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Review Article

Mediterranean diet and health status: an updated meta-analysis and a proposal for a literature-based adherence score

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Abstract

Objective: To update previous meta-analyses of cohort studies that investigated the association between the Mediterranean diet and health status and to utilize data coming from all of the cohort studies for proposing a literature-based adherence score to the Mediterranean diet.
Design: We conducted a comprehensive literature search through all electronic databases up to June 2013.
Setting: Cohort prospective studies investigating adherence to the Mediterranean diet and health outcomes. Cut-off values of food groups used to compute the adherence score were obtained.
Subjects: The updated search was performed in an overall population of 4 172 412 subjects, with eighteen recent studies that were not present in the previous meta-analyses.
Results: A 2-point increase in adherence score to the Mediterranean diet was reported to determine an 8 % reduction of overall mortality (relative risk = 0·92; 95 % CI 0·91, 0·93), a 10 % reduced risk of CVD (relative risk = 0·90; 95 % CI 0·87, 0·92) and a 4 % reduction of neoplastic disease (relative risk = 0·96; 95 % CI 0·95, 0·97). We utilized data coming from all cohort studies available in the literature for proposing a literature-based adherence score. Such a score ranges from 0 (minimal adherence) to 18 (maximal adherence) points and includes three different categories of consumption for each food group composing the Mediterranean diet.
Conclusions: The Mediterranean diet was found to be a healthy dietary pattern in terms of morbidity and mortality. By using data from the cohort studies we proposed a literature-based adherence score that can represent an easy tool for the estimation of adherence to the Mediterranean diet also at the individual level.

Keywords
Mediterranean diet
Meta-analysis
Update
Score

The Mediterranean diet has consistently been demonstrated to have a beneficial influence on health and longevity(1–3). Two meta-analyses conducted by our group in 2008 and in 2010 clearly showed a significant protection for greater adherence to the Mediterranean diet on mortality and morbidity from several causes(2,3). However, since the publication of the earliest meta-analysis further studies have been published, making an update of the literature necessary. In addition, despite the vast amount of literature available, one main issue remains yet to be solved: how can we define one's adherence to the Mediterranean diet?

Over the past years, several attempts for estimating adherence to the Mediterranean diet have been done, mainly through the creation of diet quality indices(4,5). The usefulness of these measures, the most common of which is certainly the Mediterranean dietary score created by Trichopoulou *et al.*(6), has been assessed in several longitudinal studies in association with different health outcomes(3). Although significant associations between such scores and mortality have been found in different populations, the clinical application of such scores is not easy to obtain since studies evaluating different cohorts with different dietary behaviours present

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different cut-off values for consumption of food groups and the quantification of each food component is not always available. To the best of our knowledge, no studies have been conducted that attempt to review and analyse altogether the studies investigating the Mediterranean diet score in relation to health outcomes, with the aim of proposing an adherence score that could be used not only as an epidemiological tool but also at an individual level.

Hence, the aims of the present study were to: (i) perform an updated systematic review and meta-analysis on studies investigating adherence score to the Mediterranean diet and health status, due to the high number of studies that have been published since the release of the earliest meta-analysis; and (ii) obtain from all of the available cohort studies the cut-off value for consumption of each food group, in order to propose a questionnaire for estimation of adherence to the Mediterranean diet based on descriptive data of the literature.

Methods

Updated systematic review

The databases MEDLINE (source: PubMed, 1966 to June 2013), Embase (1980 to June 2013), Web of Science, The Cochrane Library (source: The Cochrane Database of Systematic Review, 2013, issue 6), Clinicaltrials.org and Google Scholar were systematically reviewed and updated using a literature search strategy. Relevant keywords relating to the Mediterranean diet in combination as MeSH (Medical Subject Headings) terms and text words ('Mediterranean diet', or 'diet' or 'dietary pattern' 'Mediterranean', or 'adherence' or 'score' and their variants) were used in combination with words relating to health status ('health', or 'mortality' or 'morbidity', or 'cardiovascular diseases', or 'neoplastic diseases', or 'cancer', or 'neoplasm', or 'degenerative diseases', or 'Alzheimer's disease', or 'Parkinson's disease', or 'cerebrovascular disease', or 'stroke', or 'outcome', or 'prospective', or 'follow-up', or 'cohort' and their variants). The search strategy had no language restrictions and was supplemented by manually reviewing the reference list of all retrieved articles.

Two investigators (F.S., A.C.) assessed potentially relevant articles for eligibility. The decision to include or exclude studies was hierarchical and initially made on the basis of the study title, then of the study abstract and finally of the complete study manuscript. We included studies that assessed in a prospective way the possible association between a Mediterranean dietary score and health outcomes, as already reported in the previous meta-analyses[2,3]. Two researchers independently completed searches, study identification, data abstraction and tabulation, and discordances were resolved by discussion. Outcomes of interests were overall mortality, mortality from and/or incidence of cardio- and cerebrovascular diseases, mortality from and/or incidence of cancer, as well as incidence of neurodegenerative diseases.

Literature-based adherence score to the Mediterranean diet

All cohort studies that investigated the association between adherence to the Mediterranean diet and health outcomes were collected. We summarize all the amounts chosen as cut-offs for determining adherence to the Mediterranean diet, together with the author, year of publication, cohort analysed, country of the cohort, number of subjects investigated and the age of subjects, according to sex, in Tables 1 and 2.

Due to the wide distribution of median consumption of some food groups in the included studies (e.g. see legumes, whose consumption ranges from 2 to 75 g/d), data were logarithmically transformed and back-transformed for data presentation. Median (or mean) values for consumption of food groups composing the Mediterranean diet adherence score were weighted for the number of subjects enrolled in each study. This was because of the large variability in terms of subjects analysed and because the sample size of the study was found to be the most significant contributor to the robustness of results in our previous meta-analysis[3]. After that, we calculated the mean value of all of the weighted medians and the 2 SD for each food group. In order to provide meaningful estimates for clinical practice we finally rounded the resulting numbers close to the 2 SD values for each measure, by obtaining three categories of consumption for each food group.

Statistical analysis

We used RevMan version 5·0·18 for Macintosh and IBM SPSS Statistics version 18·0 for Macintosh to pool and analyse results from the individual studies. The methods and results of all the recent identified cohort prospective studies were added to the previous table and data were formally combined[3]. Pooled results are reported as relative risk (RR) and are presented with 95 % confidence interval with two-sided P values using a random-effects model (DerSimonian and Laird method) and the general variance-based method. A P value less than 0·05 was considered statistically significant. We used, when available, the results of the original studies from multivariate models with the most complete adjustment for potential confounders; the confounding variables included in this analysis are shown in Table 3.

Statistical heterogeneity was evaluated using the I^2 statistic, which assesses the appropriateness of pooling the individual study results. The I^2 value provides an estimate of the amount of variance across studies due to the heterogeneity rather than chance. Where I^2 was greater than 50 %, heterogeneity was considered substantial. Small study bias and/or publication bias was appraised by visual inspection of a funnel plot of effect size *v.* standard error and, analytically, by Egger's test.

Table 1 Values of components of adherence score to the Mediterranean diet among men (g/d)

Author	Year	Cohort	Country	*n*	Age (years)	Disease	Legumes	Cereals	Fruit	Vegetables	Fish	Meat	Dairy
Trichopoulou *et al.*[25]	1995	Greek villages	G	91	>70	OM	60	291	249	303	n.d.	109	201
Kouris-Blazos *et al.*[26]	1999	Anglo-Celts; Greek-Australian	A	70	>70	OM	50*	232·5*	291*	349·5*	n.d.	246*	296*
Lasheras *et al.*[27]	2000	Spanish volunteers	S	49	65–95	OM	13·5	248·5	211·5	313·5	n.d.	139·5	416
Knoops *et al.*[28]	2004	SENECA	B, D, F, G, H, I, N, P, S, Sw	781	73*	OM	7	248	228	306	26	130	313
Knoops *et al.*[28]	2004	FINE	F, I, N	726	77*	OM	10	231	209	248	20	113	392
Trichopoulou *et al.*[29]	2005	EPIC-Elderly	D, F, Ge, G, I, N, S, Swe, UK	24 545	>60	OM	3·3	212	176·7	156·8	32·2	111·6	285·7
Scarmeas *et al.*[30]	2006	WHICAP	USA	720	77·2*	AI	57	184	472	197	20	85	182
Benetou *et al.*[31]	2008	Greek-EPIC	G	10 582	20–86	C	10·2*	187·2*	383·2*	578·6*	26·3*	126·2*	221·2*
Trichopoulou *et al.*[32]	2009	Greek-EPIC	G	9504	20–86	OM	9·1	178·3	362·5	548·6	23·7	121·1	196·1
Buckland *et al.*[33]	2009	Spanish-EPIC	S	15 442	29–69	CHD	23·7	91·2	109·9	90·7	23·3	58·7	91·4
Buckland *et al.*[34]	2010	EPIC	D, F, G, Ge, I, N, No, S, Swe, UK	144 577	35–70	C	2·2	84·8	70·1	63·8	7·3	50·5	116·9
Sjorgen *et al.*[7]	2010	ULSAM	Swe	924	71*	OM, CVD	75	405	124	75	27	98	417
Martinez-Gonzalez *et al.*[35]	2011	SUN	S	5444	38*	CVD	21	90	235	401	87	177	182
Tognon *et al.*[8]	2011	GGPSG	Swe	497	>70	OM	13·3	213	155·5	239	53·7	109·1	446
Agnoli *et al.*[9]	2011	EPICOR Study	I	12 563	35–64	St	16	272	319	173	28	110	54
Buckland *et al.*[10]	2011	EPIC-Spain	S	15 324	49·3*	OM, CVD, C	56	214	380	282·2	64·1	96·9	198·5
van der Brandt[11]	2011	NLCS	N	1690	55–69	OM	6·5	n.d.	153·9	202·6	11·5	124	n.d.
Gardener *et al.*[12]	2011	NOMAS	USA	931	68·6*	CVD, St	16	68	149	77	12	40	104
Couto *et al.*[13]	2011	EPIC	D, F, Ge, G, I, N, No, S, Swe, UK	142 605	25–70	C	14·6*	219	247·3	211·2	37·2	98·7	326·7
Dilis *et al.*[17]	2012	Greek-EPIC	G	9740	20–86	CHD	9	176	356	547	24	121	198
Hoevenaar-Blom *et al.*[18]	2012	EPIC-NL	N	8764	20–70	CVD, St	15	250	117	103	8	141	353
Misirli *et al.*[19]	2012	Greek-EPIC	G	9617	20–86	CBVD	8·9*	163·4*	382·2*	553·5*	23·7*	108·9*	220·2*
Martinez-Gonzalez *et al.*[15]	2012	SUN	S	6271	38*	OM	21	85	245	412	86	174	164
Tognon *et al.*[16]	2012	VIP	Swe	37 546	30–60	OM	n.d.	33·7	49·2	94·7	9·6	53	206
Bamia *et al.*[20]	2013	EPIC	D, F, Ge, G, I, N, No, S, Swe, UK	143 752	25–70	C	5·7	200·1	199·6	174·1	28	91·7	276

SENECA, Survey in Europe on Nutrition and the Elderly: a Concerted Action; FINE, Finland, Italy, the Netherlands, Elderly study; EPIC, European Prospective Investigation into Cancer and Nutrition; WHICAP, Washington Heights-Inwood Columbia Aging Project; ULSAM, Uppsala Longitudinal Study of Adult Men; SUN, Seguimiento Universidad de Navarra; GGPSG, Gerontological and Geriatric Population Studies in Gothenburg; EPICOR Study, Italian Section of the European Prospective Investigation into Cancer and Nutrition; NLCS, Netherlands Cohort Study; NOMAS, Northern Manhattan Study; VIP, Västerbotten Intervention Program; G, Greece; A, Australia; S, Spain; B, Belgium; D, Denmark; F, France; H, Hungary; I, Italy; N, The Netherlands; P, Portugal; Sw, Switzerland; Swe, Sweden; Ge, Germany; No, Norway; OM, overall mortality; AI, Alzheimer's disease; C, cancer; St, stroke; CBVD, cerebrovascular disease; n.d., not determined.
*Mean values.

Table 2 Values of components of adherence score to the Mediterranean diet among women (g/d)

Author	Year	Cohort	Country	*n*	Age (years)	Disease	Legumes	Cereals	Fruit	Vegetables	Fish	Meat	Dairy
Trichopoulou *et al.*[25]	1995	Greek villages	G	91	>70	OM	49	248	216	248	n.d.	91	194
Kouris-Blazos *et al.*[26]	1999	Anglo-Celts; Greek-Australian	A	95	>70	OM	50*	232·5*	291*	349·5*	n.d.	246*	296*
Lasheras *et al.*[27]	2000	Spanish volunteers	S	112	65–95	OM	10·5	197	228	228	n.d.	105	352·5
Knoops *et al.*[28]	2004	SENECA	B, D, F, G, H, I, N, P, S, Sw	832	73*	OM	5	194	262	272	23	107	317
Trichopoulou *et al.*[29]	2005	EPIC-Elderly	D, F, Ge, G, I, N, S, Swe, UK	50 062	>60	OM	5	168·4	245·7	183·8	26·9	82·2	301·1
Lagiou *et al.*[36]	2006	SWLHC	Swe	42 237	30–49	OM, C	17·5	183·3	136·9	61·9	22·7	84·4	334·2
Scarmeas *et al.*[30]	2006	WHICAP	USA	1546	77·2*	Al	57	184	472	197	20	85	182
Benetou *et al.*[31]	2008	Greek-EPIC	G	15 041	20–86	C	7·8	144·6	375·6	531·1	21·8	93·7	214·7
Trichopoulou *et al.*[32]	2009	Greek-EPIC	G	13 845	20–86	OM	6·7	139·6	356·8	499·3	18·9	89·9	191·4
Buckland *et al.*[33]	2009	EPIC-Spain	S	25 636	29–69	CHD	19·4	84·4	155·8	113	23·1	54	155·9
Buckland *et al.*[34]	2010	EPIC	D, F, G, Ge, I, N, No, S, Swe, UK	340 467	35–70	C	3	85	113·4	97·4	9·8	44·5	147·2
Martinez-Gonzalez *et al.*[35]	2011	SUN	S	8165	38*	CVD	21	81	300	501	86	170	143
Tognon *et al.*[8]	2011	GGPSG	Swe	540	>70	OM	2	165	176·4	209·5	45·2	89·7	373·3
Agnoli *et al.*[9]	2011	EPICOR Study	I	28 118	35–64	St	17	185	319	173	28	83	50
Buckland *et al.*[10]	2011	EPIC-Spain	S	25 928	49·3*	OM, CVD, C	56	214	380	282·2	64·1	96·9	198·5
van der Brandt[11]	2011	NLCS	N	1886	55–69	OM	4·9	n.d.	212·9	218·7	8·8	106·1	n.d.
Gardener *et al.*[12]	2011	NOMAS	USA	1637	68·6*	CVD, St	9	61	131	67	10	33	92
Couto *et al.*[13]	2011	EPIC	D, F, Ge, G, I, N, No, S, Swe, UK	335 873	25–70	C	14·6*	219*	247·3*	211·2*	37·2*	98·7*	326·7*
Dilis *et al.*[17]	2012	Greek-EPIC	G	14 189	20–86	CHD	7	139	351	499	19	90	194
Hoevenaar-Blom *et al.*[18]	2012	EPIC-NL	N	25 944	20–70	CVD, St	12	165·5	174	118	7·5	94·5	380
Misirli *et al.*[19]	2012	Greek-EPIC	G	13 984	20–86	CBVD	8·9*	163·4*	382·2*	553·5*	23·7*	108·9*	220·2*
Martinez-Gonzalez *et al.*[15]	2012	SUN	S	9264	38*	OM	21	81	301	503	86	164	126
Tognon *et al.*[16]	2012	VIP	Swe	39 605	30–60	OM	n.d.	38·6	109·1	148	11·6	52	219
Bamia *et al.*[20]	2013	EPIC	D, F, Ge, G, I, N, No, S, Swe, UK	336 556	25–70	C	5·7	200·1	199·6	174·1	28	91·7	276
Buckland *et al.*[21]	2013	EPIC	D, F, Ge, G, I, N, No, S, Swe, UK	335 062	25–70	C	14*	172·3*	250·2*	218·8*	26·8*	87·4*	322·1*
Couto *et al.*[22]	2013	SWLHC	Swe	49 258	30–49	C	19·3*	195·6*	158·1*	70·4*	24·4*	87·7*	369·8*

SENECA, Survey in Europe on Nutrition and the Elderly: a Concerted Action; EPIC, European Prospective Investigation into Cancer and Nutrition; SWLHC, Scandinavian Women's Lifestyle and Health Cohort; WHICAP, Washington Heights-Inwood Columbia Aging Project; SUN, Seguimiento Universidad de Navarra; GGPSG, Gerontological and Geriatric Population Studies in Gothenburg; EPICOR Study, Italian Section of the European Prospective Investigation into Cancer and Nutrition; NLCS, Netherlands Cohort Study; NOMAS, Northern Manhattan Study; VIP, Västerbotten Intervention Program; G, Greece; A, Australia; S, Spain; B, Belgium; D, Denmark; F, France; H, Hungary; I, Italy; N, The Netherlands; P, Portugal; Sw, Switzerland; Swe, Sweden; Ge, Germany; No, Norway; OM, overall mortality; Al, Alzheimer's disease; C, cancer; St, stroke; CBVD, cerebrovascular disease; n.d., not determined.
*Mean values.

Table 3 Study characteristics of the recent prospective studies investigating adherence to the Mediterranean diet and health outcomes

Author, year (cohort)	Country	*n*/*N*	Outcome	Follow-up (years)	Age (years)	Sex	Components of the adherence score	Adjustment
Sjorgen *et al.*[7], 2010 (ULSAM)	Swe	215/924 88/924	OM CVD mortality	10·1	71*	M	1. High vegetables and legumes; 2. High cereals and potatoes; 3. High fruit; 4. High fish; 5. High PUFA:SFA; 6. Moderate alcohol; 7. Low meat and meat products; 8. Low milk and milk products	EI, smoking habit, social class, diabetes, MetS, lipid-lowering treatment, BP-lowering treatment, WC, BP, insulin, CRP
Tognon *et al.*[8], 2011 (GGPSG)	Swe	622/1037	OM	8·5	>70	M/F	1. High legumes and nuts; 2. High wholegrain cereals; 3. High fruit; 4. High vegetables and potatoes; 5. High fish and fish products; 6. High MUFA+PUFA:SFA; 7. Moderate alcohol; 8. Low meat, meat products and eggs; 9. Low dairy products	Sex, BMI, WC, PA, marital status, smoking habit, education
Agnoli *et al.*[9], 2011 (EPICOR Study)	I	178/40 681	St	7·9	35–74	F	1. High pasta; 2. High vegetables; 3. High fruit; 4. High legumes; 5. High fish; 6. High olive oil; 7. Low potatoes; 8. Low butter; 9. Moderate alcohol; 10. Low red and processed meat; 11. Low soft drinks	Age, sex, smoking habit, education, EI, BMI
Buckland *et al.*[10], 2011 (EPIC-Spain)	S	1855/40 622 399/40 622 913/40 622	OM CVD mortality C mortality	13·4	29–69	M/F	1. High legumes; 2. High cereals; 3. High fruit and nuts; 4. High vegetables; 5. High fish; 6. High MUFA:SFA; 7. Moderate alcohol; 8. Low meat and poultry; 9. Low dairy products	Age, education, BMI, WC, education, PA, smoking habit, total energy
van den Brandt[11], 2011 (NLCS) Men	N	6329/58 279	OM	4·9	55–69	M	1. High legumes; 2. High cereals; 3. High fruit and nuts; 4. High vegetables; 5. High fish; 6. High MUFA:SFA; 7. Moderate alcohol; 8. Low meat and poultry; 9. Low dairy products	Age, smoking habit, cigarettes, years of smoking, BMI, PA, hypertension, education, EI
van der Brandt[11], 2011 (NLCS) Women	N	3362/62 573	OM	4·9	55–69	F	1. High legumes; 2. High cereals; 3. High fruit and nuts; 4. High vegetables; 5. High fish; 6. High MUFA:SFA; 7. Moderate alcohol; 8. Low meat and poultry; 9. Low dairy products	Age, smoking habit, cigarettes, years of smoking, BMI, PA, hypertension, education, EI

Table 3 *Continued*

Author, year (cohort)	Country	*n*/*N*	Outcome	Follow-up (years)	Age (years)	Sex	Components of the adherence score	Adjustment
Gardener *et al.*[12], 2011 (NOMAS)	USA	518/2568	CVD	9	69	M/F	1. High legumes; 2. High cereals; 3. High fruit; 4. High vegetables; 5. High fish; 6. High MUFA:SFA; 7. Moderate alcohol; 8. Low meat and meat products; 9. Low dairy products	Age, sex, race, education, PA, EI, smoking habit, hypertension, diabetes, hypercholesterolaemia
Couto *et al.*[13], 2011 (EPIC)	D, F, Ge, G, I, N, No, S, Swe, UK	30 731/478 478	C	8·7	25–70	M/F	1. High legumes; 2. High cereals; 3. High fruit; 4. High vegetables; 5. High fish; 6. High MUFA:SFA; 7. Moderate alcohol; 8. Low meat and meat products; 9. Low dairy products	Age, sex, smoking habit, duration of smoking, education, height, BMI, EI, PA, menopause, HRT
McNaughton *et al.*[14], 2010 (BDNS)	UK	654/972	OM	14	>65	M/F	1. High legumes; 2. High cereals; 3. High fruit and nuts; 4. High vegetables; 5. High fish; 6. High MUFA:SFA; 7. Moderate alcohol; 8. Low meat and meat products; 9. Low dairy products	Age, sex, EI, social class, region, smoking habit, PA, BMI
Martinez-Gonzalez *et al.*[15], 2012 (SUN)	S	125/15 535	OM	6·8	38	M/F	1. High legumes; 2. High cereals; 3. High fruit and nuts; 4. High vegetables; 5. High fish; 6. High MUFA:SFA; 7. Moderate alcohol; 8. Low meat and meat products; 9. Low dairy products	Age, sex, years of education, BMI, smoking habit, PA, h/d spent watching TV, depression, hypertension, hypercholesterolaemia, EI, egg and potatoes
Tognon *et al.*[16], 2012 (VIP)	Swe	1453/37 546 493/35 950 499/35 950	OM C CVD	10	30–70	M	1. High vegetables and potatoes; 2. High fruit and juices; 3. High wholegrain cereals; 4. High fish and fish products; 5. High fish; 6. High MUFA+PUFA:SFA; 7. Moderate alcohol; 8. Low meat and meat products; 9. Low dairy products	Age, obesity, PA, smoking habit, education
Tognon *et al.*[16], 2012 (VIP)	Swe	923/39 605 481/38 034 181/38 034	OM C CVD	10	30–70	F	1. High vegetables and potatoes; 2. High fruit and juices; 3. High wholegrain cereals; 4. High fish and fish products; 5. High fish; 6. High MUFA+PUFA:SFA; 7. Moderate alcohol; 8. Low meat and meat products; 9. Low dairy products	Age, obesity, PA, smoking habit, education

Table 3 *Continued*

Author, year (cohort)	Country	*n*/*N*	Outcome	Follow-up (years)	Age (years)	Sex	Components of the adherence score	Adjustment
Dilis *et al.*[17], 2012 (Greek-EPIC) Men	G	150/9740	CHD mortality	10	25–70	M	1. High legumes; 2. High cereals; 3. High fruit and nuts; 4. High vegetables; 5. High fish; 6. High MUFA:SFA; 7. Moderate alcohol; 8. Low meat and meat products; 9. Low dairy products	Age, BMI, height, PA, education, smoking habit, hypertension, EI
Dilis *et al.*[17], 2012 (Greek-EPIC) Women	G	90/14 189	CHD mortality	10	25–70	F	1. High legumes; 2. High cereals; 3. High fruit and nuts; 4. High vegetables; 5. High fish; 6. High MUFA:SFA; 7. Moderate alcohol; 8. Low meat and meat products; 9. Low dairy products	Age, BMI, height, PA, education, smoking habit, hypertension, EI
Hoevenaar-Blom *et al.*[18], 2012 (EPIC-NL: MORGEN and PROSPECT)	N	4881/34 708 448/34 708	CVD Stroke	12	20–70	M/F	1. High legumes; 2. High cereals; 3. High fruit; 4. High vegetables; 5. High fish; 6. High MUFA:SFA; 7. Moderate alcohol; 8. Low meat and meat products; 9. Low dairy products	Age, sex, cohort, smoking habit, PA, education, EI
Misirli *et al.*[19], 2012 (EPIC-Greece) Men	G	204/9617	CBVD	10·6	25–70	M	1. High legumes; 2. High cereals; 3. High fruit; 4. High vegetables; 5. High fish; 6. High MUFA:SFA; 7. Moderate alcohol; 8. Low meat and meat products; 9. Low dairy products	Age, education, smoking habit, BMI, PA, hypertension, diabetes, EI
Misirli *et al.*[19], 2012 (EPIC-Greece) Women	G	191/13 984	CBVD	10·6	25–70	F	1. High legumes; 2. High cereals; 3. High fruit; 4. High vegetables; 5. High fish; 6. High MUFA:SFA; 7. Moderate alcohol; 8. Low meat and meat products; 9. Low dairy products	Age, education, smoking habit, BMI, PA, hypertension, diabetes, EI
Bamia *et al.*[20], 2013 (EPIC)	D, F, Ge, G, I, N, No, S, Swe, UK	3724/397 641	Colorectal cancer	11·6	25–70	M/F	1. High legumes; 2. High cereals; 3. High fruit and nuts; 4. High vegetables; 5. High fish; 6. High MUFA:SFA; 7. Low meat and meat products; 8. Low dairy products	Age, sex, BMI, PA, education, smoking habit, EI
Buckland *et al.*[21], 2013 (EPIC)	D, F, Ge, G, I, N, No, S, Swe, UK	10 225/335 062	Breast cancer	11	25–70	F	1. High legumes; 2. High cereals; 3. High fruit and nuts; 4. High vegetables; 5. High fish; 6. High MUFA:SFA; 7. Low meat and meat products; 8. Low dairy products	Age, BMI, height, education, PA, smoking habit, menopause, age at menopause, oral contraception, age at menarche, age at first pregnancy, HRT, SFA intake, EI

Table 3 *Continued*

Author, year (cohort)	Country	*n*/*N*	Outcome	Follow-up (years)	Age (years)	Sex	Components of the adherence score	Adjustment
Couto *et al.*[22], 2013 (SWLHC)	Swe	1278/49 285	Breast cancer	16	30–49	F	1. High legumes; 2. High cereals; 3. High fruit and nuts; 4. High vegetables; 5. High fish; 6. High MUFA:SFA; 7. Moderate alcohol; 8. Low meat and meat products; 9. Low dairy products	Age, BMI, height, education, PA, smoking habit, history of breast cancer, age at menarche, EI, beverages, potatoes, sweets, eggs
Agnoli *et al.*[23], 2013 (EPIC) Men	I	181/14 195	Colorectal cancer	11·3	25–70	M	1. High pasta; 2. High vegetables; 3. High fruit; 4. High legumes; 5. High fish; 6. High olive oil; 7. Low potatoes; 8. Low butter; 9. Moderate alcohol; 10. Low red and processed meat; 11. Low soft drinks	Age, non-alcoholic EI, BMI, smoking habit, education, PA
Agnoli *et al.*[23], 2013 (EPIC) Women	I	254/31 080	Colorectal cancer	11·3	25–70	F	1. High pasta; 2. High vegetables; 3. High fruit; 4. High legumes; 5. High fish; 6. High olive oil; 7. Low potatoes; 8. Low butter; 9. Moderate alcohol; 10. Low red and processed meat; 11. Low soft drinks	Age, non-alcoholic EI, BMI, smoking habit, education, PA
Bosire *et al.*[24], 2013 (NIH-AARP)	USA	23 453/293 464	Prostate cancer	8·9	50–71	M	1. High legumes; 2. High wholegrain cereals; 3. High fruit and nuts; 4. High vegetables; 5. High fish; 6. High MUFA:SFA; 7. Moderate alcohol; 8. Low meat and meat products; 9. Low dairy products	Age, ethnicity, education, BMI, smoking habit, PA, family history of prostate cancer, diabetes, EI, history of PSA screening

ULSAM, Uppsala Longitudinal Study of Adult Men; GGPSG, Gerontological and Geriatric Population Studies in Gothenburg; EPICOR Study, Italian Section of the European Prospective Investigation into Cancer and Nutrition; EPIC, European Prospective Investigation into Cancer and Nutrition; NLCS, Netherlands Cohort Study; NOMAS, Northern Manhattan Study; BDNS, British Diet and Nutrition Survey; SUN, Seguimiento Universidad de Navarra; VIP, Västerbotten Intervention Program; SWLHC, Swedish Women's Lifestyle and Health Cohort; NIH-AARP, National Institutes of Health-AARP Diet and Health Study; Swe, Sweden; I, Italy; S, Spain; N, The Netherlands; D, Denmark; F, France; Ge, Germany; G, Greece; No, Norway; OM, overall mortality; St, stroke; C, cancer; CBVD, cerebrovascular disease; M, males, F, females; EI, energy intake; MetS, metabolic syndrome; BP, blood pressure; WC, waist circumference; CRP, C-reactive protein; PA, physical activity; HRT, hormone replacement therapy; TV, television; PSA, prostate-specific antigen.
*Mean values.

Results

Updated systematic review and meta-analysis

The updated search from recent years resulted in the identification of eighteen additional prospective studies published up to June 2013[7–24]. Characteristics of these recent studies are displayed in Table 3. Of these, seven cohorts presented overall mortality as clinical outcome[7,8,10,11,14–16], eight incidence and/or mortality from cardio- and cerebrovascular diseases[7,9,10,12,16–19], and eight incidence and/or mortality from neoplastic diseases[10,13,16,20–24]. No updated studies for the incidence of neurodegenerative diseases have been found. On the other hand, one study resulted to be an updated analysis of a study already reported in the previous meta-analyses for the overall mortality outcome, so only the most updated study was added to this updated final analysis[13]. Altogether with the studies previously investigated, a total of thirty-five cohort prospective studies were included and entered into the final analysis. This updated analysis determined an increase of the study population up to a total of 4 172 412 subjects analysed.

Meta-analytic pooling under a random-effects model showed the already reported significant association between 2-point increased adherence to the Mediterranean diet and reduced risk of mortality from all causes (RR = 0·92; 95 % CI 0·91, 0·93; $P<0·00001$; Fig. 1), with little evidence of statistical heterogeneity across the studies ($I^2 = 47\,\%$; $P = 0·01$). This heterogeneity seems to be determined mainly by the study of van den Brandt[11]. After exclusion of this latter study, the statistical heterogeneity disappeared ($I^2 = 35\,\%$; $P = 0·08$), with no modification of the association between adherence to the Mediterranean diet and overall mortality (RR = 0·92; 95 % CI 0·91, 0·93; $P<0·00001$).

Moreover, we found that a 2-point increase of adherence to the Mediterranean diet still remained associated with a reduced risk of mortality from and incidence of CVD (RR = 0·90; 95 % CI 0·87, 0·92; $P<0·00001$; Fig. 2), showing no significant heterogeneity across the studies ($I^2 = 38\,\%$; $P = 0·07$). Likewise, among studies investigating mortality and incidence of neoplastic diseases (Fig. 3), a greater adherence to the Mediterranean diet still determined a significant protection, to a similar extent as the previous meta-analysis (RR = 0·96; 95 % CI 0·95, 0·97; $P<0·00001$), with evidence of significant heterogeneity across the studies ($I^2 = 65\,\%$; $P<0·001$). The heterogeneity seems to be determined by the recent studies investigating breast and colorectal cancer[21–23]. After exclusion of these three studies, the statistical heterogeneity disappeared ($I^2 = 36\,\%$; $P = 0·10$), with no modification

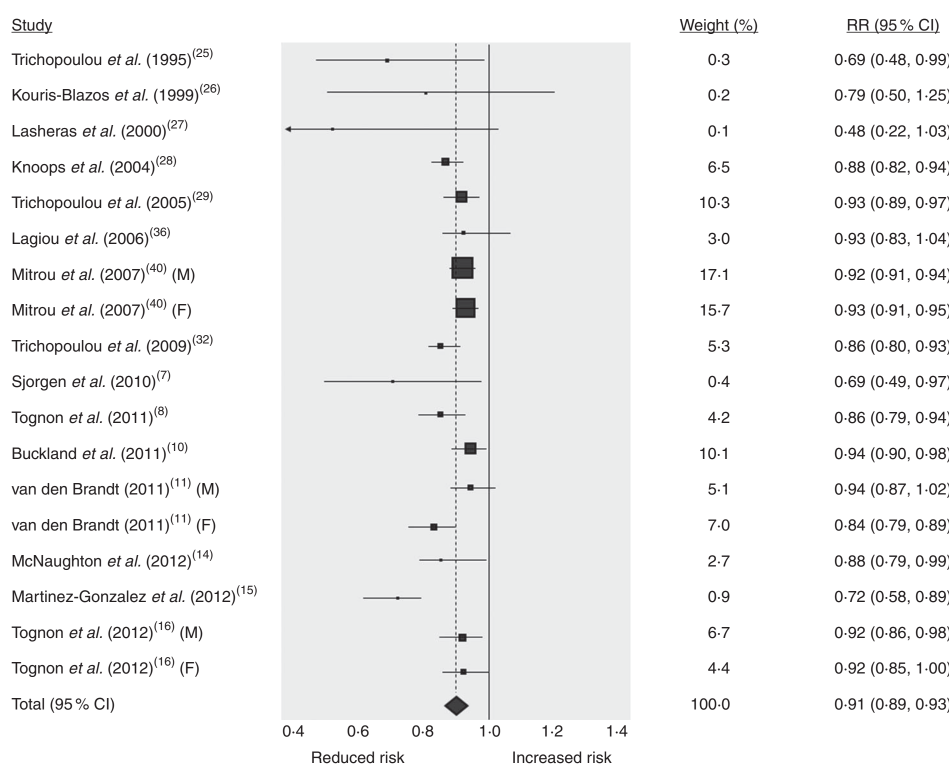

Fig. 1 Forest plot for updated meta-analysis on greater adherence score to the Mediterranean diet (2-point increase) and overall mortality risk. Plotted are the relative risk (RR; represented by ■, with the symbol size proportional to the weight in meta-analysis) and the 95 % confidence interval (represented by horizontal bars), with the summary measure (represented by - - - - - and ◆, with the associated 95 % confidence interval indicated by the symbol width) and the line of no effect (——)

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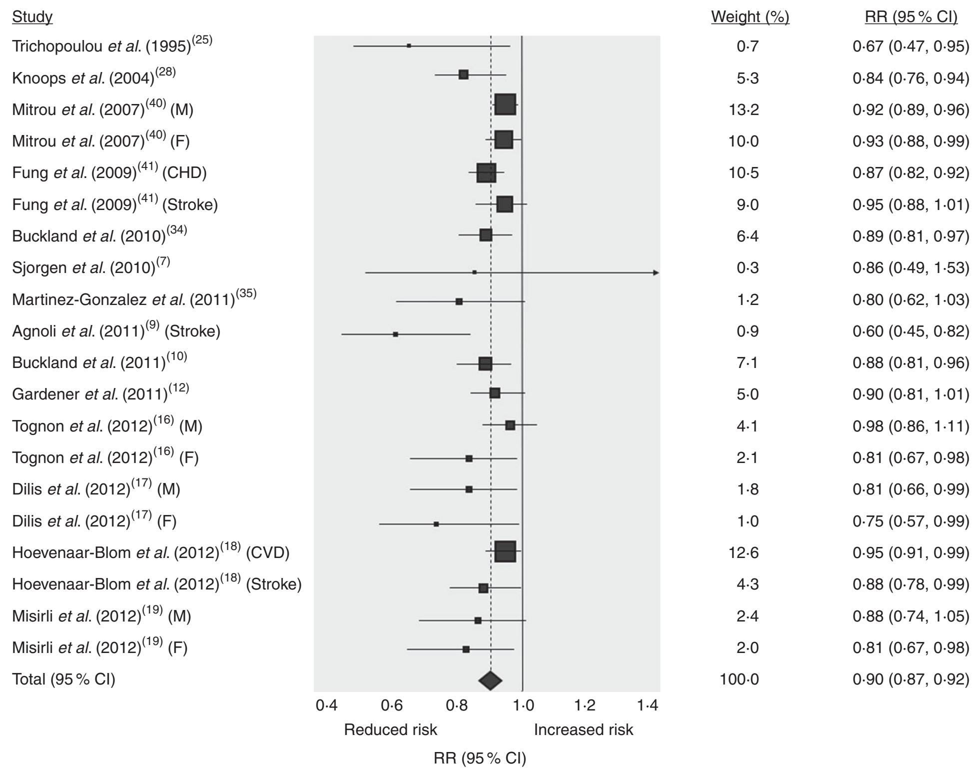

Fig. 2 Forest plot for updated meta-analysis on greater adherence score to the Mediterranean diet (2-point increase) and cardiovascular incidence and/or mortality risk. Plotted are the relative risk (RR; represented by ■, with the symbol size proportional to the weight in meta-analysis) and the 95 % confidence interval (represented by horizontal bars), with the summary measure (represented by ----- and ◆, with the associated 95 % confidence interval indicated by the symbol width) and the line of no effect (——)

on the protection of the Mediterranean diet *v.* neoplastic disease (RR = 0·96; 95 % CI 0·95, 0·97; $P < 0·00001$).

Literature-based adherence score to the Mediterranean diet

Characteristics of the studies included for this analysis are reported in Tables 1 and 2 for men and women, respectively. For the purpose of this analysis some studies previously included in the updated meta-analytic analysis were excluded, due to the lack of information on amount of consumption for the different food groups composing the adherence score.

We were able to collect data from twenty-four cohort studies for men[7–13,15–20,25–35] and twenty-six for women[8–13,15–22,25–36]. It is interesting to note that values of consumption for food groups composing adherence score to the Mediterranean diet resulted to be, in some cases, different across the studies. For instance, between two cohorts of subjects coming from the same continent (e.g. Spain and Greece) the median consumption of some food groups varied from 90 to 187 g/d (e.g. cereals for men between Martinez-Gonzalez *et al.*[35] and Buckland *et al.*[10]). More interestingly, vegetable consumption showed a wide variability even between two cohorts of subjects coming from the same country (e.g. vegetables: 75 g/d *v.* 239 g/d for Sjorgen *et al.*[7] and Tognon *et al.*[8], respectively).

We utilized such data for proposing an adherence score based on literature data. To this aim, we weighted all the median (or mean) values for the sample size of each study population and then we calculated the mean value of all the weighted medians. Hence, we calculated the 2 SD value and we rounded the number close to the ±2 SD, determining three different categories of consumption for each food group (e.g. for cereals: weighted mean = 162·7 (SD 34·6) g/d that determined three different categories <130 g; 131–200 g; >200 g). For food groups typical of the Mediterranean diet (fruit, vegetables, cereals, legumes and fish) we gave 2 points to the highest category of consumption, 1 point for the middle category and 0 point for the lowest category. Conversely, for food groups not typical of the Mediterranean diet (meat and meat products, dairy products) we gave 2 points for the lowest category, 1 point for the middle category and 0 point for the highest category of consumption. For alcohol, we used the categories related to the alcohol unit (1 alcohol unit = 12 g of alcohol), by giving 2 points to the middle category (1–2 alcohol units/d), 1 point to the lowest category (<1 alcohol unit/d) and 0 point to the highest category of consumption (>2 alcohol units/d). Finally, we introduced olive oil as part of the proposed score due to its importance in the typical Mediterranean diet and the beneficial effect of its consumption on health and

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Study	Weight (%)	RR (95 % CI)
Knoops *et al.* (2004)[28]	7·9	0·95 (0·90, 1·00)
Lagiou *et al.* (2006)[36]	1·7	0·89 (0·77, 1·03)
Fung *et al.* (2006)[42]	3·0	0·91 (0·82, 1·01)
Mitrou *et al.* (2007)[40] (M)	10·9	0·94 (0·91, 0·97)
Mitrou *et al.* (2007)[40] (F)	9·1	0·96 (0·92, 1·00)
Benetou *et al.* (2008)[31]	4·3	0·88 (0·81, 0·96)
Buckland *et al.* (2010)[34]	3·1	0·86 (0·78, 0·96)
Buckland *et al.* (2011)[10] (Spain)	7·5	0·98 (0·93, 1·03)
Couto *et al.* (2011)[13]	13·5	0·96 (0·95, 0·97)
Tognon *et al.* (2012)[16] (M)	2·8	0·85 (0·76, 0·95)
Tognon *et al.* (2012)[16] (F)	2·3	0·96 (0·85, 1·09)
Bamia *et al.* (2013)[20]	8·9	0·96 (0·92, 1·00)
Buckland *et al.* (2013)[21]	12·2	0·98 (0·96, 1·00)
Couto *et al.* (2013)[22]	4·9	1·08 (1·00, 1·17)
Agnoli *et al.* (2013)[23] (M)	0·3	0·66 (0·45, 0·98)
Agnoli *et al.* (2013)[23] (F)	0·5	0·60 (0·45, 0·79)
Bosire *et al.* (2013)[24]	7·1	1·00 (0·95, 1·06)
Total (95 % CI)	100·0	0·95 (0·93, 0·97)

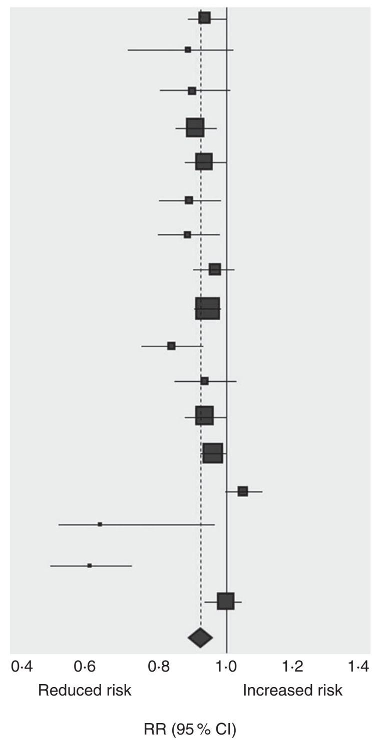

Fig. 3 Forest plot for updated meta-analysis on greater adherence score to the Mediterranean diet (2-point increase) and cancer incidence and/or mortality risk. Plotted are the relative risk (RR; represented by ■, with the symbol size proportional to the weight in meta-analysis) and the 95 % confidence interval (represented by horizontal bars), with the summary measure (represented by ----- and ◆, with the associated 95 % confidence interval indicated by the symbol width) and the line of no effect (——)

FRUIT *1 portion: 150 g*	<1 portion/d 0	1–1·5 portions/d 1	>2 portions/d 2
VEGETABLES *1 portion: 100 g*	<1 portion/d 0	1–2·5 portions/d 1	>2·5 portions/d 2
LEGUMES *1 portion: 70 g*	<1 portion/week 0	1–2 portions/week 1	>2 portions/week 2
CEREALS *1 portion: 130 g*	<1 portion/d 0	1–1·5 portions/d 1	>1·5 portions/d 2
FISH *1 portion: 100 g*	<1 portion/week 0	1–2·5 portions/week 1	>2·5 portions/week 2
MEAT AND MEAT PRODUCTS *1 portion: 80 g*	<1 portion/d 2	1–1·5 portions/d 1	>1·5 portions/d 0
DAIRY PRODUCTS *1 portion: 180 g*	<1 portion/d 2	1–1·5 portions/d 1	>1·5 portions/d 0
ALCOHOL *1 Alcohol Unit (AU) = 12 g*	<1 AU/d 1	1–2 AU/d 2	>2 AU/d 0
OLIVE OIL	Occasional use 0	Frequent use 1	Regular use 2

TOTAL:

Fig. 4 Literature-based adherence score to the Mediterranean diet (range: 0–18 points). Portion sizes derive from the calculation of mean value of weighted medians (or means) ±2 SD coming from all the cohort studies reported in Tables 1 and 2

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longevity (2 points = regular use; 1 point = frequent use; 0 point = occasional use). The final adherence score comprised nine food categories with a score ranging from 0 point (lowest adherence) to 18 points (highest adherence). Since no relevant differences for proposed food categories across men and women were obtained, a single score was computed for both sexes (Fig. 4).

Discussion

In the present study we conducted an updated meta-analysis on the association between adherence to the Mediterranean diet and health outcomes, with the additional purpose of proposing an adherence score, based on data from the literature, that can be used also at an individual level and not only in an epidemiological setting.

Greater adherence to the Mediterranean diet has long been reported to be protective against the occurrence of chronic degenerative disease[1]. Two previous meta-analyses conducted by our group reported the Mediterranean diet to be the optimal diet for preserving a good health status[2,3]. Moreover, recently, the protective role of the Mediterranean diet has been also demonstrated in a dietary intervention study conducted in Spanish middle-aged subjects. Over a follow-up period of 4·8 years, subjects following the Mediterranean diet reported to have a protection of 30 % *v.* the occurrence of CVD in a primary prevention setting[37].

We decided to update the meta-analysis previously published by our group because many studies have been released in the last 3 years. This updated analysis was conducted with the same methods used for the previous meta-analysis[3] and allowed us to add eighteen prospective studies to the final analysis[7–24]. Hence, we were able to extend the evidence to an overall study population of more than 4 000 000 subjects and to other countries such as Italy and Scandinavian countries[7–9,16,22,23]. From this updated analysis we could report that a 2-point increase in adherence score to the Mediterranean diet is actually protective *v.* the occurrence of overall mortality, incidence and/or mortality from cardiovascular and neoplastic causes, with again similar results compared with the previous analyses (−8 % for overall mortality, −10 % for CVD and −4 % for cancer).

An additional purpose of the present article was to obtain, from the most updated prospective cohort studies, data regarding the amount of consumption for food groups composing the adherence score to the Mediterranean diet in order to propose a literature-based adherence score that can be used to assess adherence to the Mediterranean diet also at an individual level.

Over the last years, research on nutritional science and on its relationship with disease has shifted from the study of single nutrients to the evaluation of food patterns, since subjects do not eat isolated nutrients and because the complex interactions among different nutrients have been reported to be extremely relevant for the healthy aspects of diet. Some attempts for estimating the adherence to the whole diet, and particularly to the Mediterranean diet, have been conducted[4,5]. The first and most widely used tool to assess adherence to the Mediterranean diet, created by Trichopoulou *et al.*[6], has been extremely widely used for epidemiological research and is based on the sex-based median amount of consumption of food groups that are characteristic of the traditional Mediterranean diet in the sample investigated. On one hand, this score has many advantages because it helped to introduce the concept of an adherence score to a specific diet and allowed to estimate the association between the adherence score and risk of disease in an epidemiological setting. On the other hand, however, it has the main disadvantage of being widely related to the availability of data coming from a sample population, differing substantially from one cohort to another, even within the same country, and more importantly because it does not give an amount of consumption for food groups composing the score that can be used in everyday clinical practice, at an individual level. This is the reason why other indices have been created. One example is that of Panagiotakos *et al.*[38] who created a simple questionnaire based on recommendations of the guidelines for a healthy diet and characterized by a few questions used for estimating the frequency of consumption (monthly or daily) of food groups more or less characteristic of the Mediterranean diet. Another example is the questionnaire developed in the PREDIMED study and recently assessed in the SUN (Seguimiento Universidad de Navarra) cohort[39]. Both these questionnaires have the advantage of being feasible for assessing adherence to the Mediterranean diet at an individual level but they are not based on data from the literature.

That is why we decided to utilize all the available data coming from the most relevant cohort studies for proposing a new evidence-based score for assessing adherence to the Mediterranean diet.

The approach we used, despite able to obtain all the literature data available in this context, may present some limitations. Different cohorts coming from the same country reported to have different cut-offs of consumption for the adherence to the Mediterranean diet, and even among the same countries the range of consumption within the same food group varied. Moreover, by analysing data it became apparent that the median of consumption was extremely related to the sample size of the population investigated. To date, smaller cohorts had, at the same time, higher consumption and vice versa. Hence, we decided to calculate the mean value of all the food groups by taking into account the sample size of the population, i.e. estimating the weighted medians for consumption of all of the food groups.

Despite all these efforts, some limitations that are intrinsic to the single studies still remain. One of these is the lack of uniformity in data regarding the same food group. Some studies report potatoes together with vegetables, while others include them as a single food group, whereas some others include legumes with nuts and not by themselves, and so on.

Nevertheless, the strength of this proposed adherence score is that food group data come from the most updated and comprehensive review of the literature in this context. If confirmed and validated in other studies, the evidence-based search strategy used for obtaining data from the available studies will hopefully help the transferability of such an adherence score into clinical practice.

Conclusion

We updated the results of our previous meta-analyses by including eighteen cohort prospective studies published in the last 3 years and we were able to show the beneficial effects of a greater adherence to the Mediterranean diet in terms of protection *v.* overall mortality and occurrence of the most important chronic diseases. In addition, by using data coming from the systematic review we proposed an adherence score based on literature data that can be also feasible for assessment of the adherence to the Mediterranean diet at an individual level.

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