# Depression and APOEɛ4 Status in Individuals with Subjective Cognitive Decline: A Meta-Analysis

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**Objective** To evaluate the associative role of depression and apolipoprotein E epsilon 4 allele (APOE¢4) in subjective cognitive decline (SCD) and its progression to objective cognitive decline.

**Methods** After literature search in electronic databases, studies were selected by following precise eligibility criteria. Meta-analyses were performed to examine the role of APOEe4 and depression in SCD or its progression to mild cognitive impairment (MCI) or dementia.

**Results** APOE $\epsilon$ 4 positivity was not different between SCD and normal individuals but was significantly higher in individuals with SCD plus than in normal individuals [odds ratio: 2.39 (95% CI: 1.87, 3.05); p<0.00001] and in SCD converters than in non-converters [odds ratio: 5.19 (95% CI: 2.36, 11.42); p<0.00001]. Depression was significantly higher in individuals with SCD [standardized mean difference: 0.63 (0.45, 0.82); p<0.00001] and SCD plus [standardized mean difference: 0.83 (0.43, 1.22); p<0.0001] than in normal individuals. However, depression was not different between SCD and MCI or between SCD converters and non-converters. Age of SCD converters was higher than non-converters [mean difference: 2.95 years (0.58, 5.31)].

ConclusionWhereas APOEc4 positivity was higher in SCD plus and SCD converters, depression was higher in SCD and SCD plus but<br/>was not different between SCD and MCI.Psychiatry Investig 2020;17(9):858-864

Key Words Subjective cognitive decline, Apolipoprotein E4, Depression, Dementia risk.

# **INTRODUCTION**

Subjective cognitive decline (SCD) is a self-perceived persistently declining cognitive function when compared to the individual's previous state of normal cognitive performance on a standardized cognitive test score adjusted for age, sex, and education. SCD plus is a higher category of SCD that increases the likelihood of preclinical Alzheimer's disease.<sup>1</sup> Presenting symptoms of SCD such as subjective memory complaints (individual informed memory problems) have a prevalence of 25% to 50% in community-dwelling elderly.<sup>2</sup> Individuals with SCD are at a greater risk of progression to any form of objective cognitive decline such as mild cognitive impairment (MCI)

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© This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/bync/4.0) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited. or Alzheimer's disease.<sup>3-5</sup> The predictability is greater when a SCD-related complaint made by the individual is also endorsed by an informant (an individual who knows the patient well). A study of a multicenter cohort of elderly found that individuals were at a 4-fold risk of developing MCI or dementia if the SCD complaint was made by both the individual and the informant, whereas either the individual's or the informant's complaint posed 2-fold risk of progression.<sup>6</sup>

Pathological changes associated with SCD and its progression include changes in both brain anatomy and biomarkers. In community-dwelling elderly, the severity of white matter lesions has been found to be associated with SCD and its worsening in the last five years.<sup>7</sup> The presence of thinner parietal and temporal cortices in individuals with SCD is associated with the later progression of SCD to dementia.<sup>8</sup> Increased amyloid beta deposition in the brain is also reported in older individuals with SCD.<sup>9</sup> Although, a significant proportion of older adults who report cognitive problems progress to objective cognitive impairment, the predictability is not straight forward and the link between SCD and objective cognitive impairment may be affected by the affective symptoms.<sup>10</sup> Moreover, the pre-

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dictability of SCD for future objective cognitive impairment may also be confounded by many factors like depression, anxiety, physical health, and somatic problems.<sup>11,12</sup>

The relationship between depression and SCD is not clear. Studies involving individuals with SCD have found associations of SCD with apolipoprotein E epsilon 4 allele (APOE $\epsilon$ 4) or with depression but the outcomes are not always consistent. In the present study, we undertake this issue by conducting a systematic review of these studies to perform a meta-analysis of important indices in order to seek a refined evidence of the relationship between APOE $\epsilon$ 4, depression and SCD.

# **METHODS**

## **Eligibility criteria**

A study was included if it 1) investigated cohorts of individuals with SCD or surveyed community-dwelling individuals; 2) reported APOEɛ4 status and the prevalence of depression in individuals with SCD; and 3) reported an association between SCD and APOEɛ4, and/or between SCD and depression, and/or between SCD and depression in APOEɛ4 positive individuals. A study was excluded if it 1) reported the relationships between APOEɛ4 and/or depression in individuals with MCI or dementia but not in individuals with SCD; 2) or reported the outcomes of either APOEɛ4 status or depression prevalence but not both in individuals with SCD; or 3) reported the outcomes without differentiating stages/forms of cognitive impairment.

### Literature survey and study selection

A comprehensive literature search was conducted in Google Scholar, PubMed, and Science Direct electronic databases by using the most relevant key terms including subjective cognitive decline, SCD, memory complaints, dementia risk, preclinical Alzheimer's disease, apolipoprotein E  $\epsilon$ 4, APOE $\epsilon$ 4, depression, and depressive symptoms. The search strategy is given in the supporting information file (Supplementary Table 1 in the online-only Data Supplement). Additional searches included screening the bibliographic sections of important research and review articles as well as the software suggested records. The literature search was restricted to research articles published in English before November 2019.

## Data and analyses

Data pertaining to demographics, study design, cognitive status/measures, APOEɛ4 positivity, depression prevalence and scale, SCD progression rates, and associational outcomes were extracted from the identified research articles. SCD was defined as the individual's complaint of worsened cognitive function (not related to an acute event) in comparison with a previously normal state, where SCD plus was considered a higher category of SCD as identified by the authors of individual studies. SCD converters were defined as the individuals who progressed to objective cognitive decline (MCI, Alzheimer's disease or any other type of dementia) during study followup period.

To attain overall estimates of the prevalence of APOEɛ4 or depression, meta-analyses of proportions were performed under a random-effects model with Stata software (Stata Corporation, TX, USA) using dichotomous data of individual studies. Meta-analyses of odds ratios (ORs) were performed to estimate the differences in the prevalence of APOEɛ4 between normal individuals and in individuals with SCD, SCD plus, or MCI. In a separate meta-analysis, the ORs reported by the included studies were pooled to obtain overall estimates.

To estimate the significance of difference between normal individuals and individuals with SCD or MCI in depression scores, age, and formal education, random-effects meta-analyses of mean differences (MD) or standardized MD (SMD) were performed with RevMan software (Nordic Cochrane Centre, Cochrane Community). The between-studies inconsistency in outcomes was estimated with the I<sup>2</sup> index.

## RESULTS

Twenty-five studies published in twenty-eight research articles were included in the meta-analysis (Figure 1).<sup>13-40</sup> From these studies, data were available for 6247 individuals with SCD {55% [95% confidence interval (CI): 51, 59] females}, 10087 normal (cognitively) individuals [56% (95% CI: 51, 60) females], and 1165 individuals with MCI [58% (95% CI: 49, 68) females]. Of these, 13 were cross-sectional and 13 were longitudinal studies. The average follow-up duration of the longitudinal studies was 5.8 years (95% CI: 4.8, 6.9). Important characteristics of the included studies are presented in Supplementary Table 1 (in the online-only Data Supplement).

The percent positivity of APOE $\epsilon$ 4 (homozygote or heterozygote) was 23% (95% CI: 19, 27) in normal, 28% (95% CI: 23, 33) in SCD, 31% (95% CI: 16, 49) in SCD plus, and 39% (95% CI: 29, 49) in MCI individual. The odds of APOE $\epsilon$ 4 positivity were not different between individuals with SCD and normal individuals [OR: 1.03 (95% CI: 0.79, 1.35); p=0.52]. However, the odds of APOE $\epsilon$ 4 positivity were significantly higher for individuals with SCD plus than for normal individuals [OR: 2.39 (95% CI: 1.87, 3.05); p<0.00001]. The odds of APOE $\epsilon$ 4 positivity were also significantly higher for SCD converters than for non-converters [OR: 5.19 (95% CI: 2.36, 11.42); p<0.00001) (Figure 2).

A pooled analysis of ORs reported by the individual studies also showed similar outcomes. In this meta-analysis, 1) the

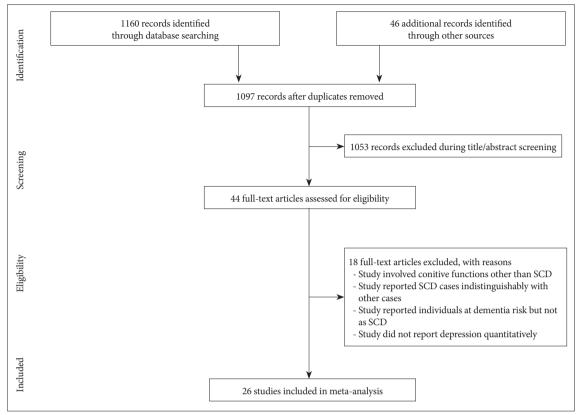


Figure 1. A flowchart of the study screening and selection process. SCD: subjective cognitive decline.

prevalence of APOEɛ4 was not different between SCD and normal individuals [pooled OR: 1.13 (95% CI: 0.86, 1.40)]; 2) the prevalence of depression was higher in individuals with SCD [pooled OR: 1.79 (95% CI: 0.33, 3.25)]; 3) the co-existence of APOEɛ4 and depression was also higher in individuals with SCD [pooled OR: 3.32 (95% CI: 0.04, 6.61)]; and 4) the risk of progression in individuals with SCD was higher in APOEɛ4 carriers [pooled OR: 1.94 (95% CI: 1.04, 2.84)] (Supplementary Figure 1 in the online-only Data Supplement).

A meta-analysis of depression scores indicated that depression was significantly higher in individuals with SCD [SMD: 0.63 (95% CI: 0.45, 0.82); p<0.00001] and SCD plus [SMD: 0.83 (95% CI: 0.43, 1.22); p<0.0001] in comparison with normal individuals. However, depression was not statistically significantly different between individuals with SCD and individuals with MCI [SMD: 0.12 (95% CI: -0.31, 0.54); p=0.70] or between SCD converters and non-converters [SMD: 0.21 (95% CI: -0.09, 0.51; p=0.17] (Figure 3).

The age of individuals with SCD or SCD plus were not different from those of normal individuals [mean difference (MD): 0.25 years (95% CI: 0.03, 0.46) and 1.07 years (95% CI: -1.55, 3.69) respectively]. However, the age of SCD converters was approximately 3 years higher than that of non-converters [MD: 2.95 years (95% CI: 0.58, 5.31); p=0.01] (Supplementary

Figure 2 in the online-only Data Supplement). Formal education was not different between the groups (Supplementary Figure 3 in the online-only Data Supplement).

## DISCUSSION

In this meta-analysis we found that, in comparison with normal individuals, APOEɛ4 prevalence was not significantly higher in individuals with SCD but was significantly higher in individuals with SCD plus than in normal individuals and in SCD converters than in non-converters. On the other hand, the level of depression was significantly higher in individuals with SCD or SCD plus than in normal individuals but was not significantly different between individuals with SCD and individuals with MCI or between SCD converters and non-converters.

In older adults, depression is found to be associated with altered cognitive function including attention deficits, memory impairment, decreased information processing speed, poor responsiveness, problems in visual and spatial performance and lower performance in complex mental tasks.<sup>41-44</sup> In addition to the outcomes of the present study, a review of 47 crosssectional studies found depressive symptoms to be positively associated with SCD.<sup>45</sup> In a study of more than 13000 cogni-

	SCD		Contr			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
1.2.1 SCD vs normal							
Choe 2018 <sup>16</sup>	8	72	15	103	5.0%	0.73 [0.29, 1.83]	
Chu 2017 <sup>17</sup>	7	63	7	46	3.9%	0.70 [0.23, 2.14]	
Dik 2001 <sup>18</sup>	80	298	216	870	10.4%	1.11 [0.82, 1.50]	
Fernandez-Blazquez 2016 <sup>19</sup>	62	370	31	185	8.7%	1.00 [0.62, 1.60]	
Jessen 2014 <sup>24</sup>	210	1061	163	863	11.0%	1.06 [0.84, 1.33]	+
Jorm 2004 <sup>25</sup>	85	257	618	2289	10.6%	1.34 [1.01, 1.76]	
Miebach 2019 <sup>28</sup>	31	105	15	76	6.6%	1.70 [0.84, 3.44]	<b>—</b>
Risacher 2015 <sup>31</sup>	33	104	53	185	8.2%	1.16 [0.69, 1.95]	
Roehr 2016 <sup>32</sup>	43	233	127	738	9.6%	1.09 [0.74, 1.60]	+
Sanchez-Benavides 2018 <sup>33</sup>	52	319	731	2098	10.3%	0.36 [0.27, 0.50]	
Scheef 2019 <sup>34</sup>	7	24	11	49	4.0%	1.42 [0.47, 4.30]	
Shorabi 2009 <sup>35</sup>	37	83	18	55	6.5%	1.65 [0.81, 3.36]	
Striepens 2011 <sup>38</sup>	11	41	16	72	5.2%	1.28 [0.53, 3.11]	
Subtotal (95% CI)		3030		7629	100.0%	1.03 [0.79, 1.35]	<b>•</b>
Total events	666		2021				
Heterogeneity: Tau <sup>2</sup> = 0.16; C Test for overall effect: Z = 0.2			12 (P < (	0.00001	l); l² = 77%	6	
1.2.2 SCD-plus vs normal							
Buckley 2016 <sup>14</sup>	8	13	10	19	2.9%	1.44 [0.34, 6.05]	
Fernandez-Blazquez 2016 <sup>19</sup>	16	53	31	185	12.1%	2.15 [1.06, 4.33]	
Sanchez-Benavides 2018 <sup>33</sup>	144	253	731	2098	85.0%	2.47 [1.90, 3.22]	
Subtotal (95% CI)		319		2302	100.0%	2.39 [1.87, 3.05]	•
Total events	168		772				
Heterogeneity: Tau <sup>2</sup> = 0.00; C Test for overall effect: Z = 7.0		'	2 (P = 0.7	3); I² =	0%		
1.2.3 SCD converters vs no							_
Bessi 2019 <sup>13</sup>	8	18	6	30	37.3%	3.20 [0.88, 11.63]	
Caselli 2014 <sup>15</sup>	17	20	163	427	40.2%	9.18 [2.65, 31.80]	
Fernandez-Blazquez 2016 <sup>19</sup> Subtotal (95% CI)	22	43 81	2	10 <b>467</b>	22.5% 100.0%	4.19 [0.80, 22.06] <b>5.19 [2.36, 11.42]</b>	
Total events	47		171				
Heterogeneity: Tau² = 0.00; C Test for overall effect: Z = 4.1			2 (P = 0.4	9); I² =	0%		
	0 (F < 0.1	5001)					
1.2.4 SCD vs MCI							
Bessi 2019 <sup>13</sup>	14	48	9	26	9.2%	0.78 [0.28, 2.16]	
Choe 2018 <sup>16</sup>	8	72	19	52	10.5%	0.22 [0.09, 0.55]	
Grambaite 2013 <sup>20</sup>	13	23	20	47	9.4%	1.75 [0.64, 4.80]	
Jessen 2014 <sup>24</sup>	210	1061	144	609	27.1%	0.80 [0.63, 1.01]	-
Merrill 2016 <sup>27</sup>	8	24	11	20	7.1%	0.41 [0.12, 1.39]	
Risacher 2015 <sup>31</sup>	33	104	131	305	20.5%	0.62 [0.39, 0.99]	
√isser 2009 <sup>39</sup> Subtotal (95% CI)	29	60 <b>1392</b>	48	108 <b>1167</b>	16.2% <b>100.0%</b>	1.17 [0.62, 2.20] 0.72 [0.50, 1.04]	•
Total events	315		382				
Heterogeneity: Tau <sup>2</sup> = 0.12; C		34. df =		04): l <sup>2</sup> :	= 55%		
Test for overall effect: Z = 1.7			J. U.	,, .			

**Figure 2.** A forest graph showing the ORs between SCD and normal/MCI individuals or between converters and non-converters from SCD to MCI in the presence of APOE¢4. Diamonds show the overall ORs where the thicknesses represent summary point and the spread shows the 95% CI of the summary point. For individual studies, the central box represents the OR and lines show the 95% CI. The size of the box represents the weight of the study relative to other studies. BDI: Beck Depression Inventory, GDS: Geriatric Depression Scale, HDRS: Hamilton Depression Rating Scale, Met: methionine allele carriers, VaI: valine allele carriers, OR: odds ratios, SCD: subjective cognitive decline, MCI: mild cognitive impairment, CI: confidence interval.

tively normal individuals over 50-years old of which 10% had depression and 27% had SCD at baseline, 11% developed MCI or dementia during 7 years of follow-up. The risk of developing MCI or dementia was significant with SCD (hazard ratio; HR: 2) as well as with depression (HR: 1.4) but the risk was highest when both depression and SCD (HR: 2.8) coexisted at baseline.<sup>46</sup> Thus, at least some of the SCD symptoms may stem from depression or depression may substantiate the symptoms of cognitive worsening arising from neurodegenerative processes.

In a longitudinal community-based study of elderly, a positive association was observed between APOEɛ4 and depression during 5 years of follow-up. This relationship persisted even after the exclusion of individuals who developed dementia within 9 years of follow-up and after controlling for the Mini-Mental State Examination score which showed that depression was not a prodromal symptom of dementia.<sup>47</sup> A meta-analysis of 9 studies also found that APOEɛ4 was positively associated

1.1.1 SCD vs normal Buckley 2016 <sup>14</sup> Choe 2018 <sup>16</sup> Chu 2017 <sup>17</sup> Fernandez-Blazquez 2016 <sup>19</sup> Jessen 2010 -worry <sup>23</sup> Jessen 2010 +worry <sup>23</sup>	0.92 14.01 7.4	0.9		Mean	SD	Total	Weight	IV. Random, 95% CI	IV, Random, 95% CI
Buckley 2016 <sup>14</sup> Choe 2018 <sup>16</sup> Chu 2017 <sup>17</sup> Fernandez-Blazquez 2016 <sup>19</sup> Jessen 2010 -worry <sup>23</sup> Jessen 2010+worry <sup>23</sup>	14.01 7.4						mongine	IV, Randoni, 95% Ci	11,114114011,007001
Choe 2018 <sup>16</sup> Chu 2017 <sup>17</sup> Fernandez-Blazquez 2016 <sup>19</sup> Jessen 2010 -worry <sup>23</sup> Jessen 2010+worry <sup>23</sup>	14.01 7.4								
Chu 2017 <sup>17</sup> Fernandez-Blazquez 2016 <sup>19</sup> Jessen 2010 -worry <sup>23</sup> Jessen 2010+worry <sup>23</sup>	7.4	7 04	14	0.28	1	19	3.9%	0.65 [-0.06, 1.36]	
Fernandez-Blazquez 2016 <sup>19</sup> Jessen 2010 -worry <sup>23</sup> Jessen 2010+worry <sup>23</sup>			72		6.28	103	7.1%	0.66 [0.35, 0.97]	
Jessen 2010 -worry <sup>23</sup> Jessen 2010+worry <sup>23</sup>		3.8	63	1.9	1.8	46	5.8%	1.75 [1.30, 2.20]	
Jessen 2010+worry 23	1.75	2.29	370	1.05	1.69	185	8.1%	0.33 [0.15, 0.51]	
	2.1	2.29	1006	1.8	2	1027	8.6%	0.14 [0.05, 0.23]	-
	3.2	2.7	382	1.8	2	1027	8.4%	0.63 [0.51, 0.75]	-
Jorm 2004 25	3.25	2.47	257	1.5	1.71	2289	8.4%	0.97 [0.84, 1.10]	-
Miebach 2019 28	1.8	1.8	105	0.7	1.3	76	7.1%	0.68 [0.38, 0.98]	
Risacher 2015 <sup>31</sup>	1.2	1.3	104	0.65	1.1	185	7.6%	0.47 [0.22, 0.71]	
Roehr 2016 <sup>32</sup>	1.94	1.97	233	1.51	1.78	738	8.3%	0.24 [0.09, 0.38]	-
Sanchez-Benavides 2018 <sup>33</sup>	0.35	0.93	319	0.11	0.52	2098	8.4%	0.41 [0.29, 0.52]	-
Scheef 2019 <sup>34</sup>	6.3	4.6	24	2.7	2.8	49	5.3%	1.02 [0.50, 1.54]	
Shorabi 2009 <sup>35</sup>	5.54	5	83	2.91	3.03	55	6.7%	0.60 [0.26, 0.95]	
Striepens 2011 <sup>38</sup>	7.45	6.9	41	3.2	3.2	72	6.3%	0.87 [0.47, 1.27]	
Subtotal (95% CI)			3073			7969	100.0%	0.63 [0.45, 0.82]	•
Heterogeneity: Tau <sup>2</sup> = 0.11; C	;hi² = 1	74.67,	df = 13	(P < 0.	00001	); I² = 9	3%		
Test for overall effect: Z = 6.6									
			,						
1.1.2 SCD-plus vs normal									
Buckley 2016 <sup>14</sup>	2.15	1.7	13	0.28	1	19	16.6%	1.38 [0.58, 2.17]	
Fernandez-Blazquez 2016 <sup>19</sup>	2.89	2.75	53	1.05	1.69	185	37.2%	0.93 [0.61, 1.25]	
Sanchez-Benavides 2018 <sup>33</sup>		1.07	253	0.11	0.52	2098	46.3%	0.55 [0.42, 0.68]	
Subtotal (95% CI)			319			2302	100.0%	0.83 [0.43, 1.22]	
Heterogeneity: Tau <sup>2</sup> = 0.08; C	hi² = 8.	.36. df	= 2 (P	= 0.02);	$ ^2 = 70$	6%			
Test for overall effect: Z = 4.0		,	``						
1.1.3 SCD converters vs nor									_
Bessi 2019 <sup>13</sup>		3.22		26.68		30	17.0%	-0.19 [-0.77, 0.40]	
Caselli 2014 BDI <sup>15</sup>	3.8	3.5	20	4.1	4.2	427	23.2%	-0.07 [-0.52, 0.38]	
Caselli 2014 GDS <sup>15</sup>	4.9	4	20	2.7	3.5	427	23.1%	0.62 [0.17, 1.07]	
Caselli 2014 HDRS <sup>15</sup>	3	3.4	20	2.3	3	427	23.2%	0.23 [-0.22, 0.68]	
Fernandez-Blazquez 2016 <sup>19</sup>	3.9	2.96	10	2.65	2.68	43	13.5%	0.45 [-0.24, 1.14]	
Subtotal (95% CI)			88			1354	100.0%	0.21 [-0.09, 0.51]	-
Heterogeneity: Tau <sup>2</sup> = 0.05; C		,	= 4 (P	= 0.14);	<sup>2</sup> = 4;	3%			
Test for overall effect: Z = 1.30	6 (P = (	0.17)							
1.1.4 SCD vs MCI									
	26.20	2 65	22	24.12	2.00	0	10 10/	0 62 [ 0 10 1 45]	
	26.38 26.45		23 25	24.12	2.99 4.55	8	12.1% 15.2%	0.63 [-0.19, 1.45]	
						18		-0.50 [-1.12, 0.11]	-
Choe 2018 <sup>16</sup>	14	7	72	11.3	6.6	52	19.2%	0.39 [0.03, 0.75]	
Grambaite 2013 <sup>20</sup>	1.1	0.8	23	0.8	0.6	47	17.0%	0.44 [-0.06, 0.95]	
Merrill 2016 <sup>27</sup>	2.2	3	24	1.3	2	20	15.5%	0.34 [-0.26, 0.94]	
Risacher 2015 <sup>31</sup>	1.2	1.3	104	1.8	1.5	305	21.0%	-0.41 [-0.64, -0.19]	
Subtotal (95% CI)			271				100.0%	0.12 [-0.31, 0.54]	
Heterogeneity: Tau <sup>2</sup> = 0.21; C			lf = 5 (F	P = 0.00	01); l²	= 81%			
Test for overall effect: Z = 0.54	4 (P = (	0.59)							
									-2 -1 0 1 2

Figure 3. A forest graph showing the SMDs between SCD and normal/MCI individuals or between converters and non-converters from SCD to MCI in the levels of depression measured with validated tools. SCD: subjective cognitive decline, MCI: mild cognitive impairment, CI: confidence interval, SMD: standardized mean difference.

with depression in individuals aged 23 to 83 years.<sup>48</sup> In the present study, we found that the odds of the coincidence of APOEɛ4 and depression were also higher in individuals with SCD. A study that used data of 11453 cognitively asymptomatic individuals from the National Alzheimer's Coordinating Center, found that the hazard of developing Alzheimer's disease was 10 times higher (HR: 10.1) among APOEɛ4 carriers with clinician-verified depression.<sup>49</sup>

In the present study, the expression of APOEɛ4 increased from 23% in normal to 28% in SCD, 31% in SCD plus, and 39% MCI individuals. Our prevalence estimate resembles that of Zhang et al.<sup>50</sup> who reported the prevalence of APOEɛ4 at 32% in individuals with SCD after reviewing 28 studies. Moreover, in our study, APOEɛ4 positivity was significantly higher in SCD converters than in non-converters. A study of individuals with MCI found that the expression of APOEɛ4 was 62% in individuals who progressed from MCI to Alzheimer's dementia.<sup>51</sup> Homozygous carriers of APOEɛ4 are reported to have a faster rate of cognitive decline between the age of 40 and 70 years.<sup>52</sup> Moreover, whereas heterozygous APOEɛ4 poses 3-fold risk of sporadic Alzheimer's disease, APOEɛ4 homozygosity poses a 14-fold risk.<sup>53</sup> A probable mechanism of APOEɛ4 action appears to be related to amyloid beta clearance from the brain. It has been demonstrated that whereas APOEɛ2 enhances amyloid beta clearance from the brain, APOEɛ4 remains inefficient in this clearance.<sup>53</sup>

Although the present study and the literature cited above indicate a relationship between depression and SCD, several

caveats need to be addressed in future research. Whether depression develops because of persistent cognitive problems in individuals with SCD or whether depression causes, coexists, or worsens cognitive decline should be delineated. The relationship between APOEe4 and SCD can be better understood in SCD plus individuals but the relationship with depression in manifesting objective cognitive decline is not as clear. This study and some others suggest that the presence of both depression and APOEe4 increases the risk of progression among individuals with SCD more than either factor alone.

Some limitations of the present study should be noted. Firstly, less data were available with regards to the prevalence or measures of depression in APOE¢4 positive vs APOE¢4 negative individuals with SCD which could better portray a relationship between depression and SCD or its progression. Secondly, less binary data were available in individual studies pertaining to the prevalence of depression which could further clarify the outcomes of the present study. Thirdly, although in most of the analyses I<sup>2</sup> remained moderate, statistical heterogeneity was high in some meta-analyses which represented high between-studies inconsistency in the outcomes. The use of various scales to measure depression, and study design features could have contributed to the heterogeneity.

#### Supplementary Materials \_

The online-only Data Supplement is available with this article at https://doi.org/10.30773/pi.2019.0324.

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None.

#### Conflicts of Interest \_

The authors have no potential conflicts of interest to disclose.

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Ct 1		Ν					Age (years)		Р	ercent femal	es		MMSE scor	e
Study	SCD	Normal	MCI	Design	FU (years)	SCD	Normal	MCI	SCD	Normal	MCI	SCD	Normal	
Bessi 2019	48		24	Longitudinal	8.5±3.7	62±8.7		69.2±6.2	73		67	27.6±2.3		2
Buckley 2016	58			Longitudinal	4.5	78±7			45			28.8±1.4		
Caselli 2014	447			Longitudinal	6.6	60±7.3			70			29.5±0.8		
Choe 2018	72	103	52	Cross sectional		70.6±5.7	70.4±5.9	72.5±6.6	60	55	62	26.5±1.9	26.8±1.7	2
Chu 2017	63	50		Cross sectional		66.7±6	69±6.8		73	37				
Dik 2001	298	870		Longitudinal	6	72.8±6.7	71.8±6.4		46	50		28.3±1.1	28.4±1	
Fernandez-Blazquuez 2016	423	185		Longitudinal	13.1	74.2±3.8	74.1±4		61	64				
Grambaite 2013	23		47	Cross sectional		58.8±7.2		63.1±6.8	44		53	29±1		2
Hong 2015	129			Longitudinal	1.9	66±8			69					
Jessen 2007; 2010; 2014; Roehr 2016	1061	863	609	Longitudinal	6	79.8±3.5	79.7±3.5	79.6±3.9	58	68	72			
Jorm 2004	257	2289		Cross sectional		$62.4 \pm 1.4$	62.5±1.5		38	50		28.5±2.2	29.2±1.4	
Kim 2003	267			Longitudinal	2	72±6	72±6		58	58				
Merrill 2016	24		20	Cross sectional		63.1±11.6		62±9.8	67		65	29.5±0.6		2
Miebach 2019	105	76		Cross sectional		$70.4 \pm 5.5$	68.3±4.9		46	55		29.2±0.9	29.4±0.9	
Meuller-Gerards 2019	292	906		Longitudinal	10	68±7	67.5±7							
Niti 2009	251	1236		Longitudinal	1.5									

3.2

2

5

# S

104

319

24

83

151

67

41

60

1347

185

2098

49

55

223

72

89

305

108

Cross sectional

Cross sectional

Cross sectional

Cross sectional

Cross sectional

Cross sectional

Longitudinal

Longitudinal

Longitudinal

Risacher 2015

Scheef 2019

Shorabi 2009

Stewart 2001

Striepens 2011

Visser 2009

Wang 2004

Slot 2018

Sánchez-Benavides 2018

BDI: Beck Depression Inventory, CES-D: Center for Epidemiologic Studies Depression Scale, GADS: Goldberg Anxiety and Depression Scale, GDS: Geriatric Depression Scale, GSM: Geriatric Mental State Schedule, FU: follow-up, HADS: Hospital Anxiety and Depression Scale, HDRS: Hamilton Depression Rating Scale, MCI: mild cognitive impairment, SCD: subjective cognitive decline, SCL-90: symptom checklist-90-R

73±6.3

66±7.2

 $55.4 \pm 6.6$ 

66.7±6.3

67.1±7.5

67±6.4

71±7.4

70±7.7

57

68

25

44

29

48

64

52

63

35

38

54

45

47

29±1.1

 $28.6 \pm 1.1$ 

29.2±1

 $28.8 \pm 1.2$ 

72±5.5

57±6

67±6.1

 $67.8\pm6.8$ 

69±7

68±7.1

66±8

74±5.3

Depression tool

BDI, GDS, HDRS

GDS-15, SCL-90

HDRS GDS

GDS

HDRS CES-D

GDS

GDS

GDS CES-D GDS

GDS

BDI

GDS CES-D

GDS

BDI

HDRS

CES-D

GADS-D

GADS-D GSM HDRS

29±1.2

29.3±1

29.1±1.1

29.3±0.9

MCI 27.1±1.5

25.5±1.6

27.6±1.3

28.9±1

28.3±1.5

26.5±2.6

Study	ES (95% CI)	% Weig
APOE4 vs no APOE4 in SCD	4.00 (0.77, 5.00)	4 50
Kim 2003 <sup>26</sup>	1.98 (0.77, 5.06)	1.59
Niti 2009 <sup>30</sup>	1.10 (0.86, 1.41)	97.01
Stewart 2001 <sup>37</sup>	2.23 (0.90, 5.49)	1.39
Subtotal (I-squared = 0.0%, p = 0.465)	1.13 (0.86, 1.40)	100.0
Progression of SCD in APOE4 vs no APOE4		
Hong 2015 <sup>21</sup>	3.04 (1.13, 8.21)	6.48
Jessen 2010 <sup>23</sup>	1.61 (0.89, 2.94)	77.27
Meuller-Gerards 2019 Men <sup>29</sup>	2.41 (0.75, 6.57)	9.59
Meuller-Gerards 2019 Women <sup>29</sup>	3.70 (1.48, 8.90)	5.90
Slot 2018 <sup>36</sup>	6.20 (1.70, 22.20)	0.77
Subtotal (I-squared = 0.0%, p = 0.663)	1.94 (1.04, 2.84)	100.0
APOE4 + depression vs no APOE4 + depression in SCD		
Niti 2009 <sup>30</sup>	2.89 (1.03, 8.12)	86.00
Stewart 2001 <sup>37</sup>	38.90 (5.48, 276.00)	0.06
Kim 2003 <sup>26</sup>	5.85 (1.77, 19.38)	13.94
Subtotal (I-squared = 0.0%, p = 0.726)	3.32 (0.04, 6.61)	100.0
Depression vs no Depression in SCD		
Kim 2003 <sup>36</sup>	2.44 (1.66, 3.58)	44.11
Niti 2009 <sup>30</sup>	0.95 (0.61, 1.48)	51.98
Stewart 2001 <sup>37</sup>	5.66 (1.97, 16.20)	3.91
Subtotal (I-squared = 78.2%, p = 0.010)	1.79 (0.33, 3.25)	100.0
Progression of SCD in depression vs no Depression		
Jessen 2010 <sup>23</sup>	1.13 (1.00, 1.24)	100.0
	1.13 (1.01, 1.25)	100.0
NOTE: Weights are from random effects analysis		
-276 0	276	

Supplementary Figure 1. A forest graph showing the pooled effect sizes of the odds ratios reported by the individual studies depicting the relationship between APOE<sup>24</sup> and depression with SCD or its progression. SCD: subjective cognitive decline, CI: confidence interval, ES: effect size.

		SCD		С	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
1.6.1 SCD vs normal									
Buckley 2016 <sup>14</sup>	76.9	6.9	66	78.9	7.9	19	0.3%	-2.00 [-5.92, 1.92]	
Choe 2018 <sup>16</sup>	70.6	5.72	72	70.4	5.95	103	1.4%	0.20 [-1.55, 1.95]	
Chu 2017 <sup>17</sup>	66.7	6.2	63	69	6.8	46	0.7%	-2.30 [-4.79, 0.19]	
Dik 2001 <sup>18</sup>	72.8	6.7	298	71.8	6.4	870	4.8%	1.00 [0.13, 1.87]	
Fernandez-Blazquez 2016 <sup>19</sup>	74.2	3.83	370	74.23	3.96	185	6.6%	-0.03 [-0.72, 0.66]	+
Jessen 2007 22	80.13	3.49	1093	79.91	3.39	995	14.8%	0.22 [-0.08, 0.52]	-
Jessen 2010 -worry <sup>23</sup>	79.8	3.6	962	79.4	3.4	990	14.3%	0.40 [0.09, 0.71]	-
Jessen 2010+worry <sup>23</sup>	79.8	3.5	369	79.4	3.4	990	11.6%	0.40 [-0.02, 0.82]	-
Jessen 2014 <sup>24</sup>	79.8	3.5	1061	79.7	3.5	863	14.2%	0.10 [-0.21, 0.41]	+
Jorm 2004 <sup>25</sup>	62.4	1.44	257	62.5	1.52	2289	17.6%	-0.10 [-0.29, 0.09]	•
Miebach 2019 <sup>28</sup>	70.4	5.5	105	68.3	4.9	76	1.8%	2.10 [0.58, 3.62]	
Roehr 2016 32	80.7	3.44	233	80.4	3.32	738	9.7%	0.30 [-0.20, 0.80]	-
Scheef 2019 <sup>34</sup>	67	6.1	24	66	7.2	49	0.5%	1.00 [-2.17, 4.17]	<u> </u>
Shorabi 2009 <sup>35</sup>	67.8	6.8	83	66.7	6.3	55	0.9%	1.10 [-1.12, 3.32]	
Striepens 2011 <sup>35</sup>	68	7.1	41	67.1	7.6	72	0.6%	0.90 [-1.89, 3.69]	
Subtotal (95% CI)			5097			8340	100.0%	0.25 [0.03, 0.46]	•
Heterogeneity: Tau <sup>2</sup> = 0.06; 0 Test for overall effect: Z = 2.2			df = 14	(P = 0.0	2); l² =	50%			
1.6.2 SCD-plus vs normal									
Buckley 2016 <sup>14</sup>	78.3	7.2	13	78.9	7.9	19	13.6%	-0.60 [-5.89, 4.69]	
Fernandez-Blazquez 2016 <sup>19</sup>	73.3	3.36	53	74.23	3.96	185	28.9%	-0.93 [-2.00, 0.14]	
Sanchez-Benavides 2018 33	59.1	7.12	253	55.4	6.62	2098	29.3%	3.70 [2.78, 4.62]	
Wang 2004 <sup>40</sup> Subtotal (95% CI)	76.1	6	87 <b>406</b>	74.9	5.9	1260	28.2% 100.0%	1.20 [-0.10, 2.50] 1.07 [-1.55, 3.69]	
Heterogeneity: Tau <sup>2</sup> = 5.89; (	Chi2 – 1	2 15 6		2 ~ 0 00	001)			1.07 [-1.00, 0.00]	
Test for overall effect: $Z = 0.8$			u – 0 (i	< 0.00	001), 1	- 937	0		
1.6.3 SCD converters vs no	n-conv	erters	;						
Bessi 2019 <sup>13</sup>	63.73	7.28	30	60.95	9.53	18	17.5%	2.78 [-2.34, 7.90]	
Caselli 2014 <sup>15</sup>	63.8	7	20	58.8	7.3	427	35.6%	5.00 [1.86, 8.14]	
Fernandez-Blazquez 2016 <sup>19</sup>	74.5	3.66	10	73.05	3.27	43	46.9%	1.45 [-1.02, 3.92]	+
Subtotal (95% CI)			60			488	100.0%	2.95 [0.58, 5.31]	
Heterogeneity: Tau <sup>2</sup> = 1.52; ( Test for overall effect: Z = 2.4			= 2 (P	= 0.22);	² = 3	4%			
1.6.4 SCD vs MCI									
Bessi 2019 <sup>13</sup>	62	8.7	48	69.2	6.19	26	12.0%	-7.20 [-10.62, -3.78]	
Choe 2018 <sup>16</sup>	70.6	5.72	72	72.5	6.6	52	15.9%	-1.90 [-4.13, 0.33]	
Grambaite 2013 <sup>20</sup>	58.8	7.2	23	63.1	6.8	47	11.7%	-4.30 [-7.83, -0.77]	
Jessen 2014 <sup>24</sup>	79.8	3.5	1061	79.7	3.85	609	20.8%	0.10 [-0.27, 0.47]	+
Merrill 2016 <sup>27</sup>	63.1	11.6	24	62	9.8	20	5.9%	1.10 [-5.22, 7.42]	
Risacher 2015 <sup>31</sup>	71.8	5.54	104	70.9	7.4	305	18.8%	0.90 [-0.45, 2.25]	+
Visser 2009 <sup>39</sup>	66	7.9	60	70	7.7	108	15.1%	-4.00 [-6.47, -1.53]	<b>_</b>
V133C1 2003		-	1392	-		1167	100.0%	-2.01 [-3.82, -0.21]	$\bullet$
Subtotal (95% CI)		7 / 1 /	df = 6 (F	o < 0.00	001);	<sup>2</sup> = 84%	6		-
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 4.05; (			,						
Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 4.05; (			,						-10 -5 0 5 10

Supplementary Figure 2. A forest graph showing the mean differences in age between SCD and normal/MCI individuals or between converters and non-converters from SCD to MCI individuals. SCD: subjective cognitive decline, MCI: mild cognitive impairment, CI: confidence interval.

		SCD		С	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.4.1 SCD vs normal									
Choe 2018 <sup>16</sup>	10.2	4.7	72	11.6	4.6	103	6.5%	-1.40 [-2.80, 0.00]	
Chu 2017 <sup>17</sup>	10	5.1	63	12.2	4.4	46	4.5%	-2.20 [-3.99, -0.41]	
Dik 2001 <sup>18</sup>	9.6	3.6	298	9.1	3.3	870	18.1%	0.50 [0.04, 0.96]	+
Fernandez-Blazquez 2016 <sup>19</sup>	11.2	6.73	370	11	6.72	185	8.2%	0.20 [-0.99, 1.39]	
Jorm 2004 <sup>25</sup>	13.4	3.5	257	13.8	2.7	2289	18.4%	-0.40 [-0.84, 0.04]	-
Miebach 2019 <sup>28</sup>	15	3.1	105	14.6	2.8	76	11.7%	0.40 [-0.46, 1.26]	+-
Sanchez-Benavides 2018 <sup>33</sup>	13.4	3.5	319	13.4	3.5	2098	18.9%	0.00 [-0.41, 0.41]	+
Scheef 2019 <sup>34</sup>	15	3.6	24	15	2.8	49	5.2%	0.00 [-1.64, 1.64]	
Striepens 2011 <sup>38</sup>	14	3	41	14.8	3	72	8.5%	-0.80 [-1.95, 0.35]	
Subtotal (95% CI)			1549			5788	100.0%	-0.18 [-0.60, 0.24]	<b>+</b>
1.4.2 SCD plus vs normal Fernandez-Blazquez 2016 <sup>19</sup> Sanchez-Benavides 2018 <sup>33</sup> Subtotal (95% CI)	10.1 12.8	5.94 3.4	53 253 <b>306</b>	11 13.4	6.72 3.5	185 2098 <b>2283</b>	5.4% 94.6% <b>100.0%</b>	-0.90 [-2.77, 0.97] -0.60 [-1.04, -0.16] - <b>0.62 [-1.05, -0.18]</b>	
Heterogeneity: Tau <sup>2</sup> = 0.00; ( Test for overall effect: Z = 2.7			· ·	= 0.76);	<sup>2</sup> = 0 <sup>6</sup>	%			
1.4.3 SCD vs MCI									
Bessi 2019 <sup>13</sup>	10.76	4.5	48	8.34	3.8	26	10.1%	2.42 [0.48, 4.36]	
Choe 2018 <sup>16</sup>	11		175	10.8	4.1	52	18.5%	0.20 [-1.11, 1.51]	
Grambaite 2013 <sup>20</sup> Merrill 2016 <sup>27</sup>	13.4		23	12.1	2.9	47	16.6%	1.30 [-0.11, 2.71]	
	16.8	3	24	16.6	3.2	20	10.9%	0.20 [-1.65, 2.05]	
		2.5	104	16	2.7	305 <b>450</b>	43.9% 100.0%	0.30 [-0.27, 0.87] 0.65 [-0.02, 1.32]	•
Risacher 2015 <sup>31</sup> Subtotal (95% CI)	16.3		374						1
Risacher 2015 <sup>31</sup>	Chi² = 5.	,		= 0.22);	² = 3				

Supplementary Figure 3. A forest graph showing the mean differences between SCD and normal/MCI individuals in education level. SCD: subjective cognitive decline, MCI: mild cognitive impairment, CI: confidence interval.