Aging and efficacy of disease-modifying therapies in multiple sclerosis: a meta-analysis of clinical trials

Yinan Zhang, Natalia Gonzalez Caldito, Afsaneh Shirani, Amber Salter, Gary Cutter, William Culpepper II, Mitchell Wallin, Peter Kosa, Bibiana Bielekova, Fred Lublin and Olaf Stüve

Abstract

Background: Disease-modifying therapies (DMTs) for multiple sclerosis (MS) are approved for the treatment of disease activity and are effective in reducing relapses and new magnetic resonance imaging (MRI) lesions. However, disease activity generally subsides with time, and age-dependent changes in DMT efficacy are not well-established. We aimed to investigate whether age impacts the efficacy of DMTs in treating disease activity in patients with relapsing–remitting MS (RRMS).

Methods: DMT efficacy related to age was assessed through a meta-analysis of clinical trials that evaluated the efficacy of DMTs in RRMS patients as measured by reductions in the annualized relapse rate (ARR), new T2 lesions, and gadolinium-enhanced lesions on MRI. Using the mean baseline patient age from each trial, a weighted linear regression was fitted to determine whether age was associated with treatment efficacy on a group level.

Results: Group-level data from a total of 28,082 patients from 26 trials of 14 different DMTs were included in the meta-analysis. There were no statistically significant associations between age and reductions in ARR, new T2 lesions, and gadolinium-enhanced lesions of the treatment group compared with placebo.

Conclusion: DMTs for RRMS show efficacy in treating disease activity independent of age as demonstrated by group-level data from DMT clinical trials. Nevertheless, clinical trials select for patients with baseline disease activity regardless of age, thereby not representing real-world patients with RRMS, where disease activity declines with age.

Keywords: multiple sclerosis, clinical trials, aging, disease-modifying therapies

Correspondence to:
Olaf Stüve
Neurology Section, VA North Texas Health Care System, Medical Service, 4500 South Lancaster Rd., Dallas, TX 75216, USA

Department of Neurology and Neurotherapeutics, The University of Texas Southwestern Medical Center, Dallas, TX, USA
olaf.stuve@ utsouthwestern.edu

Yinan Zhang
Fred Lublin
Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, USA

Natalia Gonzalez Caldito
Department of Neurology and Neurotherapeutics, The University of Texas Southwestern Medical Center, Dallas, TX, USA

Afsaneh Shirani
Department of Neurological Sciences, University of Nebraska Medical Center, Omaha, NE, USA

Amber Salter
Division of Biostatistics, Washington University School of Medicine, St. Louis, MO, USA

Gary Cutter
Department of Biostatistics, University of Alabama at Birmingham, Birmingham, AL, USA

William Culpepper II
Department of Neurology, University of Maryland School of Medicine, VA Multiple Sclerosis Center of Excellence-East and VA Post Deployment Health Services, Washington, DC, USA

Mitchell Wallin
Department of Neurology, George Washington University School of Medicine, Director, VA Multiple Sclerosis Center of Excellence-East, Washington, DC, USA

Introduction

Multiple sclerosis (MS) is a chronic immune-mediated inflammatory disorder of the central nervous system characterized by demyelination and neurodegeneration.[1] Two broad categories divide the disease into relapsing–remitting (RRMS) and progressive (PMS) phenotypes. RRMS is characterized by attacks of new or worsening neurological deficits with or without return to baseline while PMS commonly presents with progressive worsening of neurologic disability.[2] While there is currently no cure for the disease, over a dozen disease-modifying therapies (DMTs) are approved by regulatory agencies for the treatment of disease activity primarily based on reducing relapses and formation of new magnetic resonance imaging (MRI) lesions.

The majority of DMTs treat disease activity by depleting inflammatory cells, preventing their migration into the central nervous system and mitigating formation of new focal white matter lesions. This efficacy for treating disease activity has prompted trials of many of the same DMTs in people with PMS, but most failed to halt disease progression, likely due to the late intrathecal inflammatory process occurring in the setting of an intact blood–brain barrier that is more difficult to target.[3–6]

Age appears to be a strong predictor of MS disease activity. With increasing age, relapse frequency and new inflammatory MRI lesions decline;[7–9] however, there is scarce evidence on age-dependent changes in DMT efficacy in treating disease activity. The goal of this study was to

Peter Kosa
Bibiana Bielekova
Neuroimmunological
Diseases Section, National
Institute of Allergy and
Infectious Diseases,
National Institutes of
Health, Bethesda, MD,
USA

perform a meta-analysis of all blinded, randomized clinical trials of DMTs for RRMS to examine whether reductions in disease activity on a group level as measured by annualized relapse rate (ARR), new T2 lesions, and gadolinium-enhanced lesions are dependent on age. We hypothesized that age will negatively correlate with reductions in ARR, new T2 lesions, and gadolinium-enhanced lesions in people with RRMS. Establishing an association between aging and DMT efficacy will help predict treatment response in patients and inform treatment decisions given the inherent risks of adverse effects, particularly in elderly patients with MS, and the high cost of DMTs.

Methods

Search strategy and selection criteria
We searched *PubMed* from the database inception to May 2020 for clinical trials of DMTs for the treatment of RRMS. The "clinical trial" filter in *PubMed* was applied and key words for screening included "multiple sclerosis" in conjunction with either "interferon" ($n=908$), "glatiramer acetate" ($n=211$), "dimethyl fumarate" ($n=35$), "fingolimod" ($n=89$), "siponimod" ($n=5$), "ozanimod" ($n=6$), "teriflunomide" ($n=25$), "cladribine" ($n=37$), "alemtuzumab" ($n=34$), "mitoxantrone" ($n=54$), "natalizumab" ($n=107$), "rituximab" ($n=22$), "ocrelizumab" ($n=10$), "daclizumab" ($n=36$), and "laquinimod" ($n=13$). Eligibility criteria included blinded randomized phase III clinical trials in adult patients with RRMS, intervention with any of the aforementioned pharmacological agents for at least 1 year, the inclusion of a placebo control arm or interferon beta as the active comparator arm, availability of baseline patient characteristics including mean age, and outcome measurements including ARR, new T2 lesions, and/or gadolinium-enhanced lesions. Studies were excluded if more than 10% of the trial population consisted of patients with PMS. Full texts of all articles were obtained based on the assessments of titles and abstracts, and additional information from supplementary data was gathered when applicable. The screening process is depicted in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram (Figure 1).[10]

Data analysis
Extracted data included clinical trial characteristics (name of trial, year of publication, interventions, study duration, sample size), mean age of trial subjects, and outcome measures (ARR, new T2 lesions, and gadolinium-enhanced lesions). When mean values were not available, the reported median values were used. The analytic methods were adopted from a meta-analysis by Weideman *et al.*[11] Data analysis was conducted in statistical software R v.3.3.1 (RStudio v.1.0).[12,13]

Calculating ARR, new T2 lesions, and gadolinium-enhanced lesions reduction
Drug efficacy was measured by percent reduction in ARR, new T2 lesions, and gadolinium-enhanced lesions of the drug group against the placebo group. Using ARR as the example, this was calculated as

$$\%\text{ARR reduction} = \left(1 - \frac{\text{ARR}_{\text{drug}}}{\text{ARR}_{\text{placebo}}}\right) \cdot 100\%$$

where ARR_{drug} represents the ARR of the drug group and $\text{ARR}_{\text{placebo}}$ represents the ARR of the placebo group at the end of the trial. The ratio of ARR_{drug} to $\text{ARR}_{\text{placebo}}$ can be viewed as the number of relapses occurring on treatment to the number of relapses occurring while on placebo. Thus, ARR reduction is roughly equivalent to the relative risk reduction in relapse occurrences.

Assigning trial weight
A weighted regression was used to account for the varying sample size and duration of clinical trials. Using methods from previous meta-analyses,[14,15] the estimated weight of each trial was calculated using the following formula:

$$\text{Weight} = n\sqrt{D}$$

where n is the trial sample size and D is the trial duration in years. Therefore, trials enrolling more subjects and lasting longer will carry a larger weight. For trials with two treatment arms and one control arm, each pair of treatment *versus* control arms was considered an independent trial. To avoid double counting patients and falsely inflating the trial weight, the placebo group size used in calculating each trial sample size was divided by the number of treatment arms.
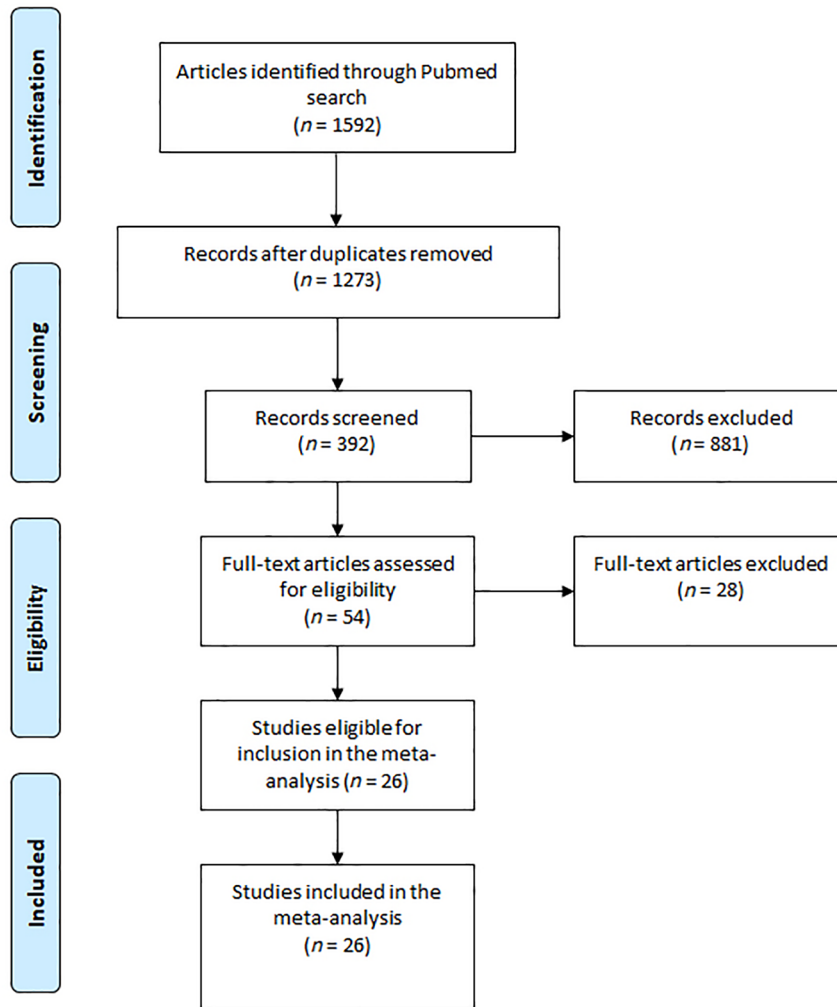
Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram illustrating search strategy and study inclusion in the meta-analysis.

Estimating efficacy against placebo in active comparator trials

For trials not using placebo, various interferon beta formulations were used as the active comparator. To estimate drug efficacy against placebo in active comparator trials, we factored in an estimated additional efficacy of interferon beta preparations against placebo on top of the known efficacy of the drug against the interferon beta control. Using ARR as the example, the ARR reduction of the drug *versus* placebo in active comparator studies using interferon beta can be thought of as

$$\text{ARR reduction}_{\text{Drug versus placebo}}$$
$$= \left(1 - \frac{\text{ARR}_{\text{drug}}}{\text{ARR}_{\text{IFN}-\beta}} \cdot \frac{\text{ARR}_{\text{IFN}-\beta}}{\text{ARR}_{\text{placebo}}}\right) \cdot 100\%$$

This represents the additional ARR reduction that a drug that was compared with interferon beta (IFN-β) would have against placebo by factoring in the ARR reduction that interferon beta preparations as a group have against placebo. By rearranging the equation for ARR reduction, it holds true that

$$\text{ARR reduction}_{\text{Drug versus placebo}} =$$
$$\left(1 - \frac{\left(1 - \left(\dfrac{\text{ARR reduction}_{\text{Drug versus IFN}-\beta}}{100}\right)\right)}{\left(1 - \dfrac{\text{ARR reduction}_{\text{IFN}-\beta \text{ versus placebo}}}{100}\right)}\right) \cdot 100\%$$

An estimated single average efficacy of interferon beta *versus* placebo was determined by taking a

weighted average for each interferon beta preparation in their respective trials against placebo.

Simple weighted regression

To assess the relationship between age and ARR, new T2 lesions, and gadolinium-enhanced lesions reduction, we fitted a simple weighted regression to all drug trials as follows using ARR as the example

$$\text{ARR Reduction}_{W_i} = \beta_{0W_i} + \beta_{1W}\,\text{Age}_i + \varepsilon_{W_i}$$

The parameter estimates of (β) [standard error (SE) and R^2] are reported for each model, the subscripts W_i are indices of the weighted terms, and ε is the error term.

Results

There were 26 trials of 14 DMTs enrolling 28,082 subjects published between 1995 and 2019 that fulfilled inclusion criteria for the meta-analysis. ARR or a relapse-related metric was the primary or coprimary outcome in all trials except in the high-dose interferon beta-1a trial, which reported time to onset of sustained disability worsening as the primary outcome.[16] New T2 lesions were reported as an outcome in 18 trials and gadolinium-enhanced lesions were reported in 19 trials. Each trial was assigned a weight dependent on the trial sample size and duration. Eleven active comparator trials compared the study drug with interferon beta instead of placebo. Six trials compared efficacy of interferon beta with placebo. Individual trial characteristics are shown in Table 1. For active comparator trials, the efficacy of the drug against placebo was estimated by combining the added estimated ARR, new T2 lesions, or gadolinium-enhanced lesion reduction of interferon beta against placebo with the ARR, new T2 lesions, or gadolinium-enhanced lesion reduction of drug to interferon beta.

Age and ARR

The mean age of patients in all trials ranged from 33.1 years in the CARE-MS I trial[17] to 40.4 years in the FREEDOMS II trial.[18] We modeled the linear regression for 26 trials as a function of age, and there was no significant association between mean age and ARR reduction [β_w (SE) = −2.13 (2.1); R^2 = 0.04; p = 0.31] [Figure 2(A)].

Age and new T2 lesions

The mean age of patients in all trials ranged from 35.4 years in the SUNBEAM trial[19] to 40.4 years in the FREEDOMS II trial.[18] We modeled the linear regression for 18 trials as a function of age, and there was no significant association between mean age and new T2 lesion reduction [β_w (SE) = 1.01 (3.9); R^2 = 0.003; p = 0.80] [Figure 2(B)].

Age and gadolinium-enhanced lesions

The mean age of patients in all trials ranged from 35.4 years in the SUNBEAM trial[19] to 40.4 years in the FREEDOMS II trial.[18] We modeled the linear regression for 19 trials as a function of age, and there was no significant association between mean age and gadolinium-enhanced lesion reduction [β_w (SE) = −2.25 (3.5); R^2 = 0.02; p = 0.53] [Figure 2(C)].

Discussion

Our meta-analysis found no significant association between age and DMT efficacy on disease activity as measured by reduction in ARR, new T2 lesions, or gadolinium-enhanced lesion in clinical trials of DMTs for RRMS. We chose to study ARR reduction since approvals of DMTs are mainly based on this outcome measure. In addition, MRI lesions are a surrogate of ARR and are correlated with disease activity.[20] In almost all RRMS trials, ARR or a similar relapse-related metric was used as the primary outcome, but studies have not examined whether ARR reduction is age-dependent. Seven subgroup analyses of MS drug trials studied whether there were differences in efficacy between younger *versus* older patients.[21–26] In each of these subgroup analyses patients were separated into two age groups of above and below age 40 years (with a cutoff of 38 for one study). These results showed that patients in the younger age group had better treatment of disease activity, but due to small differences in treatment effect, these subgroup analyses were not powered to detect statistical significance of the effect differences between the two age groups. A meta-analysis of six randomized controlled trials of 6693 patients with RRMS that reported subgroup analysis showed that patients in the <40 age group achieved significantly higher reduction of disease activity than those in the ≥40 age group.[27] Although subgroup analyses have shown that DMTs have greater efficacy in

**Table 1.** Characteristics of clinical trial included in the meta-analysis.

Trial	Index	Year	Experimental arm	Control arm	n	Mean age	Trial duration (years)	Weight	ARR reduction % (raw)	ARR reduction % (recalculated)	New T2 lesion reduction % (raw)	New T2 lesion reduction % (recalculated)	Gadolinium-enhanced lesion reduction % (raw)	Gadolinium-enhanced lesion reduction % (recalculated)
CARE-MS I	A1	2012	Alemtuzumab	Interferon beta-1a (Rebif)	563	33.07	2.00	796.20	53.85	67.98	—	—	—	—
CARE-MS II	A2	2012	Alemtuzumab	Interferon beta-1a (Rebif)	628	35.12	2.00	888.13	50.00	65.31	—	—	—	—
CLARITY	C1	2010	Cladribine	Placebo	870	38.30	1.84	1180.13	57.58	57.58	73.43	73.43	86.81	86.81
DECIDE	D1	2015	Daclizumab HYP	Interferon beta-1a (Avonex)	1841	36.30	2.76	3058.50	43.59	60.86	54.26	78.03	60.00	87.89
CONFIRM	DF1	2012	Dimethyl fumarate	Placebo	540	37.50	2.00	763.68	45.00	45.00	70.69	70.69	75.00	75.00
DEFINE	DF2	2012	Dimethyl fumarate	Placebo	818	38.30	2.00	1156.83	52.78	52.78	84.71	84.71	94.44	94.44
FREEDOMS	F1	2010	Fingolimod	Placebo	843	36.90	2.00	1192.18	55.00	55.00	74.49	74.49	81.82	81.82
FREEDOMS II	F2	2014	Fingolimod	Placebo	713	40.35	2.00	1008.33	47.50	47.50	74.16	74.16	66.67	66.67
TRANSFORMS	F3	2010	Fingolimod	Interferon beta-1a (Avonex)	866	36.35	1.00	866.00	51.52	66.36	34.62	68.60	54.90	86.35
The Copolymer 1 MS Study Group	G1	1995	Glatiramer acetate	Placebo	251	34.45	2.00	354.97	29.76	29.76	—	—	—	—
BEYOND	G2	2009	Glatiramer acetate	Interferon beta-1b (Betaseron)	1345	35.60	2.00	1902.12	5.56	34.47	−39.39	33.07	−33.33	59.64
CONFIRM	G3	2012	Glatiramer acetate	Placebo	532	36.77	2.00	752.36	27.50	27.50	54.02	54.02	65.00	65.00
CombiRx	G4	2013	Glatiramer acetate	Interferon beta-1a (Avonex)	509	38.31	3.00	881.61	28.13	50.13	—	—	—	—
MSCRG	I1	1996	Interferon beta-1a (Avonex)	Placebo	301	36.80	1.99	424.61	32.22	32.22	—	—	51.52	51.52
PRISMS	I2	1998	Interferon beta-1a (Rebif)	Placebo	283	34.90	2.00	400.22	28.91	28.91	—	—	—	—
PRISMS	I3	1998	Interferon beta-1a (Rebif)	Placebo	277	34.90	2.00	391.74	32.03	32.03	—	—	—	—

(Continued)

Table 1. (Continued)

Trial	Index	Year	Experimental arm	Control arm	n	Mean age	Trial duration (years)	Weight	ARR reduction % (raw)	ARR reduction % (recalculated)	New T2 lesion reduction % (raw)	New T2 lesion reduction % (recalculated)	Gadolinium-enhanced lesion reduction % (raw)	Gadolinium-enhanced lesion reduction % (recalculated)
INFB MS Study Group	I4	1995	Interferon beta-1b (Betaseron)	Placebo	247	35.50	5.00	552.31	30.36	30.36	—	—	—	—
ADVANCE	I5	2014	Pegylated interferon beta-1a	Placebo	1012	36.60	0.92	970.68	35.00	35.00	66.97	66.97	85.71	85.71
BRAVO	I6	2014	Interferon beta-1a (Avonex)	Placebo	672	38.00	2.00	950.35	23.53	23.53	36.49	36.49	61.54	61.54
ALLEGRO	L1	2012	Laquinimod	Placebo	1106	38.70	2.00	1564.12	23.08	23.08	29.55	29.55	37.26	37.26
BRAVO	L2	2014	Laquinimod	Placebo	659	37.10	2.00	931.97	17.65	17.65	16.50	16.50	21.37	21.37
AFFIRM	N1	2006	Natalizumab	Placebo	942	36.00	2.00	1332.19	68.00	68.00	82.72	82.72	91.67	91.67
SENTINEL	N2	2006	Natalizumab + interferon beta-1a (Avonex)	Interferon beta-1a (Avonex) + placebo	1171	38.90	2.00	1656.04	54.67	68.55	83.33	92.00	88.89	96.64
OPERA I	O1	2016	Ocrelizumab	Interferon beta-1a (Rebif)	821	37.00	1.84	1113.66	44.83	61.72	77.31	89.10	93.10	97.91
OPERA II	O2	2016	Ocrelizumab	Interferon beta-1a (Rebif)	835	37.30	1.84	1132.65	44.83	61.72	82.63	91.66	95.24	98.56
SUNBEAM	OZ1	2019	Ozanimod	Interferon beta-1a (Avonex)	895	35.35	1.13	951.40	48.57	64.32	48.24	75.15	62.79	88.74
RADIANCE	OZ2	2019	Ozanimod	Interferon beta-1a (Avonex)	874	35.55	2.00	1236.02	39.29	57.87	42.14	72.22	51.35	85.27
TEMSO	T1	2011	Teriflunomide (7 mg daily)	Placebo	548	37.73	2.07	788.43	31.48	31.48	47.56	47.56	57.14	57.14
TEMSO	T2	2011	Teriflunomide (14 mg daily)	Placebo	541	38.00	2.07	778.36	31.48	31.48	69.51	69.51	80.45	80.45
TOWER	T3	2014	Teriflunomide (7 mg daily)	Placebo	601	37.63	1.52	740.96	22.00	22.00	—	—	—	—
TOWER	T4	2014	Teriflunomide (14 mg daily)	Placebo	564	38.17	1.61	715.64	36.00	36.00	—	—	—	—
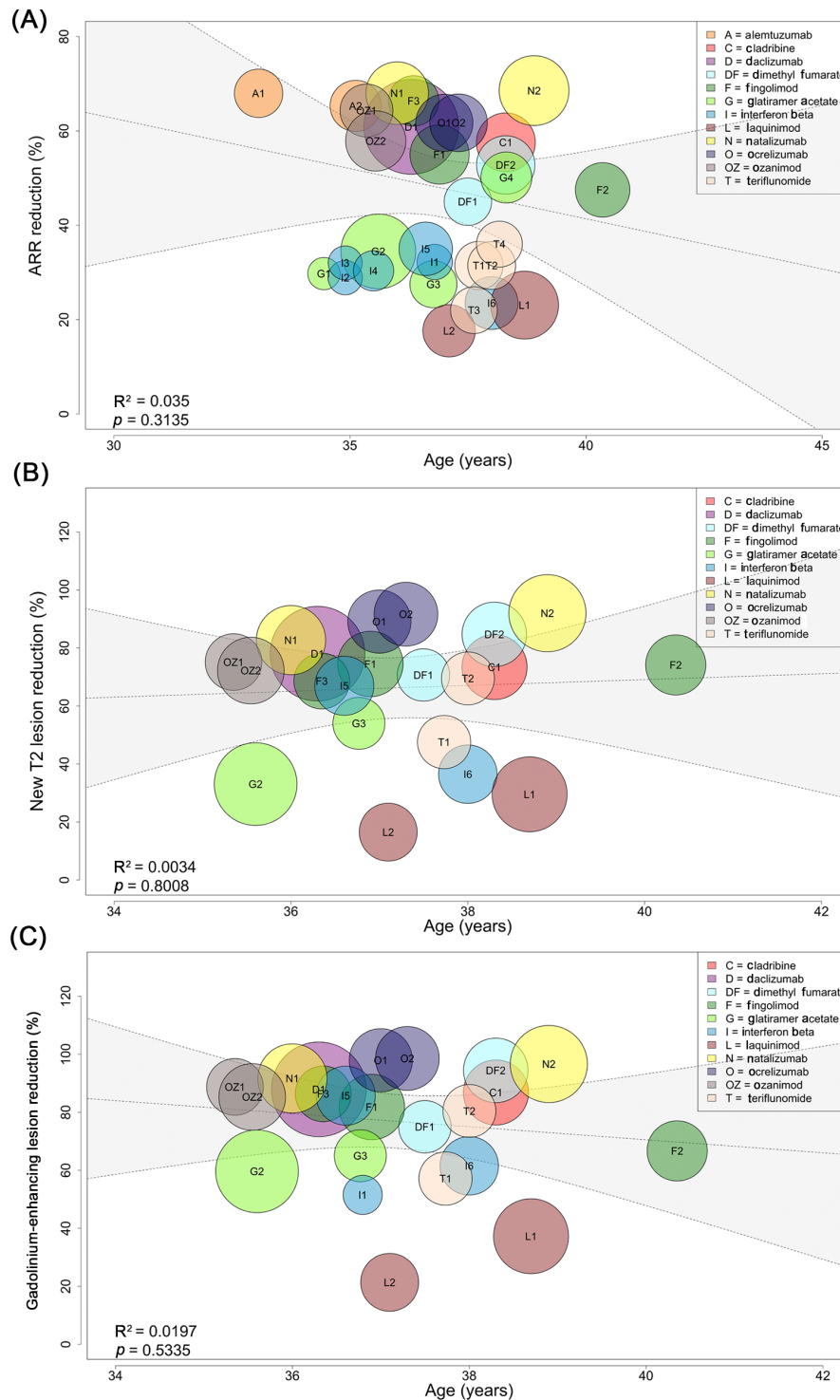
Figure 2. Efficacy of disease-modifying therapies against placebo on annualized relapse rate reduction (A), new T2 lesion reduction (B), and gadolinium-enhanced lesion reduction (C) as a function of mean baseline age in patients with relapsing–remitting multiple sclerosis. The corresponding trial indices are listed in Table 1. The gray area indicates 95% confidence interval estimates. The coefficient of determination (R^2) and *p*-values are shown in the respective plots. The diameter of each circle is proportional to the weight of the corresponding clinical trial in the meta-analysis.

younger patients, the studies do not describe a correlation between age and efficacy, thus limiting strategies to predict the average efficacy of DMTs based on age.

Analysis of data for the study was based on methods described in the meta-analysis by Weideman *et al.*, which evaluated the age-dependent efficacy of DMTs in trials of all MS subtypes using disease progression as the outcome.[11] The original study found a significant age-related decline in inhibition of disease progression using a weighted regression of percent inhibition of disability progression *versus* mean trial age. The results support observations that mechanisms driving disease progression evolve with age. While the mechanisms driving disease activity do not change with age, disease activity as the substrate for DMTs diminishes with age, which is not adequately captured in the clinical trial population that selects for patients with baseline active disease regardless of age.

Several limitations are inherent in our meta-analysis. The most significant limitation is the inaccessibility of individual-level data from MS clinical trials, which restricts us to using the mean patient age as reported in each trial and masks any age-related changes in DMT efficacy within each trial. Another limitation is the narrow range of mean age of trials for RRMS spanning from 33 to 40 years, leaving out aggregate data for younger and older patients. In addition, we assume that class differences between DMTs exhibit similar age-related changes in efficacy and that different interferon beta preparations are equivalent when preparing the regression of drug to placebo for active comparator trials. Finally, variations among clinical trials, including trial design and changes in trial population, limit accurate assessment of comparative drug efficacies.[28]

Considering that clinical trials of DMTs for RRMS exclude patients over age 55, there are no data to suggest DMTs are either effective or safe in the elderly, especially in those without disease activity. Instead, there is growing evidence showing increased prevalence of comorbidities in the aging MS population as well as greater susceptibility to treatment-related side effects such as infections and lymphopenia.[29–31] In addition, evidence suggests that relapses are rare in people with MS over age 60,[31] and continuing DMTs have lower projected benefits in the elderly.[32] Despite growing concerns regarding safety and efficacy in using DMTs in the elderly, their continued use in this population may be the result of the perceived notion that disease inactivity is due to the effect of DMTs rather than the natural disease course with aging. Further contributing to the hesitation to discontinue DMT is the concern of rebound disease activity. The currently ongoing DISCOMS trial is expected to provide data on the safety of DMT discontinuation for stable MS patients over age 55.[33]

The age gap between the MS clinical trial population and real-world population continues to widen with growing numbers of elderly people with MS, where the average age demographics for people with MS in North America are now cited to span the 50s to 60s.[34,35] This makes clinical trial results less applicable to the general MS population in terms of age and age-related changes in disease activity. As the probability of active disease declines with age and susceptibility to side effects increases, the risks *versus* benefits of using DMTs in the elderly should be reexamined. Current data from clinical trials of DMTs are not suitable for establishing an age-dependent relationship with efficacy due to selection for patients with active disease. Further dedicated studies with a real-world population on the relationship between DMT efficacy and age and the safety of DMT discontinuation are still needed to address the benefits and risks of using DMTs in aging MS patients.

Author contributions
YZ, ASa, ASh, BB, and OS conceived the study design. YZ and NGC performed data collection for the meta-analysis and ASa and PK analyzed the data. The first draft was written by YZ with input from all authors. All authors contributed to the review and approval of the final manuscript version for submission.

ORCID iD

Olaf Stüve 🔟 https://orcid.org/0000-0002-0469-6872

References

1. Lassmann H, Bruck W and Lucchinetti CF. The immunopathology of multiple sclerosis: an overview. *Brain Pathol* 2007; 17: 210–218.

2. Lublin FD, Reingold SC, Cohen JA, *et al.* Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology* 2014; 83: 278–286.

3. Wolinsky JS, Narayana PA, O'Connor P, *et al.* Glatiramer acetate in primary progressive multiple sclerosis: results of a multinational, multicenter, double-blind, placebo-controlled trial. *Ann Neurol* 2007; 61: 14–24.

4. Hawker K, O'Connor P, Freedman MS, *et al.* Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial. *Ann Neurol* 2009; 66: 460–471.

5. Lublin F, Miller DH, Freedman MS, *et al.* Oral fingolimod in primary progressive multiple sclerosis (INFORMS): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet* 2016; 387: 1075–1084.

6. Lassmann H. Targets of therapy in progressive MS. *Mult Scler* 2017; 23: 1593–1599.

7. Gartner J, Chitnis T, Ghezzi A, *et al.* Relapse rate and MRI activity in young adult patients with multiple sclerosis: a post hoc analysis of phase 3 fingolimod trials. *Mult Scler J Exp Transl Clin* 2018; 4: 2055217318778610.

8. Tremlett H, Zhao Y, Joseph J, *et al.* Relapses in multiple sclerosis are age- and time-dependent. *J Neurol Neurosurg Psychiatry* 2008; 79: 1368–1374.

9. Scalfari A, Lederer C, Daumer M, *et al.* The relationship of age with the clinical phenotype in multiple sclerosis. *Mult Scler* 2016; 22: 1750–1758.

10. Moher D, Liberati A, Tetzlaff J, *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; 339: b2535.

11. Weideman AM, Tapia-Maltos MA, Johnson K, *et al.* Meta-analysis of the age-dependent efficacy of multiple sclerosis treatments. *Front Neurol* 2017; 8: 577.

12. R Foundation. *R: A language and environment for statistical computing*. [Computer program].

Vienna, Austria: R Foundation for Statistical Computing, 2016.

13. RStudio. *Integrated Development for R.* [Computer program]. Boston, MA: RStudio, Inc., 2015.

14. Sormani MP, Bonzano L, Roccatagliata L, *et al.* Magnetic resonance imaging as a potential surrogate for relapses in multiple sclerosis: a meta-analytic approach. *Ann Neurol* 2009; 65: 268–275.

15. Sormani MP, Arnold DL and De Stefano N. Treatment effect on brain atrophy correlates with treatment effect on disability in multiple sclerosis. *Ann Neurol* 2014; 75: 43–49.

16. Jacobs LD, Cookfair DL, Rudick RA, *et al.* Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). *Ann Neurol* 1996; 39: 285–294.

17. Cohen JA, Coles AJ, Arnold DL, *et al.* Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. *Lancet* 2012; 380: 1819–1828.

18. Kappos L, Radue EW, O'Connor P, *et al.* A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med* 2010; 362: 387–401.

19. Comi G, Kappos L, Selmaj KW, *et al.* Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (SUNBEAM): a multicentre, randomised, minimum 12-month, phase 3 trial. *Lancet Neurol* 2019; 18: 1009–1020.

20. Gonzalez-Scarano F, Grossman RI, Galetta S, *et al.* Multiple sclerosis disease activity correlates with gadolinium-enhanced magnetic resonance imaging. *Ann Neurol* 1987; 21: 300–306.

21. Hutchinson M, Kappos L, Calabresi PA, *et al.* The efficacy of natalizumab in patients with relapsing multiple sclerosis: subgroup analyses of AFFIRM and SENTINEL. *J Neurol* 2009; 256: 405–415.

22. Devonshire V, Havrdova E, Radue EW, *et al.* Relapse and disability outcomes in patients with multiple sclerosis treated with fingolimod: subgroup analyses of the double-blind, randomised, placebo-controlled FREEDOMS study. *Lancet Neurol* 2012; 11: 420–428.

23. Miller AE, O'Connor P, Wolinsky JS, *et al.* Pre-specified subgroup analyses of a placebo-controlled phase III trial (TEMSO) of oral teriflunomide in relapsing multiple sclerosis. *Mult Scler* 2012; 18: 1625–1632.

24. Bar-Or A, Gold R, Kappos L, *et al.* Clinical efficacy of BG-12 (dimethyl fumarate) in patients with relapsing-remitting multiple sclerosis: subgroup analyses of the DEFINE study. *J Neurol* 2013; 260: 2297–2305.

25. Hutchinson M, Fox RJ, Miller DH, *et al.* Clinical efficacy of BG-12 (dimethyl fumarate) in patients with relapsing-remitting multiple sclerosis: subgroup analyses of the CONFIRM study. *J Neurol* 2013; 260: 2286–2296.

26. Newsome SD, Kieseier BC, Arnold DL, *et al.* Subgroup and sensitivity analyses of annualized relapse rate over 2 years in the ADVANCE trial of peginterferon beta-1a in patients with relapsing-remitting multiple sclerosis. *J Neurol* 2016; 263: 1778–1787.

27. Signori A, Schiavetti I, Gallo F, *et al.* Subgroups of multiple sclerosis patients with larger treatment benefits: a meta-analysis of randomized trials. *Eur J Neurol* 2015; 22: 960–966.

28. Zhang Y, Salter A, Wallstrom E, *et al.* Evolution of clinical trials in multiple sclerosis. *Ther Adv Neurol Disord* 2019; 12: 1756286419826547.

29. Grebenciucova E and Berger JR. Immunosenescence: the role of aging in the predisposition to neuro-infectious complications arising from the treatment of multiple sclerosis. *Curr Neurol Neurosci Rep* 2017; 17: 61.

30. Goldman MD, Dwyer L, Coleman R, *et al.* Patient-specific factors modulate leukocyte response in dimethyl fumarate treated MS patients. *PLoS One* 2020; 15: e0228617.

31. Vaughn CB, Jakimovski D, Kavak KS, *et al.* Epidemiology and treatment of multiple sclerosis in elderly populations. *Nat Rev Neurol* 2019; 15: 329–342.

32. Schwehr NA, Kuntz KM, Enns EA, *et al.* Informing medication discontinuation decisions among older adults with relapsing-onset multiple sclerosis. *Drugs Aging* 2020; 37: 225–235.

33. Medicine ULO. *Discontinuation of Disease Modifying Theraxspies (DMTs) in Multiple Sclerosis (MS) (DISCOMS)*. Bethesda, MD: National Library of Medicine.

34. Kingwell E, Zhu F, Marrie RA, *et al.* High incidence and increasing prevalence of multiple sclerosis in British Columbia, Canada: findings from over two decades (1991–2010). *J Neurol* 2015; 262: 2352–2363.

35. Wallin MT, Culpepper WJ, Campbell JD, *et al.* The prevalence of MS in the United States: a population-based estimate using health claims data. *Neurology* 2019; 92: e1029–e1040.