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# Association of sildenafil use with age-related macular degeneration: a retrospective cohort study

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## ABSTRACT

**Objective** Despite significant advances in clinical care and understanding of the underlying pathophysiology, age-related macular degeneration (AMD)—a major cause of global blindness—lacks effective treatment to prevent the irreversible degeneration of photoreceptors leading to central vision loss. Limited studies suggest phosphodiesterase type 5 (PDE5) inhibitors, such as sildenafil, may prevent AMD by increasing retinal blood flow. This study explores the potential association between sildenafil use and AMD risk in men with erectile dysfunction using UK data.

**Methods and analysis** Using the UK's IQVIA Medical Research Data, the study analysed 31 575 men prescribed sildenafil for erectile dysfunction and no AMD history from 2007 to 2015, matched with a comparator group of 62 155 non-sildenafil users in a 1:2 ratio, over a median follow-up of approximately three years.

**Results** The primary outcome was the incidence of AMD in the two groups. The study found no significant difference in AMD incidence between the sildenafil users and the non-users, with an adjusted hazard ratio (HR) of 0.99 (95% CI 0.84 to 1.16), after accounting for confounders such as age, ethnicity, Townsend deprivation quintile, body mass index category, and diagnosis of hypertension and type 2 diabetes.

**Conclusion** The study results indicated no significant association between sildenafil use and AMD prevention in UK men with erectile dysfunction, suggesting sildenafil's protective effect on AMD is likely insignificant.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Despite recent approval of the drug Syfovre by the Food and Drug Administration for atrophic age-related macular degeneration (AMD), there remains an unmet need for effective interventions to delay disease progression from its earlier stages or to prevent the advancement of AMD leading to poor quality of life and significant socioeconomic impacts.

### WHAT THIS STUDY ADDS

⇒ The study found no significant association between sildenafil use and the risk of developing AMD, after accounting for covariates such as age, ethnicity, socioeconomic status, body mass index, hypertension and type 2 diabetes.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings from this study add to the growing body of evidence concerning the potential role of commonly prescribed medications in AMD management, highlighting the concept of drug repurposing.

## INTRODUCTION

Age-related macular degeneration (AMD), the leading cause of irreversible blindness and severe visual impairment in those 65 and older, especially in high-income countries, is projected to affect nearly 300 million people worldwide by 2040.[1] Characterised by progressive macular degeneration, AMD can cause visual distortion and potential central vision loss if untreated, affecting daily activities.[2]

AMD is categorised into two types: the dry form (85%–90% of cases) marked by geographical atrophy, photoreceptor loss, and retinal degeneration, and the wet form characterised by choroidal neovascularisation with intraretinal or subretinal leakage, haemorrhage and retinal pigment epithelium (RPE) detachments.[3 4] The treatment of AMD remains a major area of unmet need. No licensed treatment has been available for dry AMD until very recently, when the US Food and Drug Administration approved pegcetacoplan under the brand name Syfovre (Apellis Pharmaceuticals) in 2023.[5–7] However, it requires intravitreal administration and carries a substantial adverse event profile, alongside significant costs.[8 9] For wet AMD, effective licensed therapies exist,[10 11] but they carry a high risk of recurrence and a high treatment burden for patients and health services. Compounded by an ageing population, AMD prevalence is increasing, posing significant socioeconomic implications.[12]

In this context, there is a growing interest in the concept of drug repurposing or AMD prevention and treatment.[13] Several drugs,

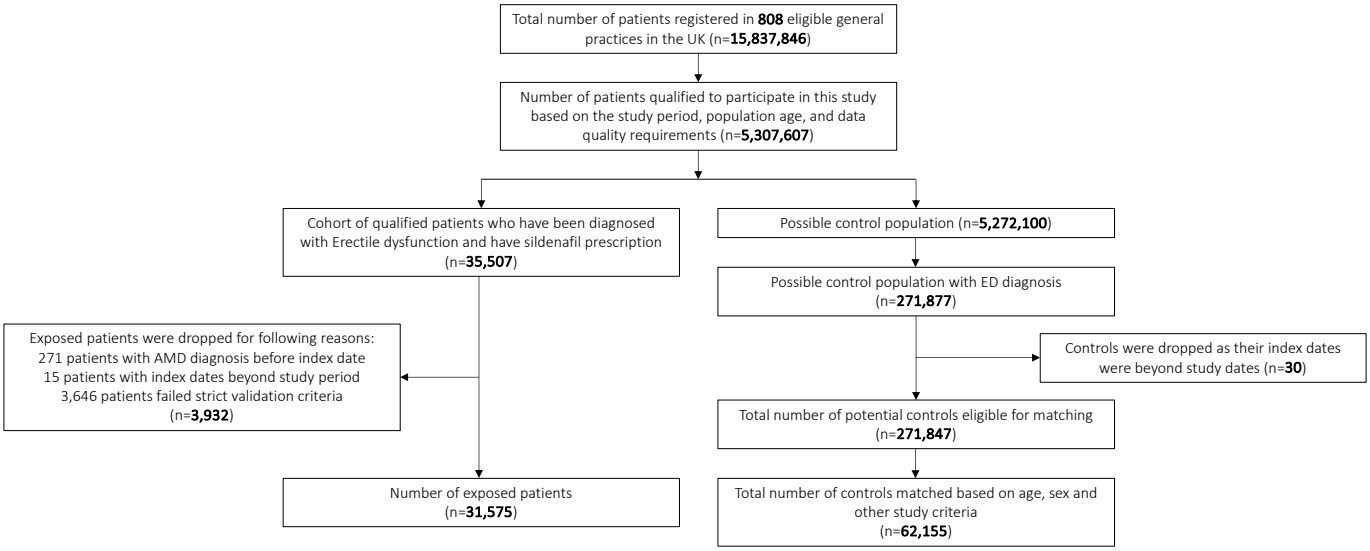


**Figure 1** Sample selection criteria to identify men with ED for inclusion in the study. AMD, age-related macular degeneration; ED, erectile dysfunction.

including metformin,[14 15] angiotensin-converting enzyme (ACE) inhibitors[16] and statins, have been investigated for their pleiotropic effects.[17]

Sildenafil serves as a notable example of drug repurposing, having been originally developed as an antihypertensive drug for the pulmonary system and angina before gaining recognition for its efficacy in treating erectile dysfunction (ED).[18] Recent research has suggested that sildenafil may hold potential in the field of anticancer therapy, either as a stand-alone treatment or in combination with other clinically efficacious chemotherapy drugs.[19] Since its initial approval as a treatment for ED in 1998, sildenafil has demonstrated a favourable safety profile and broad therapeutic versatility, leading to its widespread use and frequent citation as a successful example of drug repurposing.

Previous studies have suggested that choroidal ischaemia may be the leading cause of AMD.[20 21] Yiu *et al* conducted a study on 15 patients with AMD, using enhanced depth imaging optical coherence tomography and optical coherence tomography angiography to evaluate dynamic vascular changes through live ocular imaging following sildenafil administration.[22] The study found that the choroidal thickness and responsiveness to sildenafil decreased significantly with age but was not affected by the presence of atrophic or neovascular AMD. These findings provide a basis for exploring the potential of pharmacological agents such as sildenafil to increase choroidal perfusion and mitigate choroidal ischaemia for the treatment or prevention of AMD.

Given the substantial burden of AMD, even a modestly reduced risk of developing the disease would have significant public health implications. Therefore, the aim of this study is to investigate the association between sildenafil prescription and the risk of developing AMD in men with ED in the UK.

## MATERIALS AND METHODS

### Study design

We conducted a retrospective matched open cohort study of men with ED, comparing new users of sildenafil to non-users of sildenafil from 1 January 2000 to 25 September 2019.

### Data source

We obtained data from IQVIA Medical Research Data (IMRD-UK), a primary care database of anonymised patient medical records in the UK.[23 24] IMRD-UK includes data recorded by from over 15 million patients, with over 2.9 million currently active patients, accounting for nearly 6% of the UK population.[25] The database captures electronic medical record (EMR) data on prescriptions, diagnoses and symptoms in patients seen in general practitioner (GP) practices, and has been validated for use in pharmacoepidemiological research.[19 23 25] Diagnoses and symptoms are recorded using the Read code classification system (online supplemental table 1), while prescriptions for drugs and devices are coded according to the National Health Service (NHS) Dictionary of Medicines and Devices (dm+d).[26 27]

### Study population

GP practices were eligible for inclusion 1 year after implementing the Vision clinical system software for their EMR, or one year after attaining acceptable mortality reporting, whichever was the latest to ensure good data quality.[28 29]

Patients registered with these eligible practices for at least a year were included to ensure adequate baseline data collection and to avoid prevalent user bias. Given

**Table 1** Baseline characteristics of study participants (at start of follow-up, after 1-year latency period)

| | Sildenafil use | Non-sildenafil use |
|---|---|---|
| Number of patients (%) | **31 575 (33.7)** | **62 155 (66.3)** |
| Age at index (in years) (mean (SD)) | 60.5 (9.3) | 60.6 (9.3) |
| Age categories, n (%) | | |
| 40–49 | 4336 (13.7) | 8404 (13.5) |
| 50–59 | 10 092 (32.0) | 19 922 (32.1) |
| 60–69 | 11 463 (36.3) | 22 641 (36.4) |
| 70–79 | 5151 (16.3) | 10 124 (16.3) |
| ≥ 80 | 533 (1.7) | 1064 (1.7) |
| Ethnicity, n (%) | | |
| White | 14 691 (46.5) | 29 129 (46.9) |
| Black | 538 (1.7) | 892 (1.4) |
| South Asian | 677 (2.1) | 1169 (1.9) |
| Mixed race | 192 (0.6) | 269 (0.4) |
| Other race | 60 (0.2) | 56 (0.1) |
| Missing | 15 417 (48.8) | 30 640 (49.3) |
| Townsend, n (%) | | |
| Quintile 1 (least deprived) | 6970 (22.1) | 13 207 (21.3) |
| Quintile 2 | 5816 (18.4) | 10 979 (17.7) |
| Quintile 3 | 5267 (16.7) | 9888 (15.9) |
| Quintile 4 | 4512 (14.3) | 8344 (13.4) |
| Quintile 5 (most deprived) | 3328 (10.5) | 5570 (9.0) |
| Missing | 5682 (18.0) | 14 167 (22.8) |
| **Lifestyle variables** | | |
| BMI (kg/m$^2$) | | |
| <25 (underweight/normal) | 6160 (19.5) | 12 479 (20.1) |
| 25–29 (overweight) | 13 008 (41.2) | 24 398 (39.3) |
| 30–34 (class I obesity) | 7362 (23.3) | 13 972 (22.5) |
| ≥35 (classes II ad III obesity) | 3335 (10.6) | 7142 (11.5) |
| Missing | 1710 (5.4) | 4164 (6.7) |
| Smoking status, n (%) | | |
| Never smoker | 13 350 (42.3) | 26 654 (42.9) |
| Ex-smoker | 11 871 (37.6) | 22 513 (36.2) |
| Current smoker | 6138 (19.4) | 12 367 (19.9) |
| Missing | 216 (0.7) | 621 (1.0) |
| **Comorbidities at baseline, n (%)** | | |
| Hypertension | 13 734 (43.5) | 24 945 (40.1) |
| Type 2 diabetes | 10 794 (34.2) | 19 486 (31.4) |

BMI, body mass index.

the robust evidence demonstrating a trend of increasing ED prevalence with age,[30] and a prevalence range of 2%–9% for those under 40 years old,[31] men aged 40 and above with a clinically coded ED diagnosis were included, while those with a diagnosis of AMD on or before the index date (start of follow-up) were excluded. Data were extracted automatically using the software programme DExtER (Data Extraction for Epidemiological Research).[32]

## Exposure

To ensure that patients in the exposed group were consistently taking sildenafil for a prolonged period, we required a minimum of four records of prescription within a 12-month period, with at least one prescription per quarter for four consecutive quarters. Patients who discontinued the use of sildenafil within the first year of drug initiation were excluded. We also excluded patients who were prescribed sildenafil before the ED diagnosis. Unexposed patients were those with no record of sildenafil prescription at any time point. To mitigate selection bias, unexposed patients were matched on the index date by age (±2 years), ethnicity, Townsend deprivation quintile and country. Each exposed patient was matched with up to two unexposed patients.

## Follow-up period

The index date for exposed patients was the date of the fourth quarterly record of sildenafil prescription. To mitigate immortal time bias, unexposed patients were assigned the same index date as corresponding exposed patient. Patients were followed up from the index date until the earliest of the following: date of AMD diagnosis, treatment discontinuation (last prescription date plus 28 days), date patient transferred from the practice, death date, last date of data submitted to IMRD from the general practice and study end date (25 September 2019).

## Outcome

The primary outcome of interest was the incident diagnosis of AMD, defined by a record of a clinically relevant (Read) code in the primary care database. The codes for AMD diagnoses have been previously validated.[33] However, distinction between two types and phases of advanced AMD diagnosis, including dry vs. wet and early vs. late, is poorly coded in primary care, with the majority coded with a generic AMD code; analysis by subtype was, therefore, not possible.

## Covariates

To minimise potential confounding factors, we included several covariates in the analysis. Demographic variables such as age at index, ethnicity and Townsend deprivation quintile, along with lifestyle variables such as smoking status (categorised as smoker, ex-smoker, never smoker) and body mass index (BMI; categorised into the WHO categories of <25 kg/m$^2$ (underweight and normal weight), 25–29 kg/m$^2$ (overweight), 30–34 kg/m$^2$ (class I obesity), ≥35 kg/m$^2$ (classes II and III obesity)) were included.[34] We also included individual baseline comorbidities, such as hypertension and type 2 diabetes.

## Missing data

There were missing values for ethnicity, smoking status, Townsend deprivation quintile and BMI. We categorised the missing values for ethnicity, smoking status and Townsend quintile in our analysis, and performed

Table 2 Crude and adjusted HRs for AMD among new users of sildenafil compared with those not prescribed sildenafil

| | Sildenafil use | Non-sildenafil use |
|---|---|---|
| Patients with erectile dysfunction | 31 575 | 62 155 |
| AMD, n (%) | 234 (0.7) | 398 (0.6) |
| Total person-years of follow-up | 142 790.6 | 250 636.3 |
| Median follow-up, years | 3.6 (1.6–6.3) | 3.1 (1.3–5.5) |
| Crude incidence rate/1000 person-years | 1.64 | 1.59 |
| Unadjusted HR (95% CI) | 1.02 (0.87 to 1.20); p=0.770 | |
| Adjusted HR* (95% CI) | 0.99 (0.84 to 1.16); p=0.884 | |

*Adjusted for age, ethnicity, Townsend deprivation quintiles, BMI category, smoking status and comorbidities, including hypertension and type 2 diabetes status.
AMD, age-related macular degeneration; BMI, body mass index.

multiple imputation using chained equations with predictive mean matching to impute missing BMI data.

### Statistical analysis

Cox proportional hazards models were used to calculate the crude and adjusted HRs (aHRs) for incident AMD in men who were prescribed sildenafil compared with those who were not. The estimates were adjusted for age, ethnicity, Townsend deprivation quintile, smoking status, BMI and comorbidities (hypertension and type 2 diabetes). We checked the proportional hazards assumption using log-log plots. The statistical tests were two-tailed with an alpha level of 0.05. All analyses were performed in Stata version 16.

#### Sensitivity analysis

We conducted three subgroup analyses to explore the potential impact of age, diabetes status and the timing of the sildenafil prescription. Age is a well-established and non-modifiable risk factor for AMD and meta-analyses of studies from different population cohorts have consistently demonstrated that the age at onset of AMD typically begins at over 55 years of age with a prevalence of 2.4% for any advanced AMD in patients older than 60 years in Europe.[35 36] We stratified patients by age group, with categories of 40–49 years, 50–59 years and 60–69 years.

In addition to age, type 2 diabetes has been identified as a potential risk factor for advanced AMD in a meta-analysis[37] and we stratified patients by type 2 diabetes status. Finally, we restricted our analysis to exposed patients with a sildenafil prescription issued before the year sildenafil became available over-the-counter in the UK, that is, 1 January 2018, and corresponding controls. The last subgroup analysis was conducted to explore any potential impact of misclassification of exposure status in the primary analysis, that is, men using over-the-counter sildenafil being included in the unexposed group.[38]

## RESULTS

### Baseline characteristics

The study cohort consisted of 307 384 males aged 40 years and above with a diagnosis of ED, of whom 31 575 were prescribed sildenafil. These exposed groups were matched to 62 155 males without any record of sildenafil prescription (figure 1).

At the index date, the mean age of participants was 60.6 years with an SD of 9.3 years and a median age of 61 years, similar between the sildenafil users and non-users (table 1). The demographic and lifestyle characteristics were comparable between the exposure and the control groups. However, a higher proportion of comorbidities, including hypertension (43.5% vs 40.1%) and type 2 diabetes (34.2% vs 31.4%), were observed in the sildenafil users compared with non-users.

### Incident AMD outcomes

Table 2 presents the results of the primary as-per-protocol analysis for incident AMD outcomes. Over a total follow-up of 393 426 person-years, 234 patients in

Table 3 Subgroup analysis of risk of AMD among sildenafil users and non-users

| | Sildenafil use | | Non-sildenafil use | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Patients with ED, n | AMD, n (%) | Patients with ED, n | AMD, n (%) | Crude HR (95% CI) | P value | Adjusted HR (95% CI) | P value |
| Age, years | | | | | | | | |
| 40–49 | 4336 | 10 (0.2) | 8404 | 9 (0.1) | 1.76 (0.73 to 4.24) | 0.205 | 1.18 (0.47 to 2.92) | 0.728 |
| 50–59 | 10 092 | 39 (0.4) | 19 922 | 63 (0.3) | 1.10 (0.74 to 1.65) | 0.936 | 0.93 (0.61 to 1.40) | 0.717 |
| 60–69 | 11 463 | 77 (0.7) | 22 641 | 154 (0.7) | 0.87 (0.66 to 1.14) | 0.301 | 0.80 (0.60 to 1.05) | 0.108 |
| 70–79 | 5151 | 89 (1.8) | 10 124 | 139 (1.4) | 1.15 (0.88 to 1.49) | 0.311 | 1.14 (0.87 to 1.49) | 0.336 |
| Over 80 | 533 | 19 (3.7) | 1064 | 33 (3.2) | 1.07 (0.60 to 1.90) | 0.816 | 0.96 (0.54 to 1.72) | 0.896 |
| Type 2 diabetes status | | | | | | | | |
| With diabetes | 10 794 | 127 (1.2) | 19 486 | 148 (0.8) | 1.06 (0.83 to 1.35) | 0.616 | 1.20 (0.94 to 1.53) | 0.144 |
| Without diabetes | 20 781 | 107 (0.5) | 42 669 | 250 (0.6) | 0.86 (0.69 to 1.08) | 0.207 | 0.82 (0.65 to 1.02) | 0.078 |
| Index date prior to 2018 | 28 274 | 229 (0.81) | 55 636 | 393 (0.71) | 1.01 (0.86 to 1.19) | 0.876 | 0.98 (0.83 to 1.15) | 0.776 |

AMD, age-related macular degeneration; ED, erectile dysfunction.

the sildenafil group and 398 patients in the non-sildenafil user group developed AMD.

The crude incidence rate of AMD was 1.6 per 1000 person-years for both sildenafil users and non-users, resulting in unadjusted HR of 1.02 (95% CI 0.87 to 1.20). After adjusting for covariates, including age, ethnicity, Townsend deprivation quintile, BMI category and comorbidities, the HR was 0.99 (95% CI 0.84 to 1.16).

### Subgroup analysis

The results of the subgroup analyses (table 3) suggest that there was no significant difference in the risk of developing AMD between sildenafil users and non-users, regardless of age or type 2 diabetes status. In addition, in the subgroup analysis that was restricted to the period before sildenafil became available over the counter, that is, prior to January 2018, there remained no association between sildenafil use and risk of developing AMD (aHR 0.98, 95% CI 0.83 to 1.15, p=0.776).

## DISCUSSION

The present study aimed to examine the potential association between sildenafil use and the risk of developing AMD in a large UK cohort of men aged 40 years and above with ED. Our results revealed no association between sildenafil use and subsequent development of AMD, and this was consistent across subgroup analyses stratified by age, type 2 diabetes status and the pre-2018 period when sildenafil was unavailable over the counter in the UK.

Although there are no previous epidemiological studies exploring the use of sildenafil for the prevention of AMD, a small number of studies have investigated its potential therapeutic and preventative effects on disease progression. A randomised double-masked, placebo-controlled cross-over clinical trial involving nine men with early-stage AMD and reduced visual acuity found that treatment with sildenafil did not produce any acute visual effects.[39] This is consistent with the results of a retrospective analysis of a phase II/III study that showed no clinically significant changes after 2 years of sildenafil in 66 men with ED and a history of eye condition, including AMD.

### Strengths and limitations

To our knowledge, this is the first real-world evidence study investigating the potential association between sildenafil use and the risk of developing AMD. The study's design is a strength, as it minimises the potential for survivor bias associated with the inclusion of prevalent users of the drug.

A key limitation of our study lies in the classification of sildenafil use, which relied solely on prescriptions issued by primary care practitioners in the UK, potentially leading to exposure misclassification in some men. Despite conducting a subgroup analysis using data from before sildenafil's over-the-counter availability in the UK, the potential for exposure misclassification bias remains due to concerns about accurately capturing men who may have used sildenafil without a prescription.[40]

Furthermore, the lack of an active comparator drug indicated for ED limits our ability to draw conclusions regarding the association of sildenafil and the risk of AMD. Our cohort only included male patients with ED and thus, our findings cannot be generalised to female patients or men without ED.

Our study was unable to assess the association between sildenafil use duration, concurrent prescriptions of sildenafil and other PDE5 inhibitors, and the onset of AMD. Exploration of other PDE5 inhibitors with a longer half-life and different effect on signalling pathways, such as vardenafil and tadalafil, could be valuable.

Although dry AMD accounts for approximately 90% of all cases of AMD, the AMD read codes do not distinguish between dry and wet or early, intermediate, and late AMD stages, preventing us from evaluating the link between sildenafil use and these specific types and stages of AMD. Given the relatively short follow-up period, future research might necessitate longer durations to assess the potential risks associated with sildenafil use and AMD development.

## CONCLUSION

Our study provides no evidence of any association between the sildenafil use in men with ED and the risk of developing AMD. Our study design, which used real-world data, makes it the first of the pharmacoepidemiological studies to assess such an association. The lack of a significant association between sildenafil use and AMD in our study suggests that sildenafil is unlikely to have a clinically meaningful preventive effect on AMD. Overall, our findings contribute to the growing body of evidence on the potential effects of commonly prescribed medications on the development of AMD.

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**Contributors** KN, WHL, NJA and AKD conceived the research question. JEDH, KN and NJA designed the analysis. AS extracted analysable data. JEDH performed the analysis, with supervision and contributions by AS, NJA and KN. JEDH drafted the manuscript. All authors (JEDH, AS, WHL, JC, AKD, KN and NJA) reviewed and revised the manuscript, provided critical feedback and agreed to its publication. NJA and KN act as guarantors; the guarantors accept full responsibility for the work and the conduct of the study, had access to the data and controlled the decision to publish.

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**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** Use of IQVIA Medical Research Data (IMRD-UK) is approved by the UK Research Ethics Committee (reference number: 18/LO/0441); in accordance with this approval, the study protocol was reviewed and approved by an independent Scientific Review Committee (SRC) (reference number: 20SRC033). THIN is a registered trademark of Cegedim SA in the UK and other countries. Reference made to the THIN database is intended to be descriptive of the data asset licensed by IQVIA. This work uses deidentified data provided by patients as a part of their routine primary care.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available on reasonable request. Data may be obtained from a third party and are not publicly available. The data that support the findings of this study are available from IQVIA but restrictions apply to the availability of these data, which were used under licence for the current study, and so are not publicly available. Data are, however, available from the authors on reasonable request and with permission of IQVIA.



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