



# **The Association between Vision Impairment and Depression: A Systematic Review of Population-Based Studies**

Gianni Virgili <sup>1,2</sup>, Mariacristina Parravano <sup>2</sup>, Davide Petri <sup>3</sup>, Erica Maurutto <sup>4</sup>, Francesca Menchini <sup>4</sup>, Paolo Lanzetta <sup>4</sup>, Monica Varano <sup>2</sup>, Silvio Paolo Mariotti <sup>5</sup>, Antonio Cherubini <sup>6</sup> and Ersilia Lucenteforte <sup>3,\*</sup>

- <sup>1</sup> Department of Neurosciences, Psychology, Drug Research and Child Health (NEUROFARBA), University of Florence and AOU Careggi, 50139 Florence, Italy; gianni.virgili@unifi.it
- <sup>2</sup> IRCCS—Fondazione Bietti, 00198 Rome, Italy; mariacristina.parravano@fondazionebietti.it (M.P.); monica.varano@fondazionebietti.it (M.V.)
- <sup>3</sup> Department of Clinical and Experimental Medicine, University of Pisa, 56126 Pisa, Italy; davide.Petri@unipi.it
- <sup>4</sup> Department of Medicine—Ophthalmology, University of Udine, 33100 Udine, Italy; ericamaurutto@libero.it (E.M.); francescamenchini@gmail.com (F.M.); paolo.lanzetta@uniud.it (P.L.)
- <sup>5</sup> NCD Department, World Health Organization, 1211 Geneva, Switzerland; mariottis@who.int <sup>6</sup> Geriatria, Accettazione Geriatrica e Centro di Ricerca per L'invecchiamento IRCCS INRCA,
- 60124 Ancona, Italy; a.cherubini@inrca.it
- \* Correspondence: ersilia.lucenteforte@unipi.it

Abstract: We conducted a systematic review and meta-analysis to investigate whether depression is associated with vision impairment (VI) in population-based studies in adults. MEDLINE and EMBASE were searched, from inception to June 2020. Studies were included if they provided twoby-two data for calculating the OR of association between VI and depression, or crude and/or an adjusted odds ratio (OR) with a corresponding 95% confidence interval (CI) were reported. The proportion of VI and depression was also extracted. ORs were pooled using random-effect models, proportions were pooled using random intercepts logistic regression models. Overall, 29 articles (31 studies) were included: of those, 18 studies used survey data (622,312 participants), 10 used clinical examination data (69,178 participants), and 3 used administrative databases (48,162,290 participants). The proportion of depression (95%CI) was 0.17 (0.13–0.22) overall and 0.27 (0.21–0.33) in VI subjects. The proportion of VI was 0.10 (0.07–0.16) overall and 0.20 (0.13–0.29) in depressed subjects. The association between VI and depression was direct: crude ORs were 1.89 (1.51-2.37) for survey data, 2.17 (1.76-2.67) for clinical examination data, and 3.34 (1.01-11.11) for administrative databases; adjusted ORs were 1.75 (1.34-2.30), 1.59 (1.22-1.96), and 2.47 (0.97-6.33), respectively. In conclusion, VI and depression are prevalent morbidities and should be actively sought when either is identified, especially in older adults.

Keywords: blindness; depression; meta-analysis; systematic review; visual impairment

# 1. Introduction

Vision loss is associated with reduced performance in activities of daily living, with a greater risk of falls, social isolation, institutionalisation, and even death [1]. A recent systematic review showed that hearing and vision loss are associated with frailty among adults living in the community [2]. Depression is a major morbidity in older adults and has been shown to be even more prevalent in individuals with vision impairment (VI). Depression of any grade has been found in one-third of visually impaired older adults, approximately twice as high as the lifetime prevalence rates in the normal-sighted older population, where the prevalence of depressive symptoms is about 15% [3–9]. Depression in itself affects the quality of life, even when symptoms are only mild [7,10,11].

Depressed patients with poor vision may experience more disability, since depression can also have an impact on one's own perceived motivation and determination, toward



Citation: Virgili, G.; Parravano, M.; Petri, D.; Maurutto, E.; Menchini, F.; Lanzetta, P.; Varano, M.; Mariotti, S.P.; Cherubini, A.; Lucenteforte, E. The Association between Vision Impairment and Depression: A Systematic Review of Population-Based Studies. *J. Clin. Med.* 2022, *11*, 2412. https://doi.org/ 10.3390/jcm11092412

Academic Editor: Maria Dolores Pinazo-Duran

Received: 28 February 2022 Accepted: 22 April 2022 Published: 25 April 2022

**Publisher's Note:** MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



**Copyright:** © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). achieving goals [12]. Moreover, depression is treatable, at least partly, and numerous mental healthcare programs have been implemented and found beneficial in eye care settings [13]. Additionally, a recent Cochrane systematic review, aiming to assess the effect of different psychological interventions on quality of life in low-vision patients, pooled the results of several studies and showed that psychological therapies or group programs may improve depression and enhance self-esteem in low vision adults [14].

A PUBMED and PROSPERO search (((depression OR depressive) AND (vision OR visual))) revealed that, to date (30 March 2022), there have been no recent reviews or meta-analyses on the burden of the association between VI and depression in the general population. Our study aimed to investigate whether depression is associated with VI in community-dwelling adults. The results of our study could be important to develop public health strategies to improve the quality of life of older adults.

#### 2. Materials and Methods

We performed a systematic review and meta-analysis according to the recommendations indicated by the Cochrane network [15]. The reporting was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria [16].

# 2.1. Inclusion Criteria

We sought to include population-based cross-sectional studies of community-dwelling adults. Case–control studies and randomised controlled trials were excluded, as were studies conducted in nursing homes, or in eye clinics and low-vision services, which were objects of a previous study [17].

We accepted the diagnostic category of VI as applied by the authors of each study, which included the World Health Organisation (WHO) definition, US definitions of VI and blindness, self-reported low-vision, registry-based definitions, including administrative/insurance data. For studies using clinical examination, we had planned to use the International Classification of Diseases 11 [18] to create study subgroups according to VI severity, defined according to best-corrected visual acuity (BCVA) in the better eye as mild (<6/12), moderate to severe (<6/60), blindness, (<3/60). However, the number of these studies was small, and most used mild low-vision or worse as the primary definition of VI.

We accepted the definition of depression as reported and implemented by study authors, including validated questionnaires, diagnostic criteria of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM III or IV) or psychiatric specialist assessment, and self-reported depression.

Studies were included if they provided two-by-two data for calculating the ORs of association between VI and depression, as defined by the investigators; studies were also included if raw data were not available, but a crude and/or an adjusted odds ratio (OR) with corresponding 95% confidence interval (CI) were reported. When possible, the frequency of VI and depression was also extracted and pooled. The protocol for this review is available from the authors upon request.

# 2.2. Search Strategy

The electronic databases MEDLINE (via PUBMED) and EMBASE were searched from inception to 7 June 2020. The search strategies are shown in detail in Supplementary Materials S1.

Four independent reviewers (E.M., F.M., D.P., M.P.) analysed the output of the search and selected the studies, with a duplicate classification of literature and data extraction to ensure accuracy. Discrepancies were solved by an agreement between reviewers or with a senior reviewer (G.V.).

### 2.3. Risk of Bias Assessment

All included studies were subjected to methodological critical appraisal by means of an adapted risk of bias tool for prevalence studies [19]. A maximum of 10 stars was

assigned in 5 domains, with a maximum of 2 stars for each domain. The domains analysed in this study were lack of generalisability bias, record bias, attrition bias, detection bias, and reporting bias. The working definitions to assess bias are presented in the Supplementary Materials S2.

#### 2.4. Statistical Methods

We presented data by type of data source since we believe this is a major source of heterogeneity and is also critical to applicability.

We pooled study-specific ORs using the 'metagen' command in R software (R Foundation) as follows: random-effect models were performed using inverse variance methods for pooling, Der Simonian–Laird estimator for tau<sup>2</sup>, and the Jackson method for confidence intervals of tau<sup>2</sup> and tau. Study-specific proportions were pooled with the 'metaprop' command in R software (R Foundation) as follows: we fitted random intercept logistic regression model, used maximum-likelihood estimator for tau<sup>2</sup>, logit transformation of proportions, and Clopper–Pearson CI for individual studies. Pre-planned heterogeneity investigation was based on age 65 years or more, the inclusion of people with systemic comorbidities, the type of questionnaires used for diagnosing depression, and the definition of VI. Heterogeneity was assessed graphically and by inspecting I-square and reporting the predictive interval for primary meta-analyses.

# 3. Results

#### 3.1. Results of Searches

Our search found 7053 records; of those, 6896 articles were excluded because they did not investigate depression in subjects with VI (Figure 1). Of the 157 remaining articles, 101 were rejected for other reasons, including full-text not in English, insufficient data, presence of subthreshold depression, unclear sampling, identical study population to other included studies, and longitudinal design. Consequently, 56 remaining full-text articles investigated depression status in patients with low vision. We excluded 27 studies which were conducted in eye clinics or low-vision services and had been included in another review [17]. Thus, we included 29 studies which were population-based. One study [20] reported adjusted ORs of association between VI and depression separately by men and women and was considered as providing two datasets for analyses. Another study [21] included two datasets collected in different periods. Finally, 31 independent datasets (29 studies), hereby referred to as 'studies', were included in this review.

#### 3.2. Characteristics of Included Studies

A summary of the main characteristics of the 31 studies [3,20–47] is presented in Table 1. The number of participants ranged from 218 to 48,583,771. Overall, 10 studies [3,22,23,25,28,30,35,38,43,45] were conducted in Europe, 10 [21,24,29,32,34,37,39,42,47] in the United States, 9 [20,26,27,33,40,41,44,46] in Asia, 1 study [31] included data both from 2 European and 2 Northern American sites, and 1 study [36] was conducted on Cuban American, Mexican American, and Puerto Rican adults. Overall, 18 studies [20,21,24,26,29,31,33,35–37,39,41–44,46] were based on survey data (622,312 participants); 10 studies [3,22,23,25,27,30,34,38,45,47] used clinical examination (69,178 participants); 3 studies [28,32,40] used administrative databases (48,162,290 participants).

In total, 22 studies [3,21–23,25,26,28,29,31,33–36,38,40–43,45–47] presented raw data with a cross-tabulation of a dichotomous definition of VI and depression. Two studies [24,39] did not provide such data and reported only crude OR of this association, three studies [20,37] reported only adjusted OR, using age/gender and socioeconomic status and/or comorbidities, and four studies [27,30,32,44] reported crude and adjusted OR.

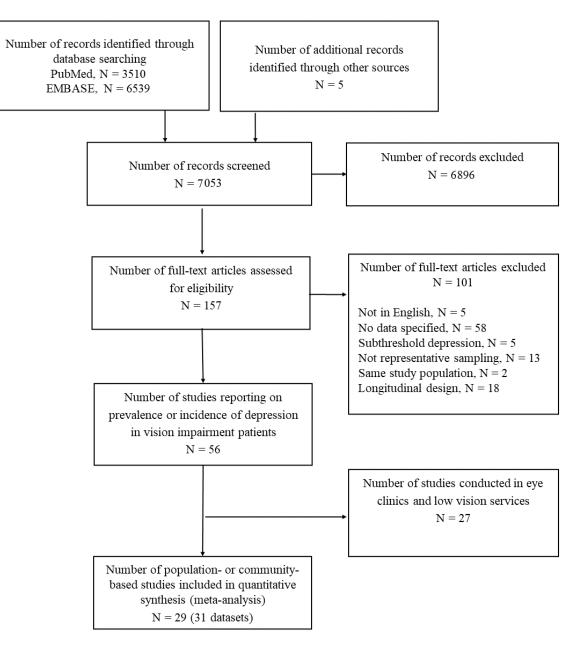


Figure 1. Flow diagram summarising the process for selecting original articles for review.

The included studies used a range of VI definitions, and in 15 studies [20–24,29,30,37,39,41–43,46], VI was self-reported (Table 1 and Supplementary Materials S3). Twelve studies [3,25–27,33–36,38,44,45,47] used clinical examination defined VI based on better-eye BCVA cut-offs between 20/40 and 20/63. Two studies [32,40] based on electronic data used VI diagnosis based on the International Diseases Code (ICD-9 or 10), one study [28] used Read Codes, which are the morbidity coding system used in all UK primary care medical records, and one study [31] used clinical records.

The tools adopted to detect depression also varied: the Centre for Epidemiologic Studies Depression (CES-D) Scale was applied in seven studies [20,21,34,36,42,45]; the Geriatric Depression Scale-15 (GDS-15) was used in six studies [3,26,33,41,44,46]; the Patient Health Questionnaire-9 (PHQ-9) was used in four studies [21,37,43,47]. Other depression diagnoses were based on the International Classification of Disease (ICD-9 or ICD-10) [22,32,40], Beck's Depression Inventory [25], the Zung Depression Status Inventory [38], the Hamilton Rating Scale [39], the Word Health Organisation Composite International Diagnostic Interview [30], the Mental Health Inventory Screening Test-5 [23], and the Depression Rating Scale [31]. In one study, depression was established by a Read code [28], while self-reported depression was accepted in four studies [24,27,29,35].

Table 1. Characteristics of included studies.

	$\mathbf{N}^\circ$ of Studies	$\mathbf{N}^\circ$ of Subjects (Range)
Overall	31	48,853,780 (218-47,852,342)
Country		
United States	10	47,917,779 (484-47,852,342)
Europe	10	328,989 (218–291,169)
Asia	9	54,220 (254–28,392)
Mixed	2	552,792 (2432-550,360)
Data source		
Survey	18	622,312 (218-550,360)
Administrative	3	48,162,290 (18,779-47,582,342)
database		
Clinical examination	10	69,178 (437-28,392)
Criteria for visual impairment		
Self-reported	15	80,100 (400-36,110)
BCVA	12	61,030 (218–28,392)
ICD	2	47,871,121(18,779-47,852,342)
Other criteria	2	841,529 (291,169-550,360)
Criteria for depression		
CES-D Scale	7	11,447 (484–2,591)
GDS-15	6	17,118 (254–13,900)
PHQ-9	4	22,782 (567-10,480)
Self-reported	4	74,552 (218–36,110)
Other criteria	10	48,727,881 (437-47,852,342)

BCVA: best-corrected visual acuity; CES-D: Centre for Epidemiologic Studies Depression; GDS: Geriatric Depression Scale; ICD: International Classification of Disease; PHQ: Patient Health Questionnaire.

Supplementary Materials S4 summarises the risk of bias evaluation of all studies, comprehensive of lack of generalisability bias, record bias, attrition bias, detection bias, and reporting bias. Most studies had a score of 1 or 2\* in the major domains of the quality scale used. Overall, 14 studies [3,21,25,26,32–34,36,37,39,41,42,47] reached a total score between 8 and 10, while 17 reached a total score between 6 and 7. Generalisability bias reached a score of 2 in 11 studies [21,25–28,32,33,36,41,47] and 1\* in 20. Lack of clarity concerning the definition of VI and/or depression was the main quality issue in this domain.

About half of the studies (19 out of 31) [3,21–23,25–27,30,33–35,38,39,41,42,44,46,47] obtained a score of 2\* for record bias, whereas the other studies collected data retrospectively or from registries. In total, 18 studies [3,21,24–26,28,29,31,32,34,36,37,39–43] were also rated with 2\* regarding attrition bias, and 13 studies gained 1\* because more than the 10% of the eligible subjects were not included. Only seven studies [21,26,35–37,41] reached 2\* for detection bias, while no information was available in all other studies regarding masking of depression assessment with respect to vision status and were assigned 1\*. Regarding reporting bias, we assigned 1\* to 9 studies, and 22 studies [3,20,22,23,25,30–34,37–47] gained a score of 2\*. There was one study [28] with zero stars due to the lack of details in the diagnostic process of depression declared.

# 3.3. Findings

Table 2 presents the meta-analysis of proportions of depressed participants, overall and among VI subjects, as well as the proportion of VI participants, overall and among depressed subjects. Supplementary Materials S5–S8 present the corresponding forest plots.

	N. Subjects (N. Studies)	<b>Pooled Proportion (95% CI)</b> 0.17 (0.13–0.22)	
Depression	929,678 (27)		
Surveys	583,563 (17)	0.19 (0.14–0.27)	
Clinical Examination	36,167 (8)	0.15 (0.10-0.23)	
Administrative	309,948 (2)	0.07 (0.03–0.16)	
databases			
<i>p</i> -value *		0.0664	
Visual Impairment	48,568,108 (28)	0.10 (0.07-0.16)	
Surveys	611,430 (16)	0.16 (0.10–0.25)	
Clinical Examinations	64,559 (9)	0.07 (0.03–0.13)	
Administrative	47,892,290 (3)	0.03 (0.01-0.07)	
databases		, , ,	
<i>p</i> -value *		0.0018	
Depression among visually	566,156 (21)	0.27 (0.21-0.33)	
impaired			
Surveys	82,804 (10)	0.29 (0.22-0.37)	
Clinical Examinations	3323 (8)	0.26 (0.17–0.38)	
Administrative	480,029 (3)	0.22 (0.08–0.46)	
databases			
<i>p</i> -value *		0.7868	
Visual Impairment among	130,048 (20)	0.20 (0.13-0.29)	
depressed			
Surveys	89,897 (10)	0.28 (0.16-0.43)	
Clinical Examinations	3459 (8)	0.15 (0.09-0.25)	
Administrative	36,692 (2)	0.08 (0.02–0.33)	
databases		. ,	
<i>p</i> -value *		0.1387	

**Table 2.** Proportion of participants with depression overall and among visual impaired, and proportion of participants with visual impairment overall and among depressed.

\* p-value for heterogeneity between groups.

The pooled *proportion of depression* was 0.17 (95% confidence interval (CI): 0.13–0.22) with predictive interval 0.03 to 0.56 (Table 2 and Supplementary Materials S5). This proportion did not differ (*p*-value = 0.0664) by data type: 0.19 (0.14–0.27) for survey data (17 studies, 583,563 participants), 0.15 (0.10–0.23) for clinical examination data (8 studies, 36,167 participants), and 0.07 for administrative databases (2 studies, 309,948 participants). As is common with meta-analyses of prevalence data, heterogeneity was very high (I-square > 99%) overall and within subgroups.

The pooled *proportion of VI* was 0.10 (0.07–0.16), with predictive interval 0.01 to 0.64 (Table 2 and Supplementary Materials S6). This proportion differed by data type (*p*-value = 0.0018): 0.16 (0.10–0.25) for survey data (16 studies, 611,430 participants), 0.07 (0.03–0.13) for clinical examination data (9 studies, 64,559 participants), and 0.03 (0.01–0.07) for administrative databases (3 studies, 47,892,290 participants). Heterogeneity was very high (I-square > 99%) overall and within subgroups.

The estimate of *proportion of depression in VI subjects* was 0.27 (0.21–0.33) with predictive interval 0.07 to 0.64 (Table 2 and Supplementary Materials S7). This proportion did not differ by data type (p = 0.7868): 0.29 (0.22–0.37) for survey data (10 studies, 82,804 VI participants), 0.26 (0.17–0.38) for clinical examination data (8 studies, 3323 VI participants), and 0.22 (0.08–0.46) for administrative databases (3 studies, 480,029 VI participants). Heterogeneity was very high (I-square > 96%) overall and within subgroups.

The estimate of *proportion of VI in depressed subjects* was 0.20 (0.13-0.29) with predictive interval 0.02 to 0.73 (Table 2 and Supplementary Materials S8). This proportion did not differ by data type (*p*-value = 0.1387): 0.28 (0.16-0.43) for survey data (10 studies, 89,897 depressed participants), 0.15 (0.09-0.25) for clinical examination data (8 studies, 3459 depressed participants), and 0.08 (0.02-0.33) for administrative databases (2 studies, 36,692 depressed participants). Heterogeneity was very high (I-square > 96%) overall and within subgroups.

Table 3 presents the association between VI and depression. The unadjusted association between VI and depression was OR (Supplementary Materials S9): 1.89 (1.51–2.37) for survey data (14 studies, 617,355 participants), 2.17 (1.76–2.67) for clinical examination data (10 studies, 69,178 participants), and 3.34 (1.01–11.11) for administrative databases (3 studies, 48,162,290 participants). Heterogeneity was moderate for clinical examination (I-square: 66%) and high for survey and administrative data (I-square > 89%). The adjusted association between VI and depression was (Supplementary Materials S10): OR 1.75 (1.34–2.30) for survey data (eight studies, 50,437 participants), 1.17 (1.00–1.37) for clinical examination data (four studies, 57,352 participants), and 2.47 (0.97–6.33) for administrative databases (two studies, 48,143,511 participants). Heterogeneity was nil for clinical examination (I-square: 0%) and high for survey data and administrative databases (I-square > 99%).

Table 3. Association between VI and depression.

	No. of Subjects (No. of Studies)	OR (95 % CI)	I <sup>2</sup>
Unadjusted OR			
Surveys	617,355 (14)	1.89 (1.51–2.37)	89%
Clinical Examination	69,178 (10)	2.17 (1.76-2.67)	66%
Administrative databases	48,162,290 (3)	3.34 (1.01–11.11)	100%
Adjusted OR			
Surveys	50,437 (8)	1.75 (1.34–2.30)	99%
Clinical Examinations	57,352 (4)	1.17 (1.00–1.37)	0%
Administrative databases	48,143,511 (2)	2.47 (0.97-6.33)	100%

#### 3.4. Subgroup Analysis

We evaluated whether study-level variables modified the association of VI with depression, using crude ORs. Differences between diagnostic depression instruments were difficult to assess statistically because of the large number of tools (Supplementary Materials S11). Overall, pooled estimates varied across subgroups (p-value = 0.0170), with the estimate for CESD, PHQ-p, and GDS being superior to the pooled OR values for self-reported and other tools. There was no difference in the strength of the association of VI with depression between 17 studies with a lower age limit of 50–65 years (2.18, 1.72–2.75, Supplementary Materials S12), compared with 10 studies including all adults (2.10, 1.33–3.32).

# 4. Discussion

Our systematic review confirms that VI and depression are common coexistent morbidities in adults and older people in the general population. This association was maintained in most studies regardless of the prevalence of either condition, which varied widely, as well as of the methods used to detect these conditions. In general, surveys found a higher prevalence of both VI and depression, compared with clinical examination. Studies based on electronic records yielded variable results but still a consistent association between depression and VI.

Of interest is subgroup analyses that suggested a similar, strong association in studies including younger adults. Although we found overall significant differences between diagnostic depression tools, we were unable to draw conclusions on the potential difference in their diagnostic sensitivity, due to the small number of studies in each group and methodological differences.

Our strategy for study selection was broad and about 2500 titles and 150 full-text articles were screened for eligibility. Despite high heterogeneity, which is expected, at least for prevalence data, due to variability in the definitions used, pooled estimates were consistent. However, the large majority of the included studies were based in high-income countries; thus, our results may not generalise to other contexts. A recent study investigated this issue in five low-middle income settings, including two national surveys (Guatemala, Maldives) and three regional/district surveys (Nepal, India, Cameroon).

Although dichotomous data for the association between depression and VI could not be extracted, the study demonstrated increased adjusted odds of severe depression and severe anxiety among adults with mobility, hearing, and visual functional difficulties in all settings, with ORs ranging from 2.0 to 14.2 [48].

The prevalence of depression in community-dwelling individuals varies across studies, with systematic review pooled estimates between 13.3% [49] and 28.4% [50] depending on the inclusion of major depression only, rather than also of preclinical depression, respectively. In 2019, the worldwide prevalence of VI and depressive disorders were 9.6% and 3.8%, respectively [51]. Furthermore, a bidirectional association between VI and depressive disorders has been reported [51]. Specifically, a large population-representative survey of 7548 participants [52] found that baseline self-reported vision loss was significantly associated with future reports of depression (hazard ratio (HR), 1.33; 95%CI, 1.15–1.55) and also that, conversely, baseline depression was significantly associated with future reports of self-reported VI (HR, 1.37; 95%CI, 1.08–1.75). This pattern was confirmed for both VI and hearing loss by Liu et al. [53], who concluded that the mental health of people with these disabilities should be the focus, and regular assessments of vision and hearing in people with depressive symptoms are recommended.

Our results are in agreement with those reported in a previous systematic review published by our group including 27 studies on patients attending eyes clinics and low vision rehabilitation services [17]. The prevalence of depression was slightly higher in patients attending clinics than in community-dwelling adult patients (0.25 vs. 0.17, respectively). Another systematic review published in 2015 and aimed at investigating the relationship between VI and depression in the elderly showed an association in all 10 included studies [54]. The review, however, did not report a pooled proportion and concluded that 'we could not definitely establish an association between VI and depression in the elderly. The reasons include a lack of standardised measures of VI and depression to allow comparability of the studies and the potential bias created by several other variables'.

The implications of our results with regard to people-centred health care concern multidisciplinary and integrated pathways of care, linking general practitioners with ophthalmologists and psychiatric/psychological professionals, which should be considered, given the frequency of this type of comorbidity [13,14,55–58]. A recent review has linked sensory loss, including at least hearing and visual loss, with frailty [2]. The attenuation of the association between VI and depression found by us with adjusted vs. crude ORs is strongly suggestive of shared effects with other systemic conditions, either through common risk factors or with a reciprocal enhancement of these disabilities [2].

Our review of observational studies aimed to investigate the burden of multimorbidity regarding two prevalent conditions but cannot prove a causal relationship between VI and depression, as stated above. Despite this limitation, case-finding in clinical [17] or population-based studies can be useful since several types of psychological interventions, mainly behavioural cognitive therapy, as well as methods for enhancing vision were found to slightly improve depression in adults with VI in a recent Cochrane review of randomised controlled studies [17].

We also acknowledge as a limitation the fact that the definitions of VI and the cut-offs used for depression diagnosis differed among studies. Regarding the risk of bias, adequate recruitment of consecutive patients was recorded in only about half the studies. In addition, whether studies used a masked assessment of depression and VI was unclear in about half the studies. Finally, about half the studies were at risk of record bias since they were retrospective or registry-based.

A potential limitation of our review is that, despite our effort to be comprehensive by taking a broad approach, we may have missed studies, given that depression data may be included as a secondary outcome in studies with different overall objectives. Another limitation may be that we did not include longitudinal studies. However, we made this choice since we did not aim to explore causality but rather to investigate the burden of co-presence of VI and depression in the general population. Longitudinal studies have

proven that VI is associated with incident depression and highlighted that this can be due to difficulties with reading, mobility, and driving [59–61]. However, studies also found that baseline depression predicts the development of VI [52]. The complex relationship between VI and depression should be considered in the broader context of multiple associations between ocular diseases and systemic conditions, specifically neurological diseases. The increasing understanding of shared causal factors is also fundamental to clarifying such complexity. Previous studies have demonstrated that eye diseases, particularly AMD, may be associated with Alzheimer's and Parkinson's disease [62,63]. On the other hand, smoking, alcohol intake, and reduced physical exercise are also risk factors for AMD, Alzheimer's, and Parkinson's disease [64–68], and also for cardiovascular disease and cancer. Understanding shared causality among complex chronic conditions may need further research. Our study highlights that VI can be used as a marker of multimorbidity and frailty in older patients, as well as the need for an integrated approach in the delivery of people-centred care, as preconised in the WHO's ICOPE framework. This association was consistent regardless of the method used to detect VI, i.e., clinical examination, interview, questionnaire, or routinely collected data.

# 5. Conclusions

In conclusion, one in five subjects with depression has VI on clinical assessment and one in four with survey data. These prevalent morbidities should be actively sought when either is identified, especially in older adults.

**Supplementary Materials:** The following supporting information can be downloaded at: https:// www.mdpi.com/article/10.3390/jcm11092412/s1, Supplementary Materials S1: Full search strategy, Supplementary Materials S2: Risk of bias assessment, Supplementary Materials S3: Characteristics of included cross-sectional population-based studies, Supplementary Materials S4: Quality assessment of included studies, Supplementary Materials S5: Forest plot of overall prevalence of depression, Supplementary Materials S6: Forest plot of overall prevalence of visual impairment, Supplementary Materials S7: Forest plot of frequency of depression in visual impairment subjects, Supplementary Materials S8: Forest plot of frequency of visual impairment in depressed subjects, Supplementary Materials S9: Forest plot of unadjusted association between visual impairment and depression, Supplementary Materials S10: Forest plot of adjusted association between vision impairment and depression, Supplementary Materials S11: Forest plot of unadjusted association between VI and depression by depression diagnostic tool, Supplementary Materials S12: Forest plot of unadjusted association between VI and depression by age inclusion criteria.

**Author Contributions:** Conceptualisation, G.V., E.M., M.V. and E.L.; data curation, G.V., D.P. and E.M.; methodology (statistics), G.V. and E.L.; supervision, G.V. and E.L.; writing—original draft preparation, G.V., E.M., M.P. and E.L.; writing—review and editing, G.V., M.P., D.P., E.M., F.M., P.L., M.V., S.P.M., A.C. and E.L. All authors have read and agreed to the published version of the manuscript.

**Funding:** The research reported in this publication was granted by the Italian Ministry of Health, under the Aging Network of Italian Research Hospitals (IRCCS).

**Data Availability Statement:** All data relevant to the study are included in the article or uploaded as Supplementary Information.

**Conflicts of Interest:** The authors have no proprietary/financial interest regarding the publication of this study. G.V., D.P., E.M., S.P.M., and A.C. have nothing to disclose. M.P. reports personal fees from Allergan, Novartis, and Bayer outside the submitted research; F.M. reports personal fees from Novartis Pharma AG; P.L. is a consultant to Allergan, Bayer, Centervue, Novartis, Roche outside the submitted research; M.V. reports personal fees from Allergan, Novartis, and Bayer, Sifi outside the submitted research; E.L. reports personal fees from Allergan, Novartis, and Bayer, Sifi outside the submitted research; E.L. reports personal fees from Angelini outside the submitted research.

# References

- Ehrlich, J.R.; Ramke, J.; Macleod, D.; Burn, H.; Lee, C.N.; Zhang, J.H.; Waldock, W.; Swenor, B.K.; Gordon, I.; Congdon, N.; et al. Association between vision impairment and mortality: A systematic review and meta-analysis. *Lancet Glob. Health* 2021, 9, e418–e430. [CrossRef]
- Tan, B.K.J.; Man, R.E.K.; Gan, A.T.L.; Fenwick, E.K.; Varadaraj, V.; Swenor, B.K.; Gupta, P.; Wong, T.Y.; Trevisan, C.; Lorenzo-López, L.; et al. Is Sensory Loss an Understudied Risk Factor for Frailty? A Systematic Review and Meta-analysis. J. Gerontol. A. Biol. Sci. Med. Sci. 2020, 75, 2461–2470. [CrossRef] [PubMed]
- 3. Evans, J.R.; Fletcher, A.E.; Wormald, R.P. Depression and Anxiety in Visually Impaired Older People. *Ophthalmology* **2007**, 114, 283–288. [CrossRef] [PubMed]
- 4. Casten, R.; Rovner, B.W.; Leiby, B.E.; Tasman, W. Depression despite anti-vascular endothelial growth factor treatment of age-related macular degeneration. *Arch. Ophthalmol.* **2010**, *128*, 506–508. [CrossRef]
- Horowitz, A.; Reinhardt, J.P.; Kennedy, G.J. Major and Subthreshold Depression among Older Adults Seeking Vision Rehabilitation Services. Am. J. Geriatr. Psychiatry 2005, 13, 180–187. [CrossRef]
- van der Aa, H.P.A.; Comijs, H.C.; Penninx, B.W.J.H.; van Rens, G.H.M.B.; van Nispen, R.M. Major Depressive and Anxiety Disorders in Visually Impaired Older Adults. *Investig. Opthalmol. Vis. Sci.* 2015, *56*, 849–854. [CrossRef] [PubMed]
- Beekman, A.T.F.; Copeland, J.; Prince, M. Review of community prevalence of depression in later life. *Br. J. Psychiatry* 1999, 174, 307–311. [CrossRef]
- Steffens, D.C.; Fisher, G.G.; Langa, K.; Potter, G.G.; Plassman, B.L. Prevalence of depression among older Americans: The Aging, Demographics and Memory Study. Int. Psychogeriatr. 2009, 21, 879–888. [CrossRef]
- Maier, A.; Riedel-Heller, S.G.; Pabst, A.; Luppa, M. Risk factors and protective factors of depression in older people 65+. A systematic review. *PLoS ONE* 2021, 16, e0251326. [CrossRef]
- 10. Cherubini, A.; Nistico, G.; Rozzini, R.; Liperoti, R.; Di Bari, M.; Zampi, E.; Ferrannini, L.; Aguglia, E.; Pani, L.; Bernabei, R.; et al. Subthreshold depression in older subjects: An unmet therapeutic need. *J. Nutr. Health Aging* **2012**, *16*, 909–913. [CrossRef]
- Morichi, V.; Dell'Aquila, G.; Trotta, F.M.; Belluigi, A.; Lattanzio, F.; Cherubini, A. Diagnosing and Treating Depression in Older and Oldest Old. *Curr. Pharm. Des.* 2015, 21, 1690–1698. [CrossRef] [PubMed]
- 12. O'Donnell, C. The Greatest Generation Meets Its Greatest Challenge: Vision Loss and Depression in Older Adults. J. Vis. Impair. Blind. 2005, 99, 197–208. [CrossRef]
- Van Der Aa, H.P.A.; Margrain, T.H.; Van Rens, G.H.M.B.; Heymans, M.; Van Nispen, R.M.A. Psychosocial interventions to improve mental health in adults with vision impairment: Systematic review and meta-analysis. *Ophthalmic Physiol. Opt.* 2016, 36, 584–606. [CrossRef] [PubMed]
- 14. Van Nispen, R.M.; Virgili, G.; Hoeben, M.; Langelaan, M.; Klevering, J.; Keunen, J.E.; Van Rens, G.H. Low vision rehabilitation for better quality of life in visually impaired adults. *Cochrane Database Syst. Rev.* **2020**, *1*, CD006543. [CrossRef] [PubMed]
- 15. Higgins, J.; Thomas, J.; Chandler, J.; Cumpston, M.; Li, T.; Page, M.J.; Welch, V.A. Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (Updated February 2022); Cochrane: London, UK, 2022.
- Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* 2021, 372, n71. [CrossRef]
- Parravano, M.; Petri, D.; Maurutto, E.; Lucenteforte, E.; Menchini, F.; Lanzetta, P.; Varano, M.; van Nispen, R.M.A.; Virgili, G. Association Between Visual Impairment and Depression in Patients Attending Eye Clinics. *JAMA Ophthalmol.* 2021, 139, 753–761. [CrossRef] [PubMed]
- 18. World Health Organisation. ICD-11 for Mortality and Morbidity Statistics (ICD-11 MMS) 2018 Version. Available online: https://Icd.Who.Int/Browse11/L-M/En (accessed on 21 April 2022).
- Bonifazi, M.; Franchi, M.; Rossi, M.; Moja, L.; Zambelli, A.; Zambon, A.; Corrao, G.; La Vecchia, C.; Zocchetti, C.; Negri, E. Trastuzumab-Related Cardiotoxicity in Early Breast Cancer: A Cohort Study. *Oncologist* 2013, *18*, 795–801. [CrossRef]
- Lyu, J.; Kim, H.-Y. Gender-Specific Associations of Sensory Impairments with Depression and Cognitive Impairment in Later Life. *Psychiatry Investig.* 2018, 15, 926–934. [CrossRef]
- Armstrong, T.W.; Surya, S.; Elliott, T.R.; Brossart, D.F.; Burdine, J.N. Depression and health-related quality of life among persons with sensory disabilities in a health professional shortage area. *Rehabil. Psychol.* 2016, *61*, 240–250. [CrossRef]
- Bernabei, V.; Morini, V.; Moretti, F.; Marchiori, A.; Ferrari, B.; Dalmonte, E.; De Ronchi, D.; Atti, A.R. Vision and hearing impairments are associated with depressive–anxiety syndrome in Italian elderly. *Aging Ment. Health* 2011, 15, 467–474. [CrossRef]
- Biddulph, J.P.; Iliffe, S.; Kharicha, K.; Harari, D.; Swift, C.; Gillmann, G.; Stuck, A.E. Risk factors for depressed mood amongst a community dwelling older age population in England: Cross-sectional survey data from the PRO-AGE study. *BMC Geriatr.* 2014, 14, 5. [CrossRef] [PubMed]
- 24. Capella-McDonnall, M.E. The effects of single and dual sensory loss on symptoms of depression in the elderly. *Int. J. Geriatr. Psychiatry* **2005**, *20*, 855–861. [CrossRef]
- 25. Carabellese, C.; Appollonio, I.; Rozzini, R.; Bianchetti, A.; Frisoni, G.B.; Frattola, L.; Trabucchi, M. Sensory Impairment and Quality of Life in a Community Elderly Population. *J. Am. Geriatr. Soc.* **1993**, *41*, 401–407. [CrossRef] [PubMed]
- 26. Nanaware, M.B.; Cheluvaraj, P. Rapid psychological assessment of depression and its relationship with physical health urban elderly. *Australas. Med. J.* 2016, *9*, 211. [CrossRef]

- 27. Cho, G.E.; Lim, D.H.; Baek, M.; Lee, H.; Kim, S.J.; Kang, S.W. Visual Impairment of Korean Population: Prevalence and Impact on Mental Health. *Investig. Opthalmol. Vis. Sci.* 2015, *56*, 4375–4381. [CrossRef]
- Court, H.; McLean, G.; Guthrie, B.; Mercer, S.W.; Smith, D. Visual impairment is associated with physical and mental comorbidities in older adults: A cross-sectional study. *BMC Med.* 2014, 12, 181. [CrossRef] [PubMed]
- 29. Crews, J.E.; Chou, C.-F.; Sekar, S.; Saaddine, J.B. The Prevalence of Chronic Conditions and Poor Health among People With and Without Vision Impairment, Aged ≥65 Years, 2010–2014. *Am. J. Ophthalmol.* **2017**, *182*, 18–30. [CrossRef]
- 30. Garin, N.; Olaya, B.; Lara, E.; Moneta, M.V.; Miret, M.; Ayuso-Mateos, J.L.; Haro, J.M. Visual impairment and multimorbidity in a representative sample of the Spanish population. *BMC Public Health* **2014**, *14*, 815. [CrossRef]
- 31. Guthrie, D.M.; Declercq, A.; Finne-Soveri, H.; Fries, B.E.; Hirdes, J.P. The Health and Well-Being of Older Adults with Dual Sensory Impairment (DSI) in Four Countries. *PLoS ONE* **2016**, *11*, e0155073. [CrossRef]
- 32. Hamedani, A.G.; VanderBeek, B.L.; Willis, A.W. Blindness and Visual Impairment in the Medicare Population: Disparities and Association with Hip Fracture and Neuropsychiatric Outcomes. *Ophthalmic Epidemiol.* **2019**, *26*, 279–285. [CrossRef]
- Harada, S.; Nishiwaki, Y.; Michikawa, T.; Kikuchi, Y.; Iwasawa, S.; Nakano, M.; Ishigami, A.; Saito, H.; Takebayashi, T. Gender difference in the relationships between vision and hearing impairments and negative well-being. *Prev. Med.* 2008, 47, 433–437. [CrossRef] [PubMed]
- Hirai, F.E.; Tielsch, J.M.; Klein, B.E.K.; Klein, R.; Obhi, S.S.; Swiderski, K.M.; Brubacher, S.P. Relationship between retinopathy severity, visual impairment and depression in persons with long-term type 1 diabetes. *Ophthalmic Epidemiol.* 2012, 19, 196–203. [CrossRef] [PubMed]
- Karlsson, J.S. Self-reports of Psychological Distress in Connection with Various Degrees of Visual Impairment. J. Vis. Impair. Blind. 1998, 92, 483–490. [CrossRef]
- Lee, D.J.; Gómez-Marín, O.; Lam, B.L. Current Depression, Lifetime History of Depression, and Visual Acuity in Hispanic Adults. J. Vis. Impair. Blind. 2000, 94, 85–96. [CrossRef]
- 37. Loprinzi, P.D.; Smit, E.; Pariser, G. Association among Depression, Physical Functioning, and Hearing and Vision Impairment in Adults with Diabetes. *Diabetes Spectr.* **2013**, *26*, 6–15. [CrossRef]
- Lupsakko, T.; Mäntyjärvi, M.; Kautiainen, H.; Sulkava, R. Combined hearing and visual impairment and depression in a population aged 75 years and older. *Int. J. Geriatr. Psychiatry* 2002, 17, 808–813. [CrossRef] [PubMed]
- 39. Lyness, J.M.; Niculescu, A.; Tu, X.; Reynolds, C.F., 3rd; Caine, E.D. The Relationship of Medical Comorbidity and Depression in Older, Primary Care Patients. *J. Psychosom. Res.* **2006**, *47*, 435–439. [CrossRef]
- Park, H.-Y.; Ryu, H.; Kang, H.-Y.; Lee, H.; Kwon, J.-W. Clinical and Economic Burden of Visual Impairment in an Aging Society of South Korea. *Asia Pac. J. Public Health* 2015, 27, 631–642. [CrossRef]
- Rahman, M.S.; Rahman, M.A.; Ali, M.; Rahman, M.S.; Maniruzzaman, M.; Yeasmin, M.A.; Ahmed, N.A.M.F.; Abedin, M.M.; Islam, S.M.S. Determinants of depressive symptoms among older people in Bangladesh. J. Affect. Disord. 2020, 264, 157–162. [CrossRef]
- 42. Rovner, B.W.; Ganguli, M. Depression and disability associated with impaired vision: The MoVies Project. *J. Am. Geriatr. Soc.* **1998**, *46*, 617–619. [CrossRef]
- 43. Schuster, A.K.; Tesarz, J.; Rezapour, J.; Beutel, M.E.; Bertram, B.; Pfeiffer, N. Visual Impairment Is Associated With Depressive Symptoms—Results From the Nationwide German DEGS1 Study. *Front. Psychiatry* **2018**, *9*, 114. [CrossRef] [PubMed]
- 44. Tsai, S.-Y.; Cheng, C.-Y.; Hsu, W.-M.; Su, T.-P.T.; Liu, J.-H.; Chou, P. Association between visual impairment and depression in the elderly. *J. Formos. Med Assoc.* 2003, *102*, 86–90. [PubMed]
- 45. Van Nispen, R.M.A.; Vreeken, H.L.; Comijs, H.C.; Deeg, D.J.H.; Van Rens, G.H.M.B. Role of vision loss, functional limitations and the supporting network in depression in a general population. *Acta Ophthalmol.* **2015**, *94*, 76–82. [CrossRef] [PubMed]
- 46. Wee, L.E.; Yong, Y.Z.; Chng, M.W.X.; Chew, S.H.; Cheng, L.; Chua, Q.H.A.; Yek, J.J.L.; Lau, L.J.F.; Anand, P.; Hoe, J.T.M.; et al. Individual and area-level socioeconomic status and their association with depression amongst community-dwelling elderly in Singapore. Aging Ment. Health 2014, 18, 628–641. [CrossRef]
- Zhang, X.; Bullard, K.M.; Cotch, M.F.; Wilson, M.R.; Rovner, B.W.; McGwin, G.; Owsley, C.; Barker, L.; Crews, J.E.; Saaddine, J.B. Association Between Depression and Functional Vision Loss in Persons 20 Years of Age or Older in the United States, NHANES 2005-2008. *JAMA Ophthalmol.* 2013, 131, 573–581. [CrossRef]
- Wallace, S.; MacTaggart, I.; Banks, L.M.; Polack, S.; Kuper, H. Association of anxiety and depression with physical and sensory functional difficulties in adults in five population-based surveys in low and middle-income countries. *PLoS ONE* 2020, 15, e0231563. [CrossRef]
- Abdoli, N.; Salari, N.; Darvishi, N.; Jafarpour, S.; Solaymani, M.; Mohammadi, M.; Shohaimi, S. The global prevalence of major depressive disorder (MDD) among the elderly: A systematic review and meta-analysis. *Neurosci. Biobehav. Rev.* 2022, 132, 1067–1073. [CrossRef]
- 50. Hu, T.; Zhao, X.; Wu, M.; Li, Z.; Luo, L.; Yang, C.; Yang, F. Prevalence of depression in older adults: A systematic review and meta-analysis. *Psychiatry Res.* **2022**, *311*, 114511. [CrossRef]
- 51. Abdolalizadeh, P.; Falavarjani, K.G. Correlation between global prevalence of vision impairment and depressive disorders. *Eur. J. Ophthalmol.* **2022**, 11206721221086152. [CrossRef]
- Frank, C.R.; Xiang, X.; Stagg, B.; Ehrlich, J. Longitudinal Associations of Self-reported Vision Impairment with Symptoms of Anxiety and Depression among Older Adults in the United States. *JAMA Ophthalmol.* 2019, 137, 793–800. [CrossRef]

- 53. Liu, W.; Yang, C.; Liu, L.; Kong, G.; Zhang, L. Bidirectional associations of vision loss, hearing loss, and dual sensory loss with depressive symptoms among the middle-aged and older adults in China. *J. Affect. Disord.* **2022**, *301*, 225–232. [CrossRef] [PubMed]
- 54. Ribeiro, M.V.M.R.; Júnior, H.N.H.-R.; Ribeiro, E.A.N.; Jucá, M.J.; Barbosa, F.T.; De Sousa-Rodrigues, C.F. Association between visual impairment and depression in the elderly: A systematic review. *Arq. Bras. Oftalmol.* **2015**, *78*, 197–201. [CrossRef]
- 55. Katon, W.J. Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. *Biol. Psychiatry* **2003**, *54*, 216–226. [CrossRef]
- 56. Lêng, C.H.; Wang, J.-D. Long term determinants of functional decline of mobility: An 11-year follow-up of 5464 adults of late middle aged and elderly. *Arch. Gerontol. Geriatr.* 2013, *57*, 215–220. [CrossRef] [PubMed]
- 57. Lee, D.J.; Gomez-Marin, O.; Lam, B.L.; Zheng, D.D.; Caban, A. Visual Impairment and Morbidity in Community-Residing Adults: The National Health Interview Survey 1986–1996. *Ophthalmic Epidemiol.* **2005**, *12*, 13–17. [CrossRef]
- Renaud, J.; Bédard, E. Depression in the elderly with visual impairment and its association with quality of life. *Clin. Interv. Aging* 2013, *8*, 931–943. [CrossRef]
- Heesterbeek, T.J.; Aa, H.P.A.; Rens, G.H.M.B.; Twisk, J.W.R.; van Nispen, R.M.A. The incidence and predictors of depressive and anxiety symptoms in older adults with vision impairment: A longitudinal prospective cohort study. *Ophthalmic Physiol. Opt.* 2017, 37, 385–398. [CrossRef] [PubMed]
- Keay, L.; Munoz, B.; Turano, K.A.; Hassan, S.E.; Munro, C.A.; Duncan, D.D.; Baldwin, K.; Jasti, S.; Gower, E.W.; West, S.K. Visual and Cognitive Deficits Predict Stopping or Restricting Driving: The Salisbury Eye Evaluation Driving Study (SEEDS). *Investig. Opthalmology Vis. Sci.* 2009, 50, 107–113. [CrossRef]
- Pérès, K.; Matharan, F.; Daien, V.; Nael, V.; Edjolo, A.; Bourdel-Marchasson, I., 1st; Ritchie, K.; Tzourio, C.; Delcourt, C.; Carriere, I. Visual Loss and Subsequent Activity Limitations in the Elderly: The French Three-City Cohort. *Am. J. Public Health* 2017, 107, 564–569. [CrossRef]
- 62. Tsai, D.-C.; Chen, S.-J.; Huang, C.-C.; Yuan, M.-K.; Leu, H.-B. Age-Related Macular Degeneration and Risk of Degenerative Dementia among the Elderly in Taiwan. *Ophthalmology* **2015**, *122*, 2327–2335.e2. [CrossRef]
- Chung, S.-D.; Ho, J.-D.; Hu, C.-C.; Lin, H.-C.; Sheu, J.-J. Increased Risk of Parkinson Disease Following a Diagnosis of Neovascular Age-Related Macular Degeneration: A Retrospective Cohort Study. Am. J. Ophthalmol. 2014, 157, 464–469.e1. [CrossRef] [PubMed]
- 64. Velilla, S.; Garcia-Medina, J.J.; García-Layana, A.; Dolz-Marco, R.; Pons-Vázquez, S.; Pinazo-Duran, M.D.; Gómez-Ulla, F.; Arevalo, J.F.; Díaz-Llopis, M.; Gallego-Pinazo, R. Smoking and Age-Related Macular Degeneration: Review and Update. *J. Ophthalmol.* **2013**, 2013, 895147. [CrossRef] [PubMed]
- Adams, M.K.M.; Chong, E.W.; Williamson, E.; Aung, K.Z.; Makeyeva, G.A.; Giles, G.; English, D.; Hopper, J.; Guymer, R.; Baird, P.; et al. 20/20–Alcohol and Age-related Macular Degeneration: The Melbourne Collaborative Cohort Study. *Am. J. Epidemiol.* 2012, 176, 289–298. [CrossRef] [PubMed]
- Choi, D.; Choi, S.; Park, S.M. Effect of smoking cessation on the risk of dementia: A longitudinal study. *Ann. Clin. Transl. Neurol.* 2018, 5, 1192–1199. [CrossRef]
- 67. Ngandu, T.; Lehtisalo, J.; Solomon, A.; Levälahti, E.; Ahtiluoto, S.; Antikainen, R.; Bäckman, L.; Hänninen, T.; Jula, A.; Laatikainen, T.; et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): A randomised controlled trial. *Lancet* **2015**, *385*, 2255–2263. [CrossRef]
- Bettiol, S.S.; Rose, T.C.; Hughes, C.J.; Smith, L.A. Alcohol Consumption and Parkinson's Disease Risk: A Review of Recent Findings. J. Park. Dis. 2015, 5, 425–442. [CrossRef]