival data using a cox proportional hazards model adjusted for age at enrollment and sex (Fig. 5b). We found that when accounting for age at enrollment there was no significant increase in survival observed (p-value = 0.1534), though the effect estimate was still favorable (Hazard Ratio = 0.38[0.1–1.43]). To directly visualize the impact of L-deprenyl on mortality hazard by age we additionally used the "bshazard" package to calculate estimates of instantaneous mortality hazard by age (Fig. 5c). Notably the age-specific hazard rate estimate is

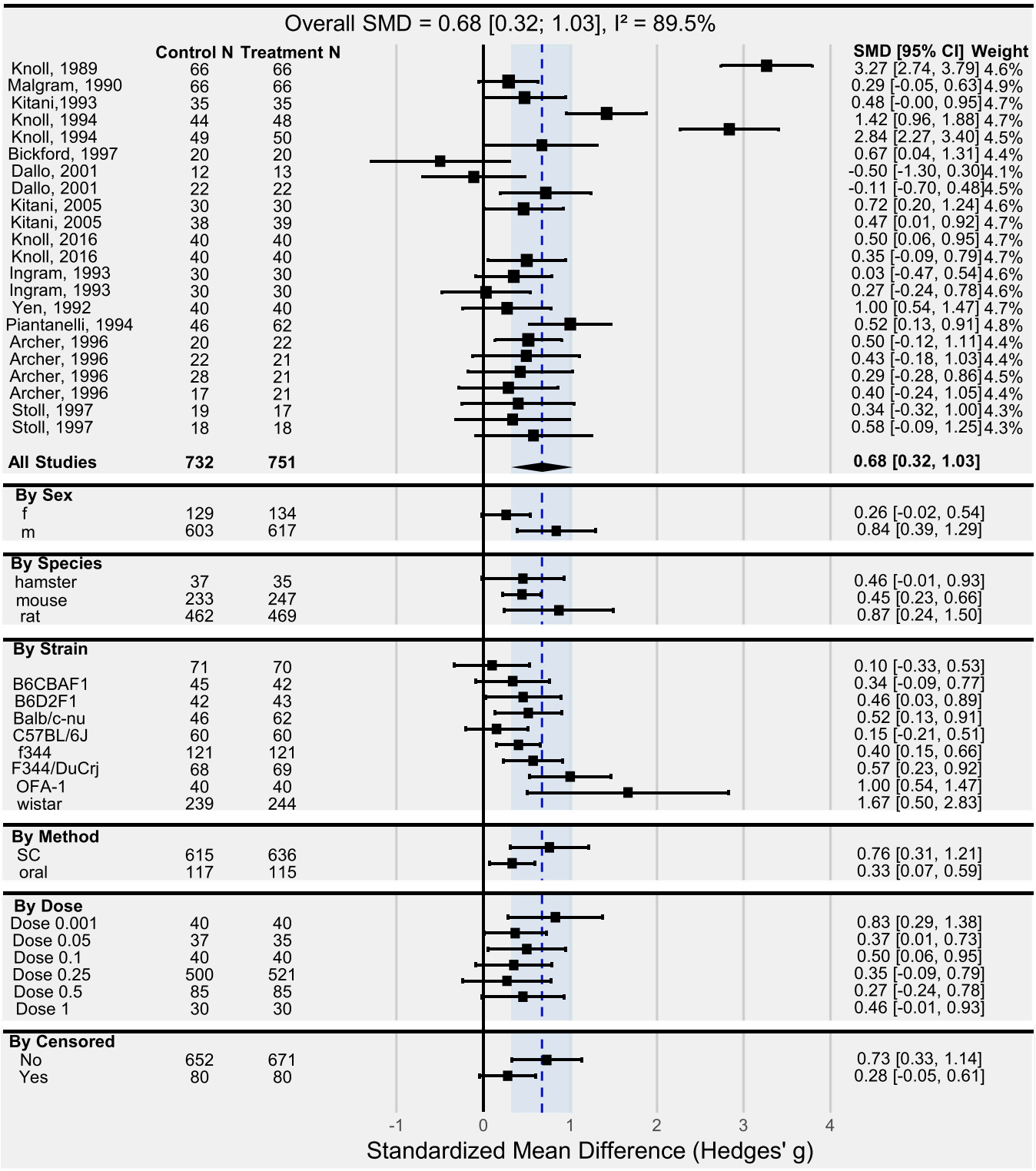

Fig. 1. L-deprenyl increases average lifespan in rodent models. Forest plot of random-effects meta-analysis of the effect of L-deprenyl on mean lifespan in rodents (Archer and Harrison, 1996; Bickford et al., 1997; Carrillo et al., 2000; Dallo, 2001; Gallagher et al., 1998; Ingram et al., 1993; Kitani et al., 1992, 1998, 2005; Knoll et al., 1989, 1994; Knoll and Miklya, 2016; Malgram' Norton et al., 1990; Piantanelli et al., 1994; Stoll et al., 1997; Yen et al., 1990; Yen and Knoll, 1992).

also lower for the L-deprenyl group through most ages, though the substantial variability and low sample size likely prevented detection of any potential significant effect.

4. Discussion

The 23 analyzed L-deprenyl lifespan experiments represent 27 years of research in 6 countries, 8 strains of rodents, 4 species, 6 doses, and 2 methods of administration. To the authors knowledge this is the largest body of evidence for a lifespan intervention in mammals besides two of

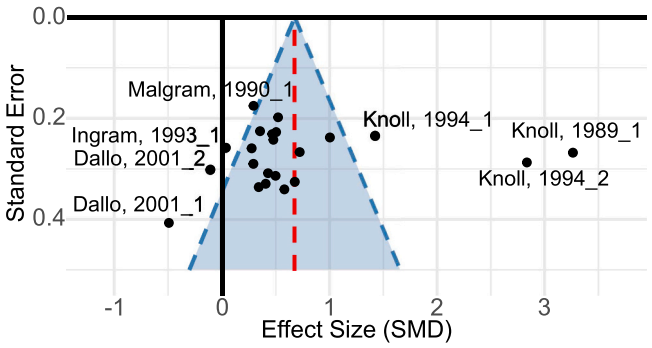

Fig. 2. Studies display no significant publication bias, but substantial heterogeneity. Funnel plot of included studies, studies outside the 95 % confidence interval labelled.

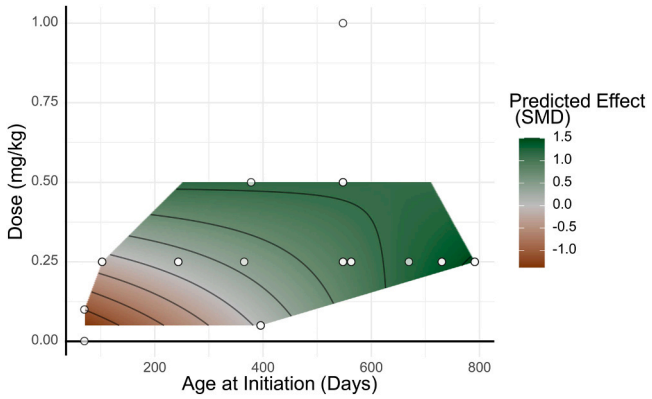

Fig. 3. L-deprenyls impact on mean lifespan is dose and age dependent. Meta-regression prediction of L-deprenyl treatment effect size on average lifespan adjusting for the effect of sex, species, strain, and delivery method. Dots represent individual studies.

the most well-known: caloric restriction and rapamycin Swindell, 2011, 2017). Given the degree to which replication poses a challenge in lifespan studies and medical research in general, it is critical to identify treatments which show robust effects across multiple studies. The findings presented here suggest L-deprenyl is likely one such intervention, with a significant moderate effect on increasing average lifespan in rodents (Fig. 1). While we found no evidence of publication bias in this study, we did observe a high degree of heterogeneity across studies (Fig. 2). Accounting for several experimental factors including sex, species, dose, age at initiation, and delivery method explained roughly 80 % of the between-study heterogeneity, though there remained substantial residual heterogeneity. This considerable residual heterogeneity suggests the presence of further unaccounted for confounders which were influencing the observed results. Given the diversity of year, location, and personnel involved in the studies it seems likely many environmental conditions may have contributed to this observed heterogeneity. While we found some evidence for an effect of sex on L-deprenyls effect, with females exhibiting smaller effects, this observation was not-significant when accounting for multiple-comparisons or adjusting for other experimental factors. A further limitation to the reliable detection of sex differences is the substantially lower number of studies conducted with females, with a total sample size across all studies less than 25 % that of males. Several factors which might reasonable contribute to a sex difference include hormonal differences, genetic differences, and reported differences in monoamine metabolism-providing further rational for inclusion of females in studies of L-deprenyl (Liiver et al., 2023). The possibility of L-deprenyls lifespan extending effects being stronger in male rodents seems plausible, however, given the tendency for many small molecules in rodents to have male biased effects (Jiang and Nelson, 2023). Given the many We found more robust evidence, however, for an impact of dose and age at treatment initiation, with effects appearing stronger at higher doses and especially in older animals (Fig. 3). This has important implications for possible translation of L-deprenyl as it suggests treatment in later life may exhibit particularly beneficial effects. Lastly, a study by Pabis et al. provided robust evidence of a negative relationship between control lifespans and intervention effect sizes, suggesting short-lived controls may inflate perceived lifespan effects (Pabis et al., 2024). To test the potential influence of short-lived controls on the lifespan effects reported we performed a correlation analysis of all studies and species subgroups. Interestingly, we found a positive relationship between mean control lifespan and treatment effect. This relationship was stronger in rats, while mice showed a non-significant negative relationship. This suggests the results reported here are unlikely to be due to irregularly short-lived controls, and indicates that L-deprenyl, or potentially treatments in rats, may even exhibit stronger effects in longer-lived populations.

It's important to note our meta-analysis did not include two lifespan studies of L-deprenyl in rodents which reported a reduction in lifespan (Carrillo et al., 2000; Gallagher et al., 1998). These studies were not added to the overall analysis as no way to determine the mean lifespan of experimental groups was possible from data presented in the original papers. It is worth mentioning the Gallagher study used a relatively high dose of 0.5 mg/kg S.C. and started at an earlier age than many other studies- 3 months. Additionally, the Carrillo study used a much higher dose, 1 mg/kg S.C., starting at 18 months. Both results, therefore, can likely be explained by the difference in dosages as extensively discussed by Kitani et al. (2006). Notably, our meta-regression model would suggest starting at a young age as in the Gallagher study may be responsible for the observed detriment, while the Carrillo study dose of 1 mg/kg S.C. was substantially higher than others tested when considering the study by Ingram et al. that used 1 mg/kg was oral and L-deprenyl has a substantial first pass (Ingram et al., 1993).

The reanalysis of the Ruehl et al. study of L-deprenyl in dogs in contrast suggests that the reported benefit in lifespan is likely less reliable when accounting for age at enrollment. There are several potential biological explanations for the lack of congruence with rodent studies, including differences in drug metabolism, causes of death, and underlying aging processes. Translation is a fundamental challenge in all biomedical research and lifespan extending treatments do not appear exempt from this, with published effects of drugs on lifespan often displaying limited predictive value for reported effects in other species (Bene and Salmon, 2023). Despite this, L-deprenyl still showed a trend towards improvement in survival when accounting for age and sex, reflective of a trend towards improved age-specific mortality hazard (Fig. 5). These findings may also be reflective of the study being insufficiently powered, with an estimated n of 35 per group required to detect an SMD effect of 0.68 at 80 % power. More sufficiently powered studies may therefore provide greater insight into the translatability of these findings. The creation of scientific programs such as the dog aging project has raised the possibility for examining potential clinical benefit of longevity interventions in companion dogs and such a framework could allow for examination of L-deprenyls effects at scale (Kaeberlein et al., 2016). L-deprenyl was also the first therapeutic approved for clinical use in canine cognitive dysfunction, and when given orally at doses of 0.5–1 mg/kg daily has been found to improve various clinical symptoms (Landsberg, 2005; Ruehl et al., 1997). This provides some further evidence that L-deprenyl is a promising candidate for investigation as a gerotheraputic.

In addition to the strengths of this study on L-deprenyls effects on lifespan, many limitations to the analysis should be further highlighted. The included studies spanned 27 years, with the most recent being in 2016 and most studies (16/22) taking place in the 20th century (Knoll and Miklya, 2016). Housing practices and animal husbandry have

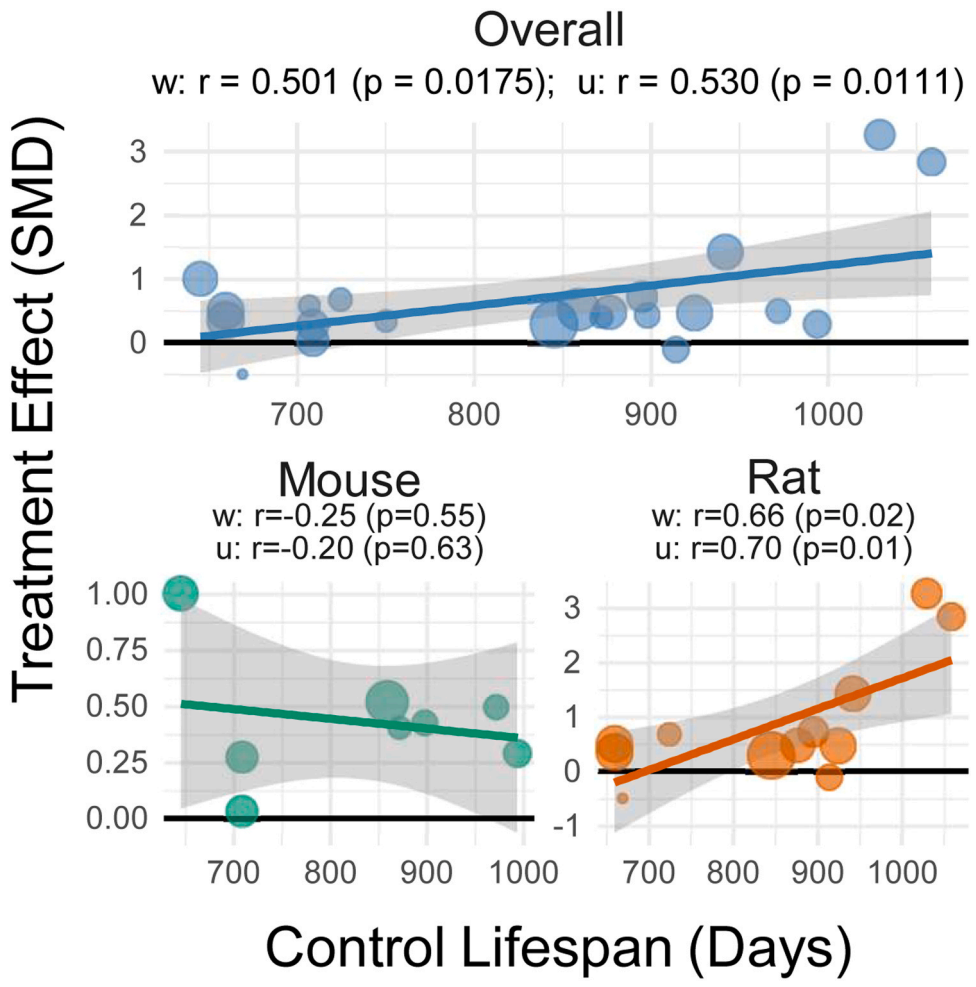

Fig. 4. L-deprenyls effect on lifespan exhibits a positive correlation with control lifespan. Plots of treatment effect by average control group lifespan, lines represent a linear trendline and bubble size reflects study weight.

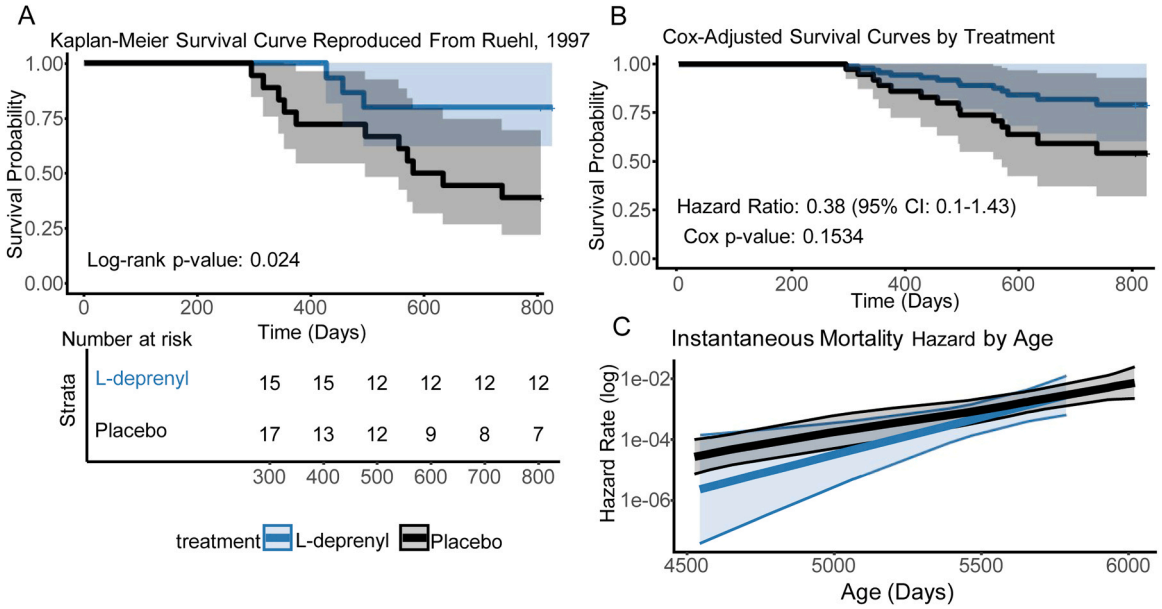

Fig. 5. L-deprenyl effects on lifespan in dogs not significant when adjusted for age at enrollment. A. Kaplan-Meier survival curve and log rank analysis reproduced from Ruehl et al. (1997). B. survival curve prediction and hazard ratio estimates for cox PH model adjusted for age at enrollment and sex. C. Log plot of instantaneous mortality hazard by age.

changed substantially over the years, with some indication this systemically influences animal lifespans (Pabis et al., 2024). It is therefore possible the findings described here may be partly influenced by these older experimental practices, with no clear evidence of which environments might produce more clinically relevant results. Further, many housing conditions such as temperature, cage mates, and diets are likely to influence lifespan and details on such factors were largely omitted from the reported studies. Another limitation is the exclusive use of mean lifespan as a metric with which to assess L-deprenyls impact on mortality. Ideally, all studies would have survival assessed more wholistically to allow for age-specific mortality effects and impact on maximal lifespan to be evaluated as well. Unfortunately, none of the included rodent studies provided raw data, and many did not provide full survival curves, thus limiting the scope of potential conclusions.

Given the long history of L-deprenyl in aging and longevity research many hypotheses for its mechanisms have been proposed. Knoll originally suggested the protective effect of L-deprenyl on dopominergic neurons, which are particularly sensitive to age, as a primary contributor to the observed extension in lifespan (Knoll et al., 1989). In support of this view, Knoll references studies which utilized levodopa and the dopamine agonist logotrile mesylate to target the dopaminergic system resulting in increased life expectancy in rodents. Interestingly, more recent studies of dopaminergic signaling and aging in invertebrate models suggest activation of dopamine D2-like receptor extended lifespan through longevity associated pathways AMPK and FOXO (Jiang et al., 2022). Other mechanisms highlighted by Knoll included the MAO-B inhibitory effects of L-deprenyl which are in opposition to age-related increases in MAO-B activity, and the ability of L-deprenyl to increase SOD and Catalase activity (Knoll, 1995). Later, Kitani expanded on the potential mechanism of L-deprenyl on lifespan, reinforcing the role of antioxidant enzyme upregulation in the brain, but also peripheral tissues, as well as immunomodulatory effects on interferons, TNF-α, interleukins, BDNF, and natural killer cells (Kitani et al., 2002). The role of antioxidants and reactive oxygen species in general in aging has been investigated for decades, with specific evidence for SOD and Catalase modulating lifespan in mammals being mixed and often highly context dependent (Karagianni and Bazopoulou, 2024). Similarly, the role of inflammation and the immune system in aging is also well studied, with several examples of modulating the immune and inflammatory responses of organisms leading to shortened or lengthened lifespans (Li et al., 2023). It therefore seems reasonable that any, or all, of these observed effects of L-deprenyl may contribute, at least in part, to the phenotypic outcome of increased lifespan. In the most recent lifespan study of L-deprenyl published in 2016, Knoll and Miklya sought to test the role of another mechanism of L-deprenyl, its activity as a catecholaminergic activity enhancer (CAE) (Knoll and Miklya, 2016). To test this, they used lower doses of L-deprenyl (0.001 mg/kg and 0.1 mg/kg) to achieve specific and non-specific enhancer effects without significantly MAO-B inhibition. Additionally, they utilized a more potent CAE, (2R)-1-(1-benzofuran-2-yl)-N-propylpentane-2-amine (BPAP), to further support the potential role of CAE activity in lifespan extension. The results of the study suggested that even lower CAE doses of L-deprenyl can extend lifespan, and BPAP was found to have an even more potent effect on longevity.

L-deprenyl has been used clinically in the treatment of both Parkinson's disease and major depressive disorder. In the context of Parkinson's disease, the most common age-related neurodegenerative movement disorder, L-deprenyl has been found to exert beneficial effects on symptoms in combination with levodopa and potentially even confer benefits to disease progression (Balestrino and Schapira, 2020; Fabbrini et al., 2012). These benefits are thought to be due in part to L-deprenyl's neuroprotective effects, particularly with respect to dopaminergic neurons. Two meta-analyses have also confirmed the benefit of L-deprenyl in combination with levodopa, and indicate its use is associated with superior unified Parkinson's disease rating scale results compared to levodopa monotherapy and alternative treatments (Binde et al., 2020; Jiang et al., 2020). Additionally, transdermal L-deprenyl is an approved treatment for major depressive disorders with similar effectiveness to other approved anti-depressant medications (Citrome, Goldberg, Portland, 2013). The results of the current study indicate a particularly beneficial effect of L-deprenyl in older individuals, raising the possibility that clinical trials targeting older adults may show greater efficacy. The doses most frequently used in the examined lifespan experiments, 0.25–0.5 mg/kg, are roughly equivalent to a 1.5–3 mg dose for a 70 kg human (Nair and Jacob, 2016). Notably, this is within the range of doses clinically used, with oral disintegrating tablets for Parkinson's being 1.25 mg and transdermal patches for depression being 6–12 mg. Given the established clinical uses of L-deprenyl, abundant safety data, and robust pre-clinical effects on lifespan, L-deprenyl appears to be a promising candidate for translation as a geroteraputic with a range of possible benefits including cognitive, neuroprotective, and mood. Carefully planned clinical trials will be required to determine if the findings presented in the current study hold relevance for L-deprenyls effects in humans.

Funding

This work was supported by the National Institute on Aging (Grant nos. T32 AG021890, 2T32AG058527-06A1); and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (Grant no. 5T32AR048522-20).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The author would like to acknowledge all of the researchers who conducted the lifespan studies that produced the data for this analysis.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.arr.2025.102873.

Data availability

Data and code have been made available in the Supplemental files.

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