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Comparative Effectiveness of Different Statins on the Risk of Incident Dementia and the Impact of Gender and Exposure time on Risk Reduction: A Meta-analysis of Observational Studies.

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Highlights

- **Dementia is associated with excess morbidity and mortality.**
- **The most common causes of dementia are Alzheimer Disease (AD) and cerebrovascular changes that produce vascular dementia.**
- **The 3-HYDROXY-3-METHYL glutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, are increasingly popular drugs for cardiovascular indications.**
- **Multiple studies have found that hyperlipidemia is associated with vascular dmentia and AD.**
- **Evidence from epidemiological investigations have reported a possible protective association**

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ABSTRACT

The impact of statins in the prevention of dementia has been a point of debate recently however, the evidence remains controversial. For this reason, we conducted this meta-analysis of relevant observational studies to assess the relationship between statin therapy and the reduction of dementia risk

Methods:

We systematically searched for relevant studies published from 2000 to 2021 using different scientific search engines. Seventeen original articles, which represent observational studies about the prophylactic effect of statin medications in reducing the risk of all-cause dementia were chosen. We then extracted data from the selected studies and performed meta-analysis of these studies using random effects model. Subgroup and sensitivity analyses were also conducted.

Results:

About 4,241,469 Participants met the eligibility criteria. Statin users had lowered all caused dementia risk than those non-statin users (RR from 17 studies RR= 0.745, 95% CI = 0.653- 0.849, P =0.000). In subgroup analyses, statins reduced the risk of dementia in both males and females (RR= 0.902, 95%, CI=0.872-0.932, P= 0.00), (RR= 0.889, 95%, CI= 0.794- 0.995, P= 0.04). Moreover, testing different statin formulae has shown that atorvastatin and rosuvastatin have significant effects (aRR=0.686, 95%CI=0.488-0.965, p-value=0.030) and (RR=0.695, 95%CI= 0.553-0.873, p-value=0.002). While simvastatin showed a non-significant effect (an RR= 0.900; 95%, CI=0.792-1.024; P=0.109). concerning exposure time, using statin for more than one year tends to show a significant influence on the risk of dementia (RR= 0.576; 95%, CI= 0.367- 0.903; P= 0.016).

Conclusion:

This analytical study revealed the great value of using statins in both males and females who are at higher risk of developing dementia. It is highly recommended for conducting a clinical study on high-risk Libyan patients.

1. Introduction

Dementia has become one of the most important health challenges in different societies. The number of cases is expected to increase to reach 65.7 million people in 2030 and 115.4 million in 2050. Increasing life expectancy especially in the developed world has necessitated the search for the best treatment strategies to lower the burden of this condition. Alzheimer's disease (AD) accounts for more than half the cases of dementia (Hendrie, 1998). Vascular dementia (VAD) represents the second most common cause of dementia after AD (O'Brien and Thomas 2015). It has been proven that increased serum total cholesterol level in midlife is associated with a higher risk of developing dementia later in life (Solomon *et al*., 2009). Increased cholesterol level in the brain was shown to be associated with an elevated level of beta-amyloid protein (β-AP) production, which is a known pathological biomarker for AD (Shie *et al*., 2002). Although, multiple studies have emphasized that the role of cholesterol as an independent factor in the pathogenesis of dementia is still controversial (McFarlane and Kędziora-Kornatowska 2020; Reitz 2012).

There is evidence that excess cholesterol could be oxidized at multiple positions on the sterol ring to generate oxysterols. These

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oxysterols can bind with specific nuclear receptors and induce the transcription of apolipoprotein E and ABCA1 transporter (Cordy *et al*., 2003). Three known isoforms of apolipoprotein E are known to exist in humans, apoE2, apoE3, and apoE4 (Mahley, 2016). The expression of the apolipoprotein E4 isoform is related to the early onset cognitive impairment by retarding the clearance of the amyloid-β protein (Verghese *et al*., 2013). Furthermore, the formation of amyloid- β protein is highly dependent on the cellular cholesterol level. Higher neuronal cholesterol level is associated with increased β- secretase activity, which acts on amyloid precursor protein (APP) and increases the production of amyloid- β protein (Cordy *et al*., 2003, Refolo *et al*., 2001).

Statins as cholesterol-lowering agents have received special attention concerning their ability to reduce the incidence of dementia. The most proposed protective mechanism of statin therapy is by reducing the microvascular and large blood vessel damage caused by hyperlipidemia, and thus reduces the risk of stroke and vascular dementia. Moreover, statins have been shown to reduce the formation of amyloid- β protein by reducing plasma cholesterol (Hosaka *et al*., 2013). Another proposed mechanism for statins' protective effect against dementia is their ability to reduce the inflammatory response induced by amyloid- β protein. It has been shown that statins can suppress the production of microglial interleukin-1 β, TNF, and nitric oxide (Cordle and Landreth., 2005). In addition to that, statins were shown to reduce the formation of isoprenoids which are one of the downstream products of cholesterol synthesis. Certain types of these isoprenoids such as farnesylpyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP) are thought to be involved in dementia disease pathogenesis, they are suggested to play a role in the prenylation of some GTPases which are involved in the pathogenesis of dementia (Hoof *et al*., 2010).

From these multiple pieces of evidence, statins seem to have multiple protective mechanisms against dementia. So based on these variable molecular mechanisms there is a requirement to further confirm their role in preventing multiple causes of dementia. Many clinical studies have demonstrated that statins could reduce the incidence of dementia and they might provide protective effects when administered especially in middle age (Lee *et al*., 2020, Wolozin *et al*., 2000). On the other hand, multiple studies showed that statins might have no role in reducing the incidence of dementia (Rea et al., 2005, Ancelin *et al*., 2012). In this regard, we conducted a meta-analysis to test whether statins are clinically effective in reducing the incidence of dementia in humans.

2. Method and materials

A literature search has been conducted to recognize all published observational studies from January 2000 up to 2021. Google, Google Scholar, and PubMed databases were used to address potential studies.The following search terms were used; statins, dementia, cognitive impairment, vascular dementia, lipid-lowering agents, simvastatin, rosuvastatin, atorvastatin, and pravastatin.

i. Eligibility_criteria

We only included studies with the following criteria:

Observational studies

Full-text articles

Articles published in the English language

Involved participants are free of dementia at the start of the study

The minimum follow-up period is one year

Participants aged 45 years or older

The outcome measures of the included studies are all-cause dementia, The methodological quality of included studies has been assessed based on the modified version of the Newcastle-Ottawa scale **(**Wells et al., 2009). This scale uses the star system to assess the study in three different areas that are:

1- Participant selection

2- Finding out the outcomes of interest

3- Comparison of the study groups

Studies were categorized as high quality, medium quality, or low quality based on the received score of 9, 7-8, and ≤6 stars respectively.

ii. Statistical analysis

In this analysis, the outcome of interest was the risk of all-cause dementia among participants using statins compared with the risk of dementia among participants not using statins. A summary of adjusted hazard ratios with a 95% CI was pooled to reduce the effect of potential confounders. The extracted data for each study also included the mean age of participants; mean follow-up period, percent of males and females in each study group, number of statin users and non-users in each study, data related to statin subtypes, and study design. Meta-analysis has been performed using the Comprehensive Meta-analysis software a trial version 3.3.

iii. Assessment of heterogeneity

The heterogeneity of involved studies has been assessed. The overall effect estimate was identified using a random effect model to reduce the possibility of heterogeneity among included studies. Publication bias was tested using Egger's test and funnel plot (Egger M *et al*., 1997). Subgroup analysis has also been performed to reduce heterogeneity based on gender, statin subtypes, and outcome measures. All statistical analyses were performed using a significance level of p-value ≤0.05. Subgroup analyses were performed based on statin subtypes, and the gender of participants. At least three datasets should be included in each subgroup analysis.

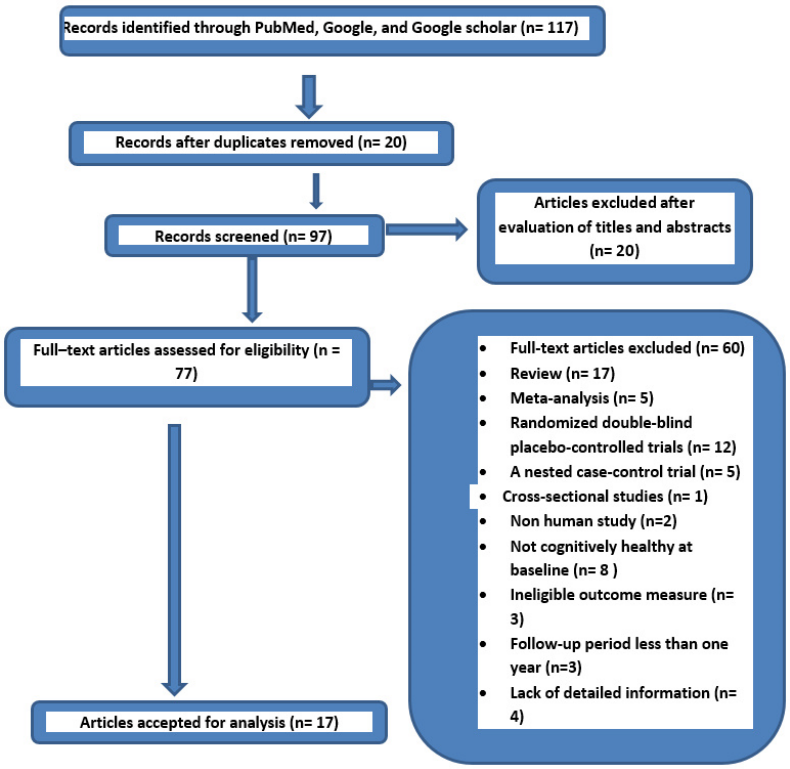
3. Results

(a) Literature search results

The electronic search retrieved 117 references. We obtained 76 papers in full-text form, after reading the topics and abstracts, meta-analysis, reviews, systemic reviews, randomized controls, and other forms of research, such as animal studies, and studies included non–cognitively healthy subjects were excluded. Full texts were further read, and 17 studies have been considered potentially eligible after quality assessment. The flowchart of literature searching is presented in (Fig. 1). Characteristics of included studies are summarized in (Table 1).

(b) Statins and incidents of dementia

Across 17 studies participants who received statins were significantly less likely to develop all-caused dementia compared to those who were not treated with statins (a RR from 17 studies a RR= 0.745 , 95% CI = 0.653- 0.849, P =0.000) (Fig, 2). There was no evidence of publication bias according to Eggers regression (t value = 1.618, df= 15, P=0.126). We used Duval and Tweedie's trim and fill method toward the right of the mean to adjust values of the effect size estimates to publication bias and the results tend to be insignificance aRR= 0.744, 95%, CI= 0.653-0.849. Funnel plot, However, significant heterogeneity was found (Q value= 1814, df= 16, I^2= 99.118, P = 0.00).



Study name	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Jui-Ming,2014	0.600	0.415	0.868	-2.707	0.007	4.70
Chih feng, 2019	0.950	0.940	0.960	-9.550	0.000	7.48
Kerstin, 2012	0.790	0.650	0.960	-2.370	0.018	6.42
Mi-young kim,2020	0.950	0.930	0.970	-4.825	0.000	7.47
C-K. Wn,2015	0.450	0.367	0.552	-7.661	0.000	6.33
Georgina,2020	0.560	0.540	0.580	-31.806	0.000	7.44
Benjamin, 2007	0.460	0.440	0.480	-34.983	0.000	7.42
C. Cramer, 2008	0.560	0.365	0.859	-2.656	0.008	4.17
Liam smeeth, 2009	0.800	0.704	0.909	-3.438	0.001	6.99
Zandi,2005	1.190	0.566	2.501	0.459	0.646	2.21
Tze-fan,2015	0.781	0.740	0.825	-8.900	0.000	7.39
G.li ,2004	1.190	0.815	1.738	0.900	0.368	4.61
Thomas D,2005	1.080	0.769	1.517	0.444	0.657	4.98
Marie-Laure,2012	1.012	0.691	1.483	0.061	0.951	4.58
Julie-M, 2017	0.862	0.832	0.893	-8.227	0.000	7.44
Ge Li,2010	0.440	0.249	0.777	-2.828	0.005	3.11
Chian-ying chou,2014	0.780	0.718	0.847	-5.868	0.000	7.26
	0.745	0.653	0.849	-4.394	0.000	

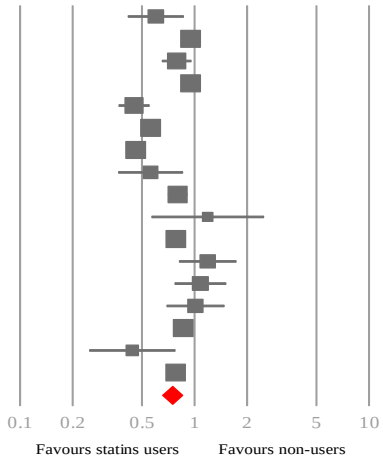


Fig. 2. The Forest plot of random-effects meta-analyses of the use of statins and the incidence of dementia

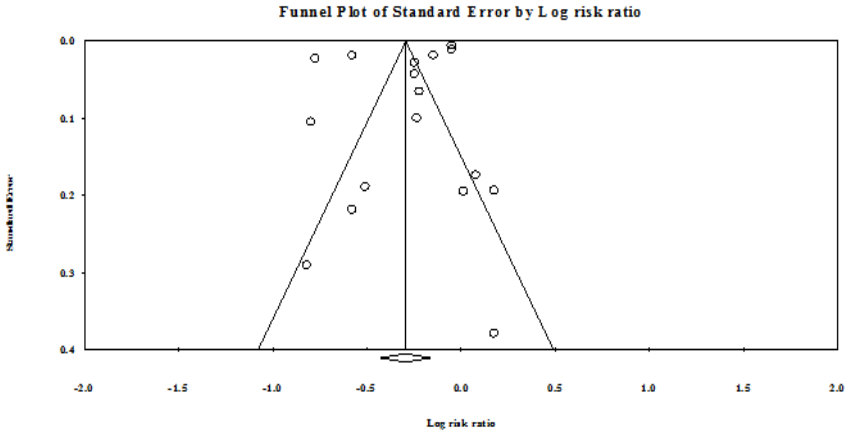


Fig. 3. Represents funnel plot of publication bias for included studies about the use of statins and incident all-cause dementia.

Table 1

Characteristics of included studies.TP=Total participants,RR=Risk ratio,and NOS= Newcastle-Ottawa scale

Author			Study design	Mean age Male %	TP	Mean follow-up years	Study period	Outcome	RR	NOS	
Benjamin	2007	USA	Prospective	74.6 Male: 94.4%	750000	3	2002-2005	Dementia	0.60(0.415-0.868)	7	(Wolozin et al., 2007)
Ge Li	2010	USA	Prospective	≥65 NA	3392	6.1	NA	AD	0.44(0.249-0.777)	7	(Li et al., 2010)
Mi-younykim	2020	Korea	Retrospective	≥65 NA	2,408,821	5	2010-2015	Dementia	0.950(0.93-0.970)	7	(Kim et al., 2020)
Jui-ming	2014	Taiwan	Retrospective	≥50 NA	2400	8	2000-2008	Dementia AD	0.60(0.415-0.868) 0.480(0.302-0.764)	7	(Chen et al., 2014)
C-k.wu	2015	Taiwan	Retrospective	72.9±5.3 NA	57669	12	1997-2010	Dementia	0.450(0.367-0.552)	8	(Wu 2015)
C Cramer	2008	USA	Retrospective	70.4±6.0 Male 42%	1674	6	1998-2004	Dementia	0.560(0.365-0.859)	8	(Cramer 2008)
Zandi	2005	USA	Prospective	75.5 ±7.1 NA	5092	5	1995-2000	Dementia AD	1.190(0.566-2.501) 1.190(0.405-3.490)	8	(Zandi et al., 2005)
G.Li	2004		Prospective	70.5±6.1 Male 40.2%	2392	3.9		Dementia AD	1.190(0.815-1.738) 0.820(0.460-1.461)	7	(Li et al., 2004)
Tze-Fan	2015	Taiwan	Case-control-retrospective	73.2±7.4 Male: 49.7%	51253	3.3	1996-2011	Dementia	0.781(0.740-0.825	7	(Chao et al.,2015
Kerstin	2012	USA	Prospective	78.6±3.3 Male 54%	3069	6	NA	Dementia AD	0.790(0.650-0.960) 0.570(0.386-0.841)	8	(Bettermann et al.,2012)
Marie-Laure	2012	France	Prospective	≥65 73.6(5.3) NA	1119	7	1999-2001	Dementia CI	1.012(0.691-1.483)	8	(Ancelin et al., 2012)
Georgina	2020	USA	Retrospective	45 Male 52.5%	288515	3	NA	Dementia AD	0.560(0.540-0.580) 0.464(0.440-0.490)	8	(Torrandell-Haro et al., 2020)
Cheh-Feng	2019	Taiwan	Retrospective	Male 54.6%	100610	12	2002-2013	Dementia	0.950(0.940-0.960)	8	(Chang et al., 2019)
Julie-M	2017	USA	Retrospective	≥65 NA	399979	7.2	2006-2013	AD	0.862(0.832-0.893)	8	(Zissimopoulos et al., 2017)
Liam-Smeeth	2009	UK	Prospective	70±4.8 Male:49%	129288	11	1995-2006	Dementia	0.800(0.704-0.909)	8	(Smeeth et al., 2009)
Thomas D	2005	USA	Prospective	72.3±5.6 33.7%	2798	1	1991-1994	Dementia AD	1.080(0.769-1.517) 1.210(0.763-1.918)	8	(Thomas et al., 2005)
Chian-Ying Chou	2014	Taiwan	Retrospective	NA	33,398	10	2000-2010	Dementia	0.78(0.72–0.85)	7	(Chen et al., 2014)

(c) Subgroup Analyses

A. Use of statins and incidents of dementia in male and female patients

In four studies of the effect of gender on the outcome of interest among statin users in comparison to non-users, a significant risk reduction was observed in males (a RR= 0.902, 95%, CI=0.872-0.932, P= 0.00) and females participants (a RR= 0.889, 95%, CI= 0.794- 0.995, P= 0.04) (Fig. 4 and 5) respectively.

B. The use of different statins and incidents of dementia

Subgroup analysis showed that the use of different statins has a variable effect on the incidence of dementia. Atorvastatin and rosuvastatin have shown a significant risk reduction (aRR=0.686, 95%CI=0.488-0.965, p-value=0.030), (aRR=0.695, 95%CI= 0.553-0.873, p-value=0.002) (Fig. 6 and 7). On the other hand, simvastatin has a nonsignificant influence on dementia risk (a RR= 0.900; 95%, CI=0.792-1.024, P=0.109), and pravastatin has shown a marginal effect (a RR=0.791, 95%, CI= 0.625-1.004, P= 0.054), (Fig. 8 and 9).

C. The use of statins and incidents of dementia according to the exposure time:

Regarding the exposure time to statins, four studies evaluated the association between using statins for more than one year and dementia risk, The overall pooled RR was (a RR=0.576; 95%, CI=0.367-0.903, P=0.016). On the other hand, the overall pooled RR for dementia risk in the patients who were using statins for less than one year was (a RR= 0.932, 95%, CI= 0.760- 1.142, P= 0.498), (Figs 10 and 11).

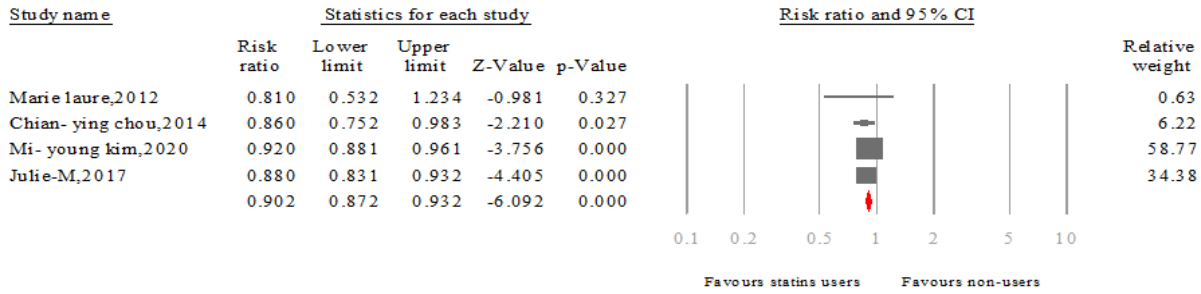


Fig. 4. Represents the effect of statin use on the incidence of dementia among males.

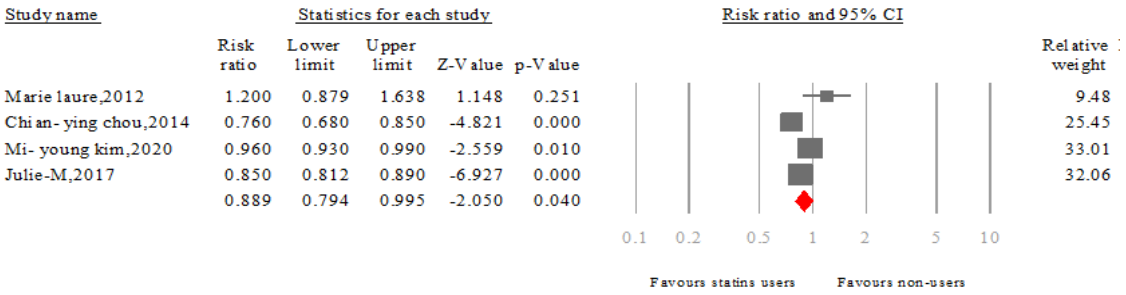


Fig. 5. Represents the effect of statin use on the incidence of dementia among females

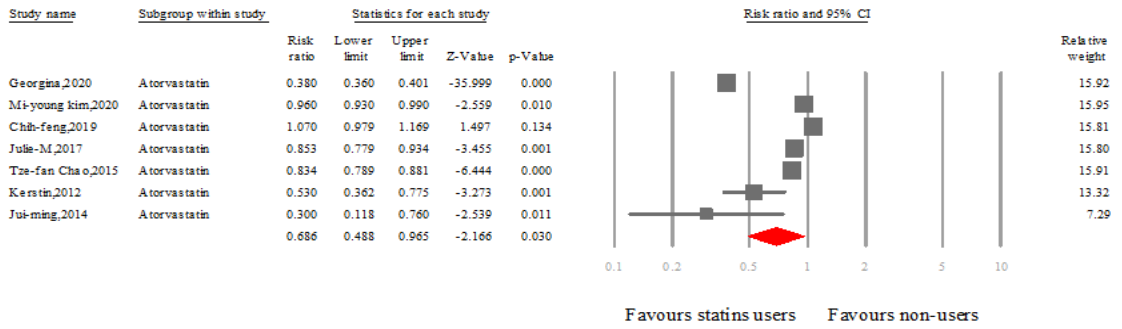


Fig. 6. Represents the use of atorvastatin and incidents of dementia

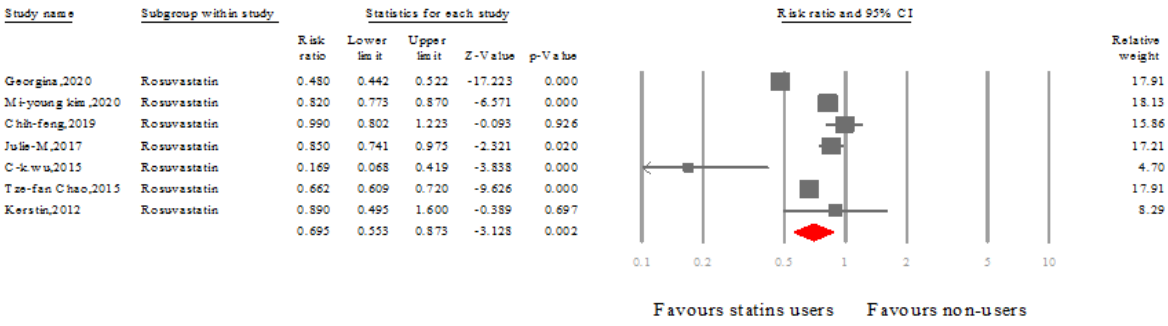


Fig. 7. Represents the use of rosuvastatin and incidents of dementia

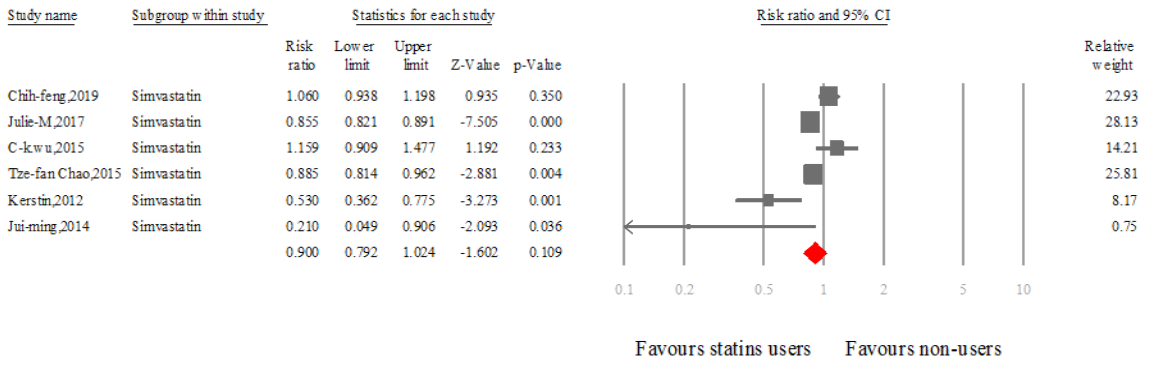


Fig. 8. Represents the use of simvastatin and incidents of dementia

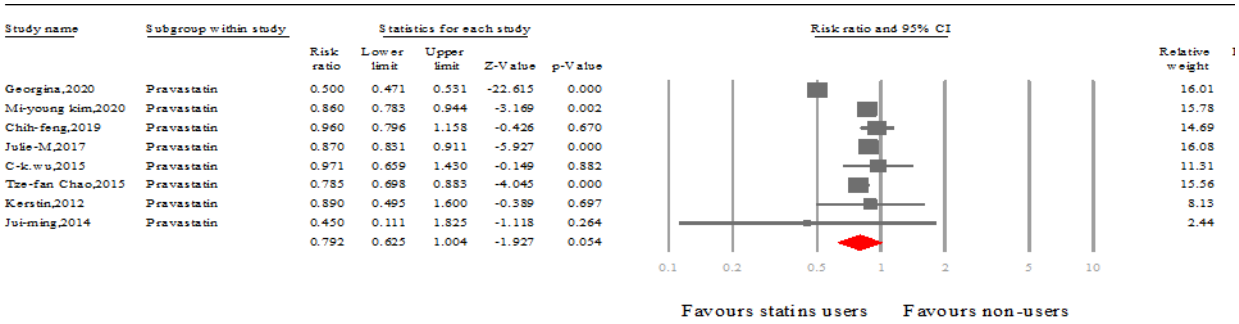


Fig. 9. Represents the use of pravastatin and incidents of dementia

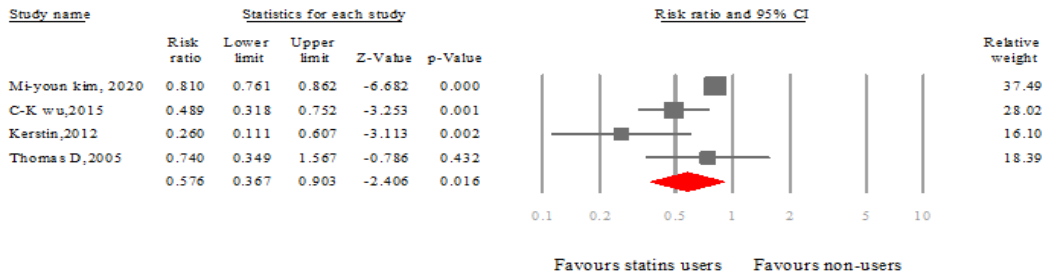


Fig.10. Represents statin therapy for more than one year

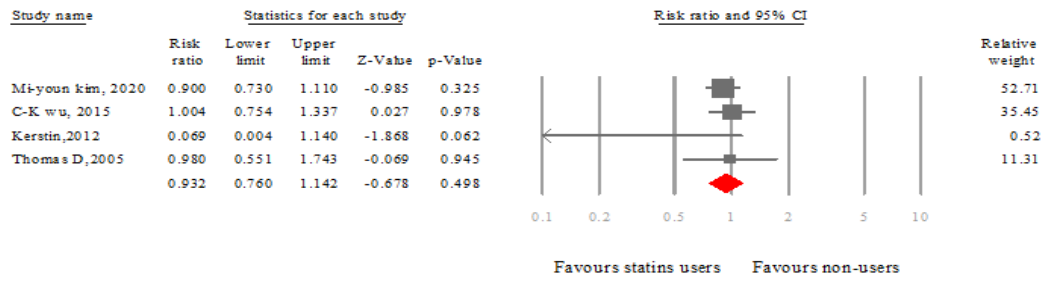


Fig. 11. Represents statin therapy for less than one year

4. Discussion

Our meta-analysis provides evidence of a powerful correlation between the use of statins and dementia risk. It included a total of 17 observational studies with aggregate data of 4,241,469 individuals. We found that statin users without baseline cognitive dysfunction had a significantly reduced risk of developing dementia. Although, a previous meta-analysis by Zhou *et al.* (2007) concluded that statin use did not show a beneficial effect on the risk of dementia, and other observational and randomized-controlled studies have shown no association between the use of statins and dementia risk (Zandi *et al.*, 2005; Li *et al.*, 2010; Chitnis *et al.*, 2015; Hammad *et al.*, 2019; Zingel *et al.*, 2021). In this analysis, the

percentages of risk reduction of dementia under statins exposure were 76.4 %. These findings are parallel with the pooled results of previously published meta-analyses (Poly et al., 2020; Wong et al., 2013; Song et al., 2013), likewise other observational and randomized-controlled studies (Zarmini *et al*.,2004; Hajjar *et al*., 2002; Sparks *et al*., 2005; Jick *et al*., 2000). These studies have provided strong evidence of an association between statin use and reduced incidence of dementia. In subgroup analysis, statins appear to have a prophylactic role against dementia regardless of gender. So both male and female statin users have a significant reduction in dementia risk (Figs.4 and5). This finding is compatible with the results of Poly and his colleagues (2020). Some studies found that the effect of different statins on the incidence of dementia seems to be affected by gender, race, and ethnicity (Zissimopoulos, 2017). The pharmacokinetics of statins are slightly affected by gender, for instance, estrogens are metabolized in the liver by cytochrome P450 enzymes, especially with CYP3A4 isoenzymes which are also responsible for the metabolism of some statins namely; simvastatin, lovastatin, and atorvastatin. Both statins and estrogens are conjugated with sulfate and glucuronide. Therefore, statins could compete with estrogens for the same enzymes and transporters, resulting in drug-hormone interactions (Bottorff and Hansten 2000; Faubion *et al*., 2019) as illustrated in Fig, 12.

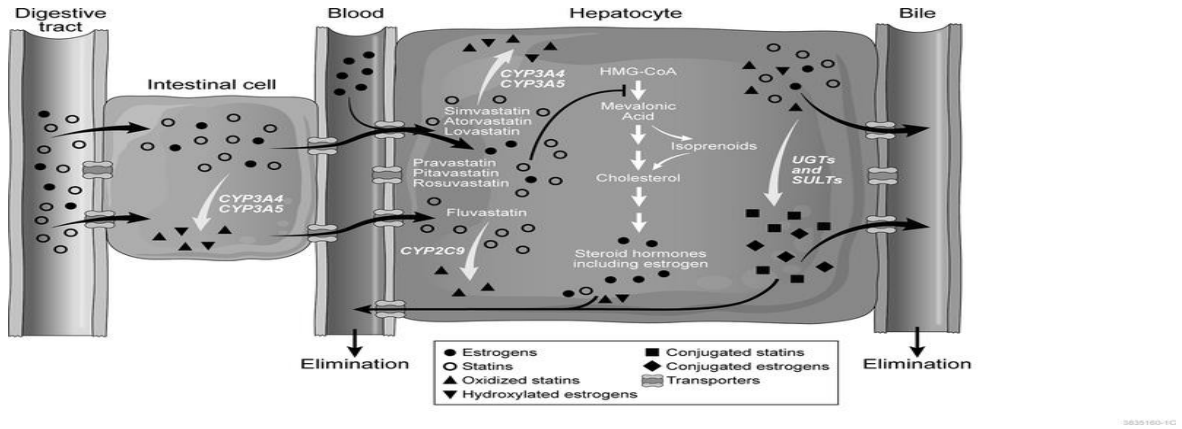


Fig.12. Shows the mechanism of action of statins and potential interactions with estrogen

Furthermore, it has been found that polymorphism in ESR1 gene expression in women has a great effect on total cholesterol levels and the efficacy of statins (Smiderle et al., 2016). This might support our finding that risk reduction tends to be more pronounced in male patients. Important to reference that the types of dementia vary by gender, for example, women have more susceptibility to developing Alzheimer´s disease, while men have more risk of developing vascular dementia (Smiderle et al., 2016). So these factors may have contributed to the heterogeneity of the involved studies, as some of them overlooked the effect of race, gender, and ethnic groups.

A comparison between the various statin formulae; atorvastatin, rosuvastatin, simvastatin, and pravastatin was performed, to evaluate which statin possesses a more protective effect against dementia. It was found that patients who were on rosuvastatin therapy had the lowest risk of developing dementia, followed by patients who used atorvastatin, whereas the pravastatin group exhibited marginal value. These findings are similar to the results of another meta-analysis that has been performed by Poly *et al*. (2020). This outcome might have been attributed to their potency rather than any other pharmacological properties (Pan *et al*., 2018). Furthermore, it seems that exposure time is an imperative factor in reducing the risk of dementia. The group that has been subjected to statins for more than one year, had more benefits than those that received statins for less than one year against the development of dementia. This result is equivalent to the result concluded by Chen *et al*. (2014), who suggested that long-term use of statins is associated with reduced dementia risk. Moreover, Pan *et al*. (2018) have demonstrated that statin exposure duration was inversely related to the risk of dementia.

As known, there is a close link between a full understanding of the pathogenesis of any disease and the way drugs work in preventing its occurrence or how to treat it. Unfortunately, this meta-analysis is not focusing on how statins can prevent the risk of all types of dementia. But we can justify their role based on the previously mentioned hypotheses; statins provide microvascular protection against hypercholesterolemia, and they possess anti-inflammatory action, in addition to the prenylation hypothesis. The most important limitation of our study is the high level of heterogeneity among included studies. This heterogeneity was due to the demographic and ethnic-racial characteristics of the study populations, sample size, study design, follow-up period, and in the magnitude of statin use and dementia risk. Furthermore, some important variables, such as different comorbidities, medications, BMI, and smoking status, which may influence dementia risk, were missing in our subgroup analyses because of the lack of data.

Since the current meta-analysis was designed by including studies that have high methodological quality, low bias, and full adjustment of age, gender, and different kinds of morbidities (stroke, diabetes, hypertension, and ischemic heart disease). It might open the window about the value of using statins as a prophylactic medication in Libyan patients, especially those who have a high risk of developing dementia, and their age above forty.

5. Conclusion

With rising cases of dementia of different types, there is an urgent need to take measures for preventing and treating this neurological disease. This analytical study revealed the great value of using statins in both males and females who are at high risk of developing dementia. Rosuvastatin, atorvastatin, and pravastatin showed the best results in terms of the prevention of dementia, especially with prolonged exposure periods. It is highly recommended for conducting a clinical study on Libyan patients who are more susceptible to dementia.

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