H.2.1.3 Development of choroidal neovascularisation (CNV) due to AMD: risk outcomes for developing CNV

Ocular risk factors

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
5 or more drusen								
Macular photocoagulation study group (1997) Prospective cohort	670	Very serious[1,2,3]	N/A	Not serious	Not serious	HR (95% CI)	2.1 (1.3, 3.5)	LOW
1 or more large drusen								
Macular photocoagulation study group (1997) Prospective cohort	670	Very serious[1,2,3]	N/A	Not serious	Serious[6]	HR (95% CI)	1.5 (1.0, 2.2)	VERY LOW
Large drusen								
Bressler 1990 Prospective cohort	127	Very serious[1,2,4]	N/A	Not serious	Not serious	HR (95% CI)	Large drusen (≥50µm): 2.4 (1.1, 5.1)	LOW
Large Drusen								
Finger (2014) Retrospec	200	Very serious[1,2,4]	N/A	Not serious	Not serious	HR (95% CI)	Drusen ≥125µm: 1.96 (1.14, 3.36)	LOW

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
tive cohort								
Large drusen								
Klein (2007) Prospecti ve cohort	3,917	Serious[1,2]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	Drusen > 125µm vs <63µm in diameter: 60.4 (17.7, 206)	MODERATE
No. of large drusen (quartile 1 as reference category)								
Sandberg (1998) Prospecti ve cohort	127	Very serious[1,2,4]	N/A	Not serious	Not serious	HR (95% CI)	Quartile 2: 2.09 (0.66, 7.84) Quartile 3: 0.83 (0.20, 3.52) Quartile 4: 3.25 (1.11, 11.75)	LOW
Drusen area								
Klein (2007) Prospecti ve cohort	3,917	Serious[1,2]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	Drusen area >16877 µm² vs ≤2596 µm²: 40.4 (5.5, 297)	MODERATE
Soft distinct drusen vs hard distinct drusen								
Klein et al (2007) Prospecti ve cohort	3,917	Serious[1,2]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	Soft distinct drusen vs hard distinct drusen: 7.4 (2.4, 22.6)	MODERATE
Soft indistinct vs soft distinct drusen or hard distinct drusen								
Klein et al (2007) Prospecti ve cohort	3,917	Serious[1,2]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	Soft indistinct vs soft distinct drusen or hard distinct drusen: 18.3 (8.9, 37.4)	MODERATE

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Reticular drusen vs Soft distinct drusen								
Klein et al (2008) Prospective cohort	3,917	Serious[1,2]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	9.89 (2.16, 45.23)	MODERATE
Reticular drusen vs Soft indistinct drusen								
Klein et al (2008) Prospective cohort	3,917	Serious[1,2]	N/A	Not serious	Very serious[7]	Time-adjusted odds ratios (95% CI)	2.82 (0.66, 12.01)	VERY LOW
Reticular pseudodrusen								
Finger (2014) Retrospective cohort	200	Very serious[1,2,4]	N/A	Not serious	Serious[6]	HR (95% CI)	Reticular pseudodrusen: 1.19 (0.72, 1.94)	VERY LOW
Confluent drusen								
Bressler 1990 Prospective cohort	127	Very serious[1,2,4]	N/A	Not serious	Serious[6]	HR (95% CI)	1.8 (0.8, 3.9)	VERY LOW
Hyperpigmentation								
Macular photocoagulation study group (1997)	670	Very serious[1,2,3]	N/A	Not serious	Not serious	HR (95% CI)	2.0 (1.4, 2.9)	LOW

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Prospecti ve cohort								
Hyperpigmentation								
Bressler 1990 Prospecti ve cohort	127	Very serious[1,2,4]	N/A	Not serious	Not serious	HR (95% CI)	2.5 (1.3, 4.9)	LOW
Hyperpigmentation (none/questionable as reference category)								
CAPT (2008) Prospecti ve cohort	1,052	Serious[2]	N/A	Not serious	Not serious	HR (95% CI)	<250 um: 1.28 (0.94, 1.75) >=250 um: 1.84 (1.22, 2.76)	MODERATE
Hyperpigmentation								
Klein (2007) Prospecti ve cohort	3,917	Serious[1,2]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	Increased pigment present vs absent: 5.8 (2.9, 11.7)	MODERATE
Retinal pigment epithelium depigmentation								
Klein et al (2007) Prospecti ve cohort	3,917	Serious[1,2]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	RPE depigmentation present vs absent: 7.8 (3.6, 16.6)	MODERATE
Pigmentary changes								
Finger (2014) Retrospec tive cohort	200	Very serious[1,2,4]	N/A	Not serious	Not serious	HR (95% CI)	Pigmentary Changes: 2.49 (1.51, 4.10)	LOW
Pigmentary abnormalities								

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Klein et al (2007) Prospective cohort	3,917	Serious[1,2]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	Pigmentary abnormalities present vs absent: 15.2 (7.3, 31.6)	MODERATE
Cataract surgery								
Chew (2009) Prospective cohort	5,841	Very serious[2,5]	N/A	Not serious	Serious[6]	HR (95% CI)	Right eye 1.20 (0.82, 1.75) Left eye 1.07 (0.72, 1.58)	VERY LOW

1. Evidence of bias from study sample (for example, the paper is not clear about how many people were eligible for the study and were not included, there was no meaningful comparison between those included in the study and the population of interest for important differences)
2. Evidence of bias from study attrition (for example, the paper is not clear about how many people were lost to follow up in the study and/or had missing data, there was no meaningful comparison between those lost to follow up or with missing data in the study and the rest of the included sample)
3. Evidence of bias from prognostic factor measurement (for example, the paper is not clear about how the factor was measured, factors that require definition (e.g. hypertension) were not defined, arbitrary or questionable cut off points were used for continuous values)
4. Evidence of bias from confounding factor measurement (for example, the paper is not clear about how the confounding factors were measured, it is not clear which confounders were adjusted for in analysis, not all the important confounders were adjusted for)
5. Evidence of bias from outcome measurement (for example, the paper is not clear about how the outcome was measured and what investigations were used, there appears to be no masking or confirmation with multiple readers, outcomes were taken from healthcare database codes where there is likely to be inconsistency in measurement or definition)
6. Downgraded one level for non-significant effect
7. Downgraded two levels for confidence interval crossing 2 lines of a defined minimal important difference

Demographic and medical risk factors

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Definite systemic hypertension								
Macular photocoagulation	670	Very serious[1,2,3]	N/A	Not serious	Not serious	HR (95% CI)	1.7 (1.2, 2.4)	LOW

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
study group (1997) Prospective cohort								
Hypertension (normal as reference category)								
CAPT (2008) Prospective cohort	1,052	Serious[2]	N/A	Not serious	Serious[6]	HR (95% CI)	Suspect: 0.69 (0.45, 1.07) Definite: 1.23 (0.90, 1.68)	LOW
Age (50-59 years as reference category)								
CAPT (2008) Prospective cohort	1,052	Serious[2]	N/A	Not serious	Not serious	HR (95% CI)	60-69 years: 2.06 (1.06, 3.97) 70-79 years: 2.61 (1.39, 4.92) >79 years: 2.81 (1.33, 5.94)	MODERATE
Age								
Klein (2007) Prospective cohort	3,917	Serious[1,2]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	Age (by increasing categories, 43-54 years, 55-64 years, 65-74 years, 75-86 years): 2.9 (2.2, 3.8)	MODERATE
Age								
Sandberg (1998) Prospective cohort	127	Very serious[1,2,4]	N/A	Not serious	Not serious	HR (95% CI)	Age, y, continuous: 1.08 (1.02, 1.14)	LOW

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Smoking (never as reference category)								
CAPT (2008) Prospective cohort	1,052	Serious[2]	N/A	Not serious	Not serious	HR (95% CI)	Former: 1.01 (0.76, 1.35) Current: 1.98 (1.16, 3.39)	MODERATE
Smoking								
Wilson (2004) Retrospective cohort	326	Serious[5]	N/A	Not serious	Not serious	HR (95% CI)	Current smoker: 1.77 (1.06, 2.97)	MODERATE
Smoking								
Klein (2008) Prospective cohort	2,119	Serious[1,2]	N/A	Not serious	Very Serious[7]	Time-adjusted odds ratios (95% CI)	Past vs never smokers: 1.12 (0.62, 2.01) Current vs never smokers: 0.69 (0.27, 1.76)	VERY LOW
Diabetes								
Hahn (2013) Prospective cohort	6,621	Very serious[2,3,4,5]	N/A	Not serious	Serious[6]	HR (95% CI)	1.11 (0.97, 1.27)	VERY LOW
Long term use of aspirin (no regular use as reference category)								
Klein (2012) Prospective cohort	4,926	Not serious	N/A	Not serious	Serious[6]	HR (95% CI)	Regular aspirin use: 1.07 (0.68, 1.67)	MODERATE
Aspirin user								

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Wilson (2004) Retrospective cohort	326	Serious[5]	N/A	Not serious	Not serious	HR (95% CI)	0.63 (0.40, 0.98)	MODERATE
History of MI								
Klein (2013) Prospective cohort	1,700	Serious[1]	N/A	Not serious	Very Serious[7]	Time-adjusted odds ratios (95% CI)	1.56 (0.48, 5.08)	VERY LOW
History of CVD								
Klein (2013) Prospective cohort	1,700	Serious[1]	N/A	Not serious	Very Serious[7]	Time-adjusted odds ratios (95% CI)	1.66 (0.65, 4.26)	VERY LOW
History of angina								
Klein (2013) Prospective cohort	1,700	Serious[1]	N/A	Not serious	Very Serious[7]	Time-adjusted odds ratios (95% CI)	0.92 (0.27, 3.13)	VERY LOW
Exercise								
Knudtson (2006) Prospective cohort	3,684	Very Serious[1,2,3]	N/A	Not serious	Not serious	Time-adjusted odds ratios (95% CI)	Sedentary: reference Active: 0.3 (0.1, 0.7)	LOW
Ethnicity (white as reference category)								
van der Beek (2011)	1,772,962	Very Serious[1,2,3,5]	N/A	Not serious	Not serious	HR (95% CI)	Black at age 60: Exudative AMD: 0.70 (0.59, 0.83)	LOW

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Prospecti ve cohort							Blacks at age 80: Exudative AMD: 0.45 (0.37, 0.54) Latinos at age 60: Exudative AMD: 1.28 (1.13, 1.45) Latinos at age 80: Exudative AMD: 0.89 (0.76, 1.05) Asian Americans at age 60: Exudative AMD: 1.08 (0.89, 1.31) Asian Americans at age 80: Exudative AMD: 0.54 (0.40, 0.73)	
Stein (2011) Prospecti ve cohort	44,103	Very Serious[1,2,3,5]	N/A	Not serious	Very Serious[7]	HR (95% CI)	Vietnamese: 0.70 (0.37, 1.35) Japanese: 0.64 (0.40, 1.04) Chinese: 0.95 (0.71, 1.27) Filipino: 1.18 (0.67, 2.09)	VERY LOW

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
							Korean: 0.97 (0.56, 1.66) Indian: 1.08 (0.71, 1.62) Pakistani: 0.45 (0.06, 3.21)	

1. Evidence of bias from study sample (for example, the paper is not clear about how many people were eligible for the study and were not included, there was no meaningful comparison between those included in the study and the population of interest for important differences)
2. Evidence of bias from study attrition (for example, the paper is not clear about how many people were lost to follow up in the study and/or had missing data, there was no meaningful comparison between those lost to follow up or with missing data in the study and the rest of the included sample)
3. Evidence of bias from prognostic factor measurement (for example, the paper is not clear about how the factor was measured, factors that require definition (e.g. hypertension) were not defined, arbitrary or questionable cut off points were used for continuous values)
4. Evidence of bias from confounding factor measurement (for example, the paper is not clear about how the confounding factors were measured, it is not clear which confounders were adjusted for in analysis, not all the important confounders were adjusted for)
5. Evidence of bias from outcome measurement (for example, the paper is not clear about how the outcome was measured and what investigations were used, there appears to be no masking or confirmation with multiple readers, outcomes were taken from healthcare database codes where there is likely to be inconsistency in measurement or definition)
6. Downgraded one level for non-significant effect
7. Downgraded two levels for confidence interval crossing 2 lines of a defined minimal important difference

Diet and nutrition

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
Alcohol use (<1 drink/week as reference category)								
Ajani (1999) Prospective cohort	21,041	Very serious[1,2]	N/A	Not serious	Serious[4]	HR (95% CI)	1 drink/week: 1.12 (0.47, 2.68) 2-4 drinks/week: 0.88 (0.39, 1.96) 5-6 drinks/week: 1.20 (0.52, 2.78)	VERY LOW

Studies	Sample size	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect measure	Effect size	Quality
							≥1 drink/day: 1.33 (0.70, 2.50)	
Daily Alcohol consumption, g (0 as reference category)								
Boekhoorn (2008) Prospective cohort	4,229	Serious[1,3]	N/A	Not serious	Serious[4]	HR (95% CI)	≤10: 0.96 (0.45, 2.03) >10 to ≤20: 0.60 (0.21, 1.72) >20: 0.40 (0.13, 1.25)	LOW

1. Evidence of bias from study attrition (for example, the paper is not clear about how many people were lost to follow up in the study and/or had missing data, there was no meaningful comparison between those lost to follow up or with missing data in the study and the rest of the included sample)
2. Evidence of bias from outcome measurement (for example, the paper is not clear about how the outcome was measured and what investigations were used, there appears to be no masking or confirmation with multiple readers, outcomes were taken from healthcare database codes where there is likely to be inconsistency in measurement or definition)
3. Evidence of bias from study sample (for example, the paper is not clear about how many people were eligible for the study and were not included, there was no meaningful comparison between those included in the study and the population of interest for important differences)
4. Downgraded one level for non-significant effect