Tremfya® ▼
(guselkumab)

Demonstrated sustained relief in Psoriasis at 5 years and in Psoriatic Arthritis at 2 years*[1,2]

COMPLETE SKIN CLEARANCE

- **At Week 16:** PASI 100 achieved in more than 1/3 of PsO patients treated with TREMFYA®.†[3]
- **Long term:** PASI 100 response rate of over 50% at Week 52 sustained at 5 years in PsO patients treated with TREMFYA®.†[1]

RAPID JOINT EFFICACY

- **At Week 4:** ACR20 achieved in 20% of PsA patients treated with TREMFYA®.[2]
- **Long term:** 74% ACR20 response rate seen at 1 year and sustained at 2 years in PsA patients treated with TREMFYA®.¶[2,4]

PROVEN DURABILITY

- Most patients who started on TREMFYA®, stayed on TREMFYA® long-term.[2,5]

To access educational videos, clinical papers, patient support and more visit **https://www.janssenmedicalcloud.co.uk/** or scan the QR code.

*Sustained improvements in psoriasis disease severity (as measured by PASI 90 and PASI 100 scores) and sustained improvements in psoriatic arthritis disease severity (as measured by ACR scores, HAQ-DI scores and resolution of enthesitis and dactylitis).[1,2] †PASI 100 analysis not part of the statistical analysis plan. 37.4% of patients treated with TREMFYA® achieved PASI 100 at Week 16 (n=329) vs 0.6% of patients treated with placebo (n=174; p<0.001; Non-responder imputation [NRI]).[3] ‡Patients achieving PASI 100 at Week 52: 50.5% (Treatment failure rules [TFR]), 51.3% (As observed), and 47.1% (NRI). In patients randomised to TREMFYA® at baseline. Patients achieving PASI 100 at Week 252: 51% (TFR), 52.8% (As observed) and 39.5% (NRI).[1] ¶In patients treated with TREMFYA® q8w. 74.6% (n=248) of TREMFYA® q8w patients achieved ACR20 at 1 year, and 74% (n=248) of TREMFYA® q8w patients achieved ACR20 at 2 years (NRI).[2,4] Complete skin clearance: Psoriasis Area and Severity Index [PASI] 100.[6] ACR20 – 20% improvement in a set of core measures: tender joint count, swollen joint count, patient's assessment of pain, patient's global assessment of disease activity, physician's assessment of physical function, patient's assessment of physical function and acute-phase reactant value.[7] Durability, also known as patient retention or drug survival, is a combination of efficacy, safety, tolerability and patient satisfaction or preference.[8] VOYAGE 1 was a Phase 3, double-blind, placebo- and active comparator-controlled clinical trial that evaluated the efficacy and safety of TREMFYA® in patients with moderate-to-severe plaque psoriasis.[1] DISCOVER-2 was a Phase 3, double-blind, multi-centre, placebo-controlled clinical trial that evaluated the efficacy and safety of TREMFYA® in bio-naïve patients with active PsA.[9] TREMFYA® is indicated for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy.[10] TREMFYA®, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy.[10]

References: 1. Griffiths CEM, et al. Maintenance of Response Through 5 Years of Continuous Guselkumab Treatment: Results From the Phase 3 VOYAGE 1 Trial. Presented at the 16th Annual Coastal Dermatology Symposium. October 15-16, 2020. **2.** McInnes IB, et al. Arthritis Rheumatol. 2021 Nov 1. doi: 10.1002/art.42010. **3.** Blauvelt A, et al. J Am Acad Dermatol 2017;76:405-417. **4.** McInnes IB, et al. Arthritis Rheumatol. 2021;73:604-616. **5.** Blauvelt A, et al. J Am Acad Dermatol 2021;S0190-9622:02816-4. **6.** Strober B, et al. J Am Acad Dermatol 2016;75:77-82.e7. **7.** Felson DT, LaValley MP. Arthritis Res Ther 2014;16:101. **8.** Geale K, et al. Rheumatol Adv Pract 2020;4:rkaa070. **9.** Mease PJ, et al. Lancet 2020;395:1126-1136 (Including supplementary appendix). **10.** TREMFYA® (guselkumab) 100 mg Summary of Product Characteristics.

ACR, American College of Rheumatology; **HAQ-DI**, Health Assessment Questionnaire - Disability Index; **PASI**, Psoriasis Area and Severity Index; **PsA**, psoriatic arthritis; **PsO**, psoriasis; **q8w**, every 8 weeks.

Tremfya▼ 100 mg solution for injection in pre-filled pen
PRESCRIBING INFORMATION
ACTIVE INGREDIENT(S): Guselkumab
Please refer to Summary of Product Characteristics (SmPC) before prescribing. **INDICATION(S):** Treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. Treatment of active psoriatic arthritis in adult patients, alone or in combination with methotrexate, who have had an inadequate response or have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy. **DOSAGE & ADMINISTRATION:** For use under guidance/supervision of physician experienced in diagnosis and treatment of conditions for which Tremfya is indicated. Subcutaneous injection. Avoid areas showing psoriasis. **Adults:** For both indications, 100 mg at weeks 0 and 4, followed by maintenance dose every 8 weeks. In the case of psoriatic arthritis, for patients at high risk for joint damage according to clinical judgement, consider a dose of 100 mg every 4 weeks. Consider discontinuation if no response after 16 weeks of treatment for plaque psoriasis and after 24 weeks for psoriatic arthritis. **Children:** No data available in children/adolescents <18 years. **Elderly:** No dose adjustment required, limited information in subjects aged ≥ 65 years, very limited information > 75 years. **Renal & Hepatic impairment:** Not studied. **CONTRAINDICATIONS:** Serious hypersensitivity to active substance or excipients; clinically important, active infection. **Refer to SmPC for full list of excipients. SPECIAL WARNINGS & PRECAUTIONS:** ***Infections:*** Potential to increase risk. If signs/symptoms of clinically important chronic/acute infection occur, monitor closely and discontinue Tremfya until resolved. ***Tuberculosis:*** Evaluate patients for TB pre-treatment; monitor for signs/symptoms of active TB during and after treatment. Consider anti-TB therapy prior to Tremfya if past history of latent/active TB and adequate treatment course not confirmed. ***Serious hypersensitivity reaction:*** Includes anaphylaxis. Some serious hypersensitivity reactions occurred several days after treatment and included urticaria and dyspnoea. If occurs, discontinue Tremfya immediately and initiate appropriate therapy. ***Hepatic Transaminase Elevations:*** An increased incidence of liver enzyme elevations has been observed in patients treated with Tremfya q4w compared to patients treated with Tremfya q8w or placebo. When prescribing Tremfya q4w in psoriatic arthritis, consider evaluating liver enzymes at baseline and thereafter according to routine patient management. If increases in ALT or AST are observed and drug-induced liver injury is suspected, Tremfya should be temporarily interrupted until this diagnosis is excluded. ***Immunisations:*** Consider completing all appropriate immunisations prior to Tremfya. Do not use live vaccines concurrently with Tremfya; no data available; before live vaccination, withhold Tremfya for at least 12 weeks and resume at least 2 weeks after vaccination. **SIDE EFFECTS: Very common:** Respiratory tract infection. **Common:** headache, diarrhoea, arthralgia, injection site reactions, transaminases increased. **Other side effects:** hypersensitivity, anaphylaxis, rash, gastroenteritis, herpes simplex infections, tinea infections, neutrophil count decreased, urticaria. **Refer to SmPC for more detail on side effects. PREGNANCY:** Avoid use of Tremfya; no data. Women of childbearing potential should use effective contraception during and for at least 12 weeks after treatment. **LACTATION:** It is unknown whether guselkumab is excreted in human milk. A decision should be made to discontinue, or abstain from initiating treatment with Tremfya taking into account the benefit of breast-feeding to the child and the benefit of Tremfya therapy to the woman. **INTERACTIONS:** No dose adjustment when co-administering with CYP450 substrates. Concomitant immunosuppressive therapy or phototherapy not evaluated. **Refer to SmPC for full details of interactions. LEGAL CATEGORY:** Prescription Only Medicine (POM) **PRESENTATIONS, PACK SIZES, MARKETING AUTHORISATION NUMBER(S) & BASIC NHS COSTS**

PRESENTATIONS	PACK SIZES	MARKETING AUTHORISATION NUMBER(S)	BASIC NHS COSTS
Pre-filled pen (100mg)	X 1	NI: EU/1/17/1234/002 GB: PLGB 00242/0665	£2250

MARKETING AUTHORISATION HOLDER: Northern Ireland: Janssen-Cilag International NV, Turnhoutseweg 30, B-2340 Beerse, Belgium. Great Britain: Janssen-Cilag Limited, 50-100 Holmers Farm Way, High Wycombe, Buckinghamshire, HP12 4EG, UK **FURTHER INFORMATION IS AVAILABLE FROM:** Janssen-Cilag Limited, 50-100 Holmers Farm Way, High Wycombe, Buckinghamshire, HP12 4EG, UK. Prescribing information last revised: June 2021

Adverse events should be reported. ▼This medicinal product is subject to additional monitoring and it is therefore important to report any suspected adverse events related to this medicinal product. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Janssen-Cilag Limited on 01494 567447 or at dsafety@its.jnj.com.

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Independent evaluation of melanoma polygenic risk scores in UK and Australian prospective cohorts*

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Summary

Background Previous studies suggest that polygenic risk scores (PRSs) may improve melanoma risk stratification. However, there has been limited independent validation of PRS-based risk prediction, particularly assessment of calibration (comparing predicted to observed risks).

Objectives To evaluate PRS-based melanoma risk prediction in prospective UK and Australian cohorts with European ancestry.

Methods We analysed invasive melanoma incidence in the UK Biobank (UKB; n = 395 647, 1651 cases) and a case-cohort nested within the Melbourne Collaborative Cohort Study (MCCS, Australia; n = 4765, 303 cases). Three PRSs were evaluated: 68 single-nucleotide polymorphisms (SNPs) at 54 loci from a 2020 meta-analysis (PRS68), 50 SNPs significant in the 2020 meta-analysis excluding UKB (PRS50) and 45 SNPs at 21 loci known in 2018 (PRS45). Ten-year melanoma risks were calculated from population-level cancer registry data by age group and sex, with and without PRS adjustment.

Results Predicted absolute melanoma risks based on age and sex alone underestimated melanoma incidence in the UKB [ratio of expected/observed cases: E/O = 0·65, 95% confidence interval (CI) 0·62–0·68] and MCCS (E/O = 0·63, 95% CI 0·56–0·72). For UKB, calibration was improved by PRS adjustment, with PRS50-adjusted risks E/O = 0·91, 95% CI 0·87–0·95. The discriminative ability for PRS68- and PRS50-adjusted absolute risks was higher than for risks based on age and sex alone (Δ area under the curve 0·07–0·10, $P < 0·0001$), and higher than for PRS45-adjusted risks (Δ area under the curve 0·02–0·04, $P < 0·001$).

Conclusions A PRS derived from a larger, more diverse meta-analysis improves risk prediction compared with an earlier PRS, and might help tailor melanoma prevention and early detection strategies to different risk levels. Recalibration of absolute risks may be necessary for application to specific populations.

study design, data collection, data analysis, manuscript preparation or publication decisions.

Conflicts of interest

The authors declare they have no conflicts of interest.

Data availability

Bona fide researchers can apply to access the UK Biobank data for health-related research that is in the public interest as described on the UK Biobank website (https://www.ukbiobank.ac.uk/enable-your-research). The MCCS data can be made available on request to pedigree@cancervic.org.au.

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*Plain language summary available online

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Polygenic risk scores (PRSs) aggregate the effects of many genetic variants across the genome into a single score aiming to reflect an individual's genetic risk of disease. PRSs are increasingly showing potential for risk-stratified cancer prevention, early detection and screening.[1–4] This includes cutaneous melanoma, a relatively lethal form of skin cancer with a high and growing global burden: there were an estimated >324 000 new invasive melanoma diagnoses and > 57 000 deaths worldwide in 2020, predicted to rise to >424 000 new invasive diagnoses and > 84 000 deaths in 2040.[5] While around 75% of melanomas globally have been attributed to excess ultraviolet radiation exposure,[6] multiple other risk factors are known, including number of naevi (e.g. 3·63-fold relative risk for people with at least one atypical naevus)[7] and genetic predisposition.[8–10] Previous case–control studies have shown that incorporating melanoma PRS into risk prediction models improves discriminatory accuracy compared with models using only traditional risk factors.[11,12]

The lack of proper evaluation of model calibration using prospective cohorts has hindered the integration of PRS into risk assessment for clinical and public health practice.[13,14] Calibration measures the agreement between the predicted risks from the model and the observed risks in a population. A poorly calibrated model could lead to under- or overscreening of individuals in a risk-stratified screening programme, reducing the programme's benefits and cost-effectiveness. To date, calibration of PRS-based predicted absolute melanoma risks has not been assessed.[12,15] This is important because absolute risks (e.g. 10-year risk) are commonly used for risk communication in clinical settings and to determine eligibility in national cancer screening programmes.[16]

Recently, a larger and more population-diverse melanoma genome-wide association study (GWAS) increased the number of known susceptibility variants to 68 independent associations located in 54 genetic regions (loci),[10] more than doubling the number of known risk loci compared with an earlier GWAS and PRS [with 45 single-nucleotide polymorphisms (SNPs) at 21 loci included in the PRS in a 2018 study].[12] Therefore, it is also of interest to compare the risk prediction performance of the previously proposed PRS with an analogous PRS based on the new GWAS.

To address these research questions, we evaluated different PRS-based predicted melanoma risks in prospective UK and Australian cohorts, assessing their associations with melanoma, calibration and discriminative ability.

Patients and methods

Study samples

The UK Biobank[17] (UKB) is a prospective cohort study of around 500 000 participants recruited in 2006–2010 ('baseline'). Deaths and invasive melanoma diagnoses, the primary outcome, were ascertained using linkage to death and cancer registry records (Appendix S1; see Supporting Information). Records were censored for completeness on 31 March 2016 and 31 October 2015 for participants recruited in England/Wales and Scotland, respectively. All participants were genotyped, with further genotype imputation described previously.[17]

The prospective Melbourne Collaborative Cohort Study[18] (MCCS) recruited 41 513 Melbourne residents in 1990–1994. To broaden the range of measured lifestyle exposures, particularly Mediterranean diet, there was an increased effort to recruit Greek and Italian migrants. A sub-cohort was defined by randomly selecting 4710 participants from those who attended the second follow-up wave in 2003–2007 ('baseline' for the current analysis). Records of deaths and invasive melanoma diagnoses were ascertained using linkage to death and cancer registries (Appendix S1), and were censored for completeness on 30 June 2016. Sub-cohort members and all MCCS participants who developed invasive melanoma within 10 years of the second follow-up visit and before 30 June 2016 were genotyped, followed by imputation of additional genetic variants (Appendix S1).

In both studies, we applied extensive quality control to genetic data, and excluded non-European participants and those with melanoma diagnosis before baseline (Appendix S1). We ascertained participants' self-reported sex, ethnicity, ease of tanning [noting that the 'ethnic group(s)' question in MCCS has also been interpreted as country of birth] and age at baseline. The first 20 genetic principal components (PCs) were calculated to account for potential population stratification (i.e. confounding of genetic associations by ancestry). For UKB, we also obtained information on skin and hair colour, education and the postcode-based Townsend Deprivation Index (derived from national census data on unemployment, car ownership, home ownership and overcrowding; see Appendix S1).[19]

All participants provided informed consent at recruitment. UKB was approved by the North West Centre for Research Ethics Committee (11/NW/0382) and the MCCS by the Cancer Council Victoria Human Research Ethics Committee.

Polygenic risk scores

We calculated three PRSs based on: (i) 68 SNPs at 54 loci from a 2020 meta-analysis[10] (PRS68); (ii) 50 SNPs at 42 loci significant in the 2020 meta-analysis after exclusion of UKB participants to avoid overfitting and to ensure a truly independent validation dataset (PRS50); and (iii) 45 SNPs at 21 loci as analysed in a 2018 study[12] (PRS45). Table S1 (see Supporting Information) shows all of the variants in the three PRSs, and their odds ratios and allele frequencies. After quality control, the UKB data included all variants for the three PRSs, while the MCCS data included 66, 49 and 43 variants for PRS68, PRS50 and PRS45, respectively. We followed a previously described approach[20] to determine genotype-specific relative risks at each variant, then used genotype dosages and a log-additive model to obtain a PRS-specific relative risk for each participant and each PRS (Appendix S1).

Statistical methods

Population-average and polygenic risk score-adjusted predicted absolute melanoma risks

DevCan v6·7·8 was used to calculate sex-and-age-specific absolute 10-year risks of melanoma, with 5-year groupings for age, adjusting for death as competing risk.[21] The calculation was performed using population-wide cancer incidence, and cancer and all-cause mortality data from each of Victoria (Australia), Scotland and England/Wales (Appendix S1). For Victoria, we used data for 2009–2013; for Scotland and England/Wales, we performed separate calculations using data for 2001–2005, 2006–2010 and 2011–2015. UKB participants were assigned absolute risks for Scotland if recruited in Glasgow or Edinburgh, and risks for England/Wales otherwise. We rescaled the 10-year absolute risks for each participant to account for different individual follow-up times (Appendix S1). PRS-adjusted predicted absolute melanoma risks were obtained by multiplying the corresponding sex-and-age-specific absolute risks by the participants' PRS-specific relative risk (separately for each PRS).

Association between polygenic risk scores and participant characteristics

Associations between each PRS (log transformed) and participant characteristics were calculated using multivariable generalized linear regression models (R function 'glm') that included age, sex, ethnicity, ease of tanning and 20 PCs; and univariable models separately for age, sex, ethnicity and ease of tanning. For UKB, we also evaluated associations of PRS with skin and hair colour, education and the Townsend Deprivation Index (using univariable and multivariable models). To account for multiple testing, a Bonferroni multiple-testing correction for 28 tests and the three PRSs was applied (significance at $P < 0{\cdot}0006$).

Association between polygenic risk scores and melanoma incidence

Associations between the PRS (log transformed) and melanoma incidence were evaluated using Fine–Gray competing risks regression with death as the competing risk, adjusting for age, sex, ethnicity, ease of tanning and 20 PCs. The function 'crr' (R package 'cmprsk') was used to calculate subhazard ratios (SHRs) and 95% confidence intervals (CIs). To facilitate comparisons with other studies, we calculated SHRs per 1 SD of each PRS (for MCCS, SD was based on sub-cohort participants). Significance was defined at $P < 0{\cdot}017$, applying a Bonferroni multiple-testing correction for the three PRSs. We compared the fully adjusted results to the unadjusted and partially adjusted results, and also tested the association for PRS risk quintiles and deciles (Appendix S1). For the MCCS, the results were verified using a weighted Cox regression model designed for case-cohort studies (Appendix S1).

Calibration

Calibration of unadjusted (age-and-sex-specific) and PRS-adjusted predicted absolute risks was evaluated by comparing the expected ('E') with the observed ('O') numbers of melanoma cases ('E/O' ratio) for all participants and separately for male and female participants, overall and for each risk quintile (Appendix S1). Robust 95% CIs were used for the MCCS case-cohort design.[22] Calibration of risk quintiles was further evaluated after rescaling of risks to achieve $E/O = 1$ overall (separately for male and female participants). For UKB, calibration by Townsend Deprivation Index quartiles was also assessed.

Discrimination

The area under the receiver operating characteristic curve (AUC) was calculated for the PRS-based relative risk, as well as the unadjusted (age-and-sex-specific) and PRS-adjusted predicted absolute risks (Appendix S1). The AUC represents the probability that the predicted risk is higher for a randomly chosen case than a noncase, with 0·5 corresponding to random ranking and 1·0 to perfect discrimination. P values for AUC comparisons were obtained using the Delong test for correlated curves (function 'roc.test', R package 'pROC'). We also calculated the classification true and false positive rates, true and false

negative rates, sensitivity, specificity and positive and negative likelihood ratios at 5%, 10%, . . . and 95% risk thresholds.

R^2 on the liability scale

We converted the AUC values for the PRS relative risk, as well as the unadjusted and PRS-adjusted absolute risks, to the explained variation (R^2) on the liability scale[23] (Appendix S1).

Estimated 10-year absolute risks by PRS quintile and age

To illustrate risk stratification, the predicted absolute 10-year melanoma risk by PRS50 quintile was estimated based on the association results in the UKB and MCCS (Appendix S1).

Results

After quality checks, we analysed genetic and phenotypic data from 395 647 UKB participants and, separately, 4765 MCCS participants (Table 1 and Table S2; see Supporting Information). Of these UKB participants, 1651 (0·4%) were diagnosed with invasive melanoma during the follow-up period (median 7·2 years, interquartile range 6·5–7·8). The MCCS case-cohort included 303 participants diagnosed with melanoma in the 10 years following the baseline for this study. Figure S1 (see Supporting Information) shows the PRS distributions in cases and noncases.

Associations of melanoma polygenic risk score with participant characteristics including traditional melanoma risk factors

In both cohorts, all three PRSs were strongly and consistently associated with self-reported ease of tanning (Table S3; see Supporting Information). We also found multiple associations between the PRS and genetic PCs (Table S3). In the UKB, skin and hair colour were also highly associated with all three PRSs

Table 1 Characteristics of UK Biobank and Melbourne Collaborative Cohort Study participants

UK Biobank			
	Cohort (n = 395 647)	Cases (n = 1651)	
Incident melanoma cases, n (%)	1651 (0·4)	1651 (100)	
Death before melanoma, n (%)	11 832 (3·0)	0 (0)	
Sex male, n (%)	183 417 (46·4)	815 (49·4)	
Age (years), mean (SD)	56·9 (8·0)	59·0 (7·5)	
Follow-up time (years), mean (SD)	7·2 (0·79)	7·3 (0·81)	
Ethnicity, n (%)			
British	378 305 (95·6)	1588 (96·2)	
Irish	11 375 (2·9)	45 (2·7)	
White or any other white background	5965 (1·5)	18 (1·1)	
Missing	2 (0·0)	0 (0)	
Ease of tanning, n (%)			
Never tan, only burn	69 500 (17·6)	343 (20·8)	
Mildly or occasionally tanned	83 561 (21·1)	400 (24·2)	
Moderately tanned	156 426 (39·5)	641 (38·8)	
Very tanned	78 190 (19·8)	244 (14·8)	
Not stated	7970 (2·0)	23 (1·4)	
Melbourne Collaborative Cohort Study			
	All participants with follow-up 2 visit (n = 20 556)	**Sub-cohort (n = 4528)**	**Cases (n = 303)**
Incident melanoma cases, n (%)	304 (1·5)	66 (1·5)	303 (100)
Death before melanoma, n (%)	2585 (12·6)	343 (7·6)	0 (0)
Sex male, n (%)	8047 (39·1)	1737 (38·4)	178 (58·7)
Age (years), mean (SD)	63·5 (7·2)	63·4 (7·2)	65·0 (6·9)
Follow-up time (years), mean (SD)	9·7 (1·3)	9·7 (1·2)	9·6 (1·5)
Ethnicity, n (%)			
Australian or New Zealand[a]	15 387 (74·9)	3400 (75·1)	277 (91·4)
British, Irish	1459 (7·1)	316 (7·0)	16 (5·3)
Greek, Italian, Maltese	3705 (18·0)	812 (17·9)	10 (3·3)
Any other white background	5 (0·0)	0 (0)	0 (0)
Ease of tanning, n (%)			
Burn, rarely tan	4940 (24·0)	1095 (24·2)	85 (28·1)
Burn, then tan	10 111 (49·2)	2230 (49·2)	163 (53·8)
Tan, rarely burn	5505 (26·8)	1203 (26·6)	55 (18·2)

[a]Participants with non-European ancestry were excluded, so participants who self-reported Australian or New Zealand ethnicity in the Melbourne Collaborative Cohort Study were descended from European migrants.

Table 2 Associations between melanoma polygenic risk score (PRS) and melanoma incidence, after adjustment for traditional risk factors and genetic principal components (all P values are significant after Bonferroni multiple-testing correction). For associations per PRS quintile and decile, see Table S5 and Figure S2 in the Supporting Information

		UK Biobank		MCCS	
Covariates	PRS	SHR[a] (95% CI)	P value	SHR[a] (95% CI)	P value
Age, sex	PRS68	1·78 (1·70–1·86)	$< 1 \times 10^{-15}$	1·65 (1·49–1·83)	$< 1 \times 10^{-15}$
	PRS50	1·72 (1·65–1·80)	$< 1 \times 10^{-15}$	1·64 (1·48–1·82)	$< 1 \times 10^{-15}$
	PRS45	1·61 (1·54–1·68)	$< 1 \times 10^{-15}$	1·42 (1·28–1·58)	$5{\cdot}7 \times 10^{-11}$
Age, sex, ethnicity	PRS68	1·78 (1·71–1·87)	$< 1 \times 10^{-15}$	1·51 (1·35–1·68)	$9{\cdot}5 \times 10^{-14}$
	PRS50	1·72 (1·65–1·80)	$< 1 \times 10^{-15}$	1·50 (1·35–1·67)	$1{\cdot}5 \times 10^{-13}$
	PRS45	1·61 (1·54–1·68)	$< 1 \times 10^{-15}$	1·29 (1·16–1·45)	$7{\cdot}7 \times 10^{-6}$
Age, sex, ethnicity, ease of tanning, 20 genetic PCs	PRS68	1·80 (1·71–1·88)	$< 1 \times 10^{-15}$	1·47 (1·31–1·67)	$3{\cdot}6 \times 10^{-10}$
	PRS50	1·73 (1·65–1·81)	$< 1 \times 10^{-15}$	1·47 (1·30–1·66)	$5{\cdot}4 \times 10^{-10}$
	PRS45	1·61 (1·53–1·69)	$< 1 \times 10^{-15}$	1·25 (1·10−1·42)	$6{\cdot}2 \times 10^{-4}$
Age, sex, ethnicity, ease of tanning, 20 genetic PCs, education, Townsend Deprivation Index	PRS68	1·80 (1·71–1·89)	$< 1 \times 10^{-15}$	–	–
	PRS50	1·73 (1·65–1·81)	$< 1 \times 10^{-15}$	–	–
	PRS45	1·61 (1·54–1·69)	$< 1 \times 10^{-15}$	–	–
Age, sex, ethnicity, ease of tanning, 20 genetic PCs, skin colour, hair colour	PRS68	1·74 (1·65–1·83)	$< 1 \times 10^{-15}$	–	–
	PRS50	1·67 (1·59–1·76)	$< 1 \times 10^{-15}$	–	–
	PRS45	1·55 (1·47–1·63)	$< 1 \times 10^{-15}$	–	–
Age, sex, ethnicity, ease of tanning, 20 genetic PCs, education, Townsend Deprivation Index, skin colour, hair colour	PRS68	1·74 (1·66–1·83)	$< 1 \times 10^{-15}$	–	–
	PRS50	1·67 (1·60–1·76)	$< 1 \times 10^{-15}$	–	–
	PRS45	1·55 (1·47–1·63)	$< 1 \times 10^{-15}$	–	–

CI, confidence interval; MCCS, Melbourne Collaborative Cohort Study; PC, principal component; SHR, subhazard ratio. [a]SHR per 1 SD of PRS on a log scale, with death as competing risk (for the MCCS, the SD was based on sub-cohort participants).

(Table S4; see Supporting Information). Self-reported ethnicity was associated with the PRS in univariable analyses, but not in multivariable analyses that adjusted for genetic PCs (Appendix S1 and Table S4; see Supporting Information).

Association of melanoma polygenic risk score with melanoma incidence

All three PRSs were associated with melanoma incidence (Table 2), with generally stronger associations in the UKB than in the MCCS (e.g. nonoverlapping 95% CIs for the PRS68 and PRS45 fully adjusted SHR estimates). Moreover, in both cohorts, the PRS45 SHR estimates were smaller than, and outside the 95% CIs for the PRS50 and PRS68 estimates; the fully adjusted SHRs per 1 SD of PRS45, PRS50 and PRS68 were 1·61, 1·73 and 1·80 in the UKB, and 1·25, 1·47 and 1·47 in the MCCS, respectively.

In the UKB, associations between the PRS and melanoma incidence were robust to inclusion of different covariates, and only minimally (3–4%) attenuated when additionally adjusting for skin and hair colour. In the MCCS, associations between the PRS and melanoma incidence were slightly more attenuated (12–14%) by the inclusion of traditional melanoma risk factors and genetic PCs as covariates, but remained highly statistically significant.

We also considered the association of PRS quintiles and deciles with melanoma incidence (Figure S2 and Table S5; see Supporting Information). The results were consistent with the analysis of the PRS as a continuous score, with stronger associations observed in the UKB than in the MCCS (Appendix S1).

Calibration of absolute melanoma risks with and without polygenic risk score

We found that absolute 10-year melanoma risks calculated based on population-level cancer registry data have risen sharply in England/Wales over 2001–2015, especially for men and older age groups, with some increases also observed in Scotland (Figure S3; see Supporting Information). Nonetheless, we observed an underprediction of melanoma incidence in the UKB when using sex-and-age-specific risks based on 2001–2005, 2006–2010 and 2011–2015 population-level data, with ratios of expected to observed cases E/O being 0·41 (95% CI 0·39–0·43), 0·55 (0·53–0·58) and 0·65 (0·62–0·68), respectively (Table S6; see Supporting Information). The 2011–2015 period corresponds to the last 5 years of follow-up of UKB participants, so the absolute 10-year risks based on this period were used for further analysis.

We found that PRS68- and PRS50-adjusted absolute risks still underpredicted melanoma incidence in the UKB (E/O = 0·89, 95% CI 0·85–0·94, and E/O = 0·91, 95% CI 0·87–0·95, respectively (Figure 1a), but less so than the unadjusted risks based on age and sex alone. For PRS45-adjusted absolute risks the E/O was 0·73 (95% CI 0·70–0·77). The underprediction of risks was similar for men and women (Figures S4 and S5), and stronger for participants with higher socioeconomic status as quantified by the Townsend Deprivation Index (e.g. unadjusted absolute risks: least deprived quartile E/O = 0·57, 95% CI 0·52–0·62; most deprived quartile E/O = 0·85, 95% CI 0·76–0·95; Figure S6; see Supporting Information).

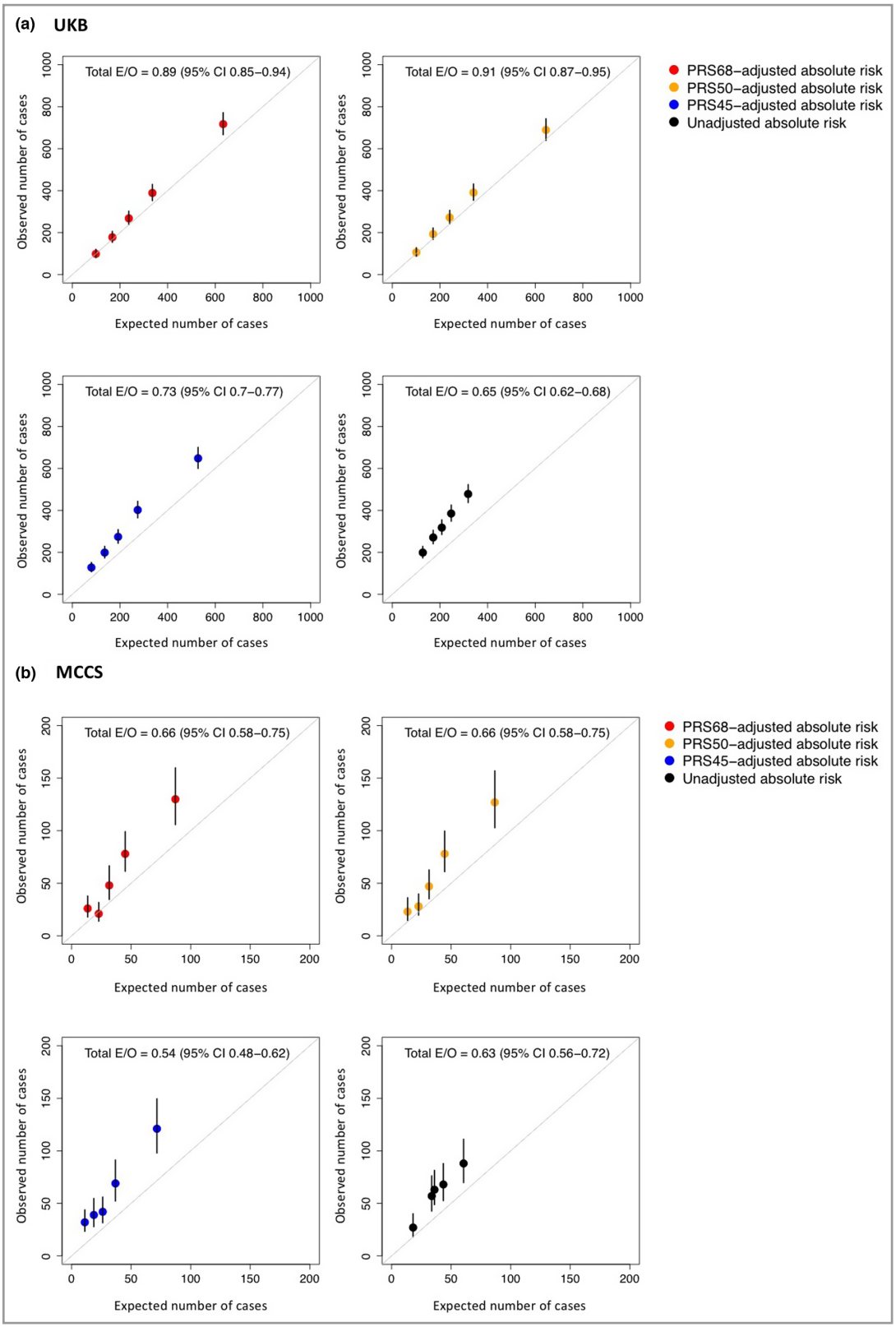

Figure 1 Calibration of polygenic risk score (PRS)-adjusted and unadjusted (based on age and sex only) absolute melanoma risks in the UK Biobank (UKB) and the Melbourne Collaborative Cohort Study (MCCS), by risk quintile. (a) Calibration of absolute melanoma risks in the UKB based on population-wide data for 2011–2015. (b) Calibration of absolute melanoma risks in the MCCS based on population-wide data for 2009–2013. Bars show 95% confidence intervals (CIs). E/O, expected/observed.

The calibration results were similar in the MCCS, where the sex-and-age-specific absolute melanoma risks based on population-wide cancer registry data for Victoria, Australia, also underestimated melanoma incidence (E/O = 0·63, 95% CI 0·56–0·72; Figure 1b). The PRS68- and PRS50-adjusted absolute risks resulted in similarly underpredicted incidence (both E/O = 0·66, 95% CI 0·58–0·75), and the underprediction was more pronounced for PRS45 (E/O = 0·54, 95% CI 0·48–0·62). Across unadjusted and PRS-adjusted risks, the underprediction was stronger for men than for women (Figures S4 and S5).

For PRS68 and PRS50, we did not find relative under- or overprediction by absolute risk quintile when recalibrating the mean overall absolute risks to E/O = 1 (Figure 2 and Appendix S1).

Discriminative ability of absolute melanoma risks with and without polygenic risk score

Figure 3 shows the discriminative ability of the unadjusted (age-and-sex-specific) and PRS-adjusted absolute risks, including sensitivity, specificity and AUC. In the UKB, PRS adjustment of absolute risks improved discrimination (AUC difference between PRS-adjusted and unadjusted risks for each of the three PRSs: ΔAUC 0·07–0·10, $P < 10^{-10}$). In the MCCS, the incremental improvement from PRS adjustment was smaller (ΔAUC 0·03–0·07, P < 0·0001 for PRS68 and PRS50, P = 0·07 for PRS45); however, the AUC for the unadjusted absolute risks was higher in the MCCS than in the UKB, resulting in similar AUCs for the PRS-adjusted absolute risks (0·69 for PRS68 in both cohorts). In both the UKB and the MCCS, the PRS68- and PRS50-adjusted absolute risks had higher discriminative ability than the PRS45-adjusted absolute risks (P < 0·0001).

At a threshold of the top predicted risk decile, the PRS68- and PRS50-adjusted absolute risks had >90% specificity and >24% sensitivity for predicting melanoma incidence in both the UKB and the MCCS (Appendix 1 and Table S7; see Supporting Information). At a threshold of the top predicted risk quartile, the PRS68- and PRS50-adjusted absolute risks had >75% specificity and >46% sensitivity for predicting melanoma incidence in both the UKB and the MCCS.

Explained variation on the liability scale

PRS68 explained ~5% variation on the liability scale, with similar estimates for PRS50 (~4·5%) and a slight decrease for PRS45 (2·1–3·7%; Appendix S1 and Table S8; see Supporting Information). PRS-adjusted absolute risks explained more variation than the unadjusted risks, for example PRS50-adjusted absolute risk 6·2% (95% CI 5·3–7·2%) in the UKB and 7·0% (4·8–9·6%) in the MCCS; unadjusted risks 1·4% (1·0–2·0%) and 3·0% (1·6–4·9%), respectively.

Estimated 10-year absolute risks by polygenic risk score quintile and age

Figure 4 shows the estimated 10-year absolute risks of melanoma by sex, age and top/bottom PRS50 quintile. The population-average 10-year risk of invasive melanoma at age 50 years was estimated to be reached 10–20 years earlier for those in the top PRS50 quintile, and 10–30 years later for those in the bottom PRS50 quintile.

Sensitivity analyses

The results presented above were robust to the factors assessed in multiple sensitivity analyses (Appendix S1).

Discussion

We evaluated the performance of three melanoma PRSs using data from large-scale UK and Australian cohorts. We found that PRS adjustment of age-and-sex-specific absolute risks determined from population data improved the discriminative ability of the risk prediction. The PRS68- and PRS50-adjusted sex-and-age-specific absolute risks in our study had AUCs of 0·68–0·69, suggesting moderate discriminative ability. Whether this discriminative accuracy would be sufficient for specific risk-stratified melanoma prevention or early detection approaches will depend on the benefits, harms and costs of the specific interventions. We have provided data on the sensitivity and specificity of the PRS-adjusted absolute risks at different risk thresholds to enable health-economic evaluations of risk-stratified strategies.

Our analysis of estimated absolute risks by age and top/bottom PRS50 quintile suggests that risk thresholds corresponding to the population-average risks at age 50 years might be reached 10–20 years earlier by individuals with the 20% highest PRS, and 10–20 years later by individuals with the 20% lowest PRS. The prediction could likely be improved by incorporating information from variants that do not meet genome-wide significance thresholds in association studies.[24] Due to extensive, population-dependent correlations between genetic variants (linkage disequilibrium), optimizing the set of variants used in a PRS and the weights allocated to them is an active area of research. The choice of method can be disease dependent (a reflection of different genetic architectures), so further work is needed to carry out a comprehensive comparison of different methods for melanoma.

Calibration of absolute melanoma risks was not straightforward, with age-and-sex-specific risks derived from population data (without consideration of PRS) underpredicting melanoma risks for participants of both cohorts. Adjustment of age-and-sex-specific risks by PRS reduced the underprediction, but further work will be required to build well-calibrated risk prediction models. Potential reasons for the underprediction include that our analyses were restricted to only participants with European ancestry, which could lead to higher melanoma incidence compared with the whole UK and Victorian populations. Increases in melanoma risks determined from population-wide data might also be due to changes in risk exposure and/or different diagnostic practices. Finally, the higher incidence of melanoma in UKB and MCCS participants than in the general population could reflect some

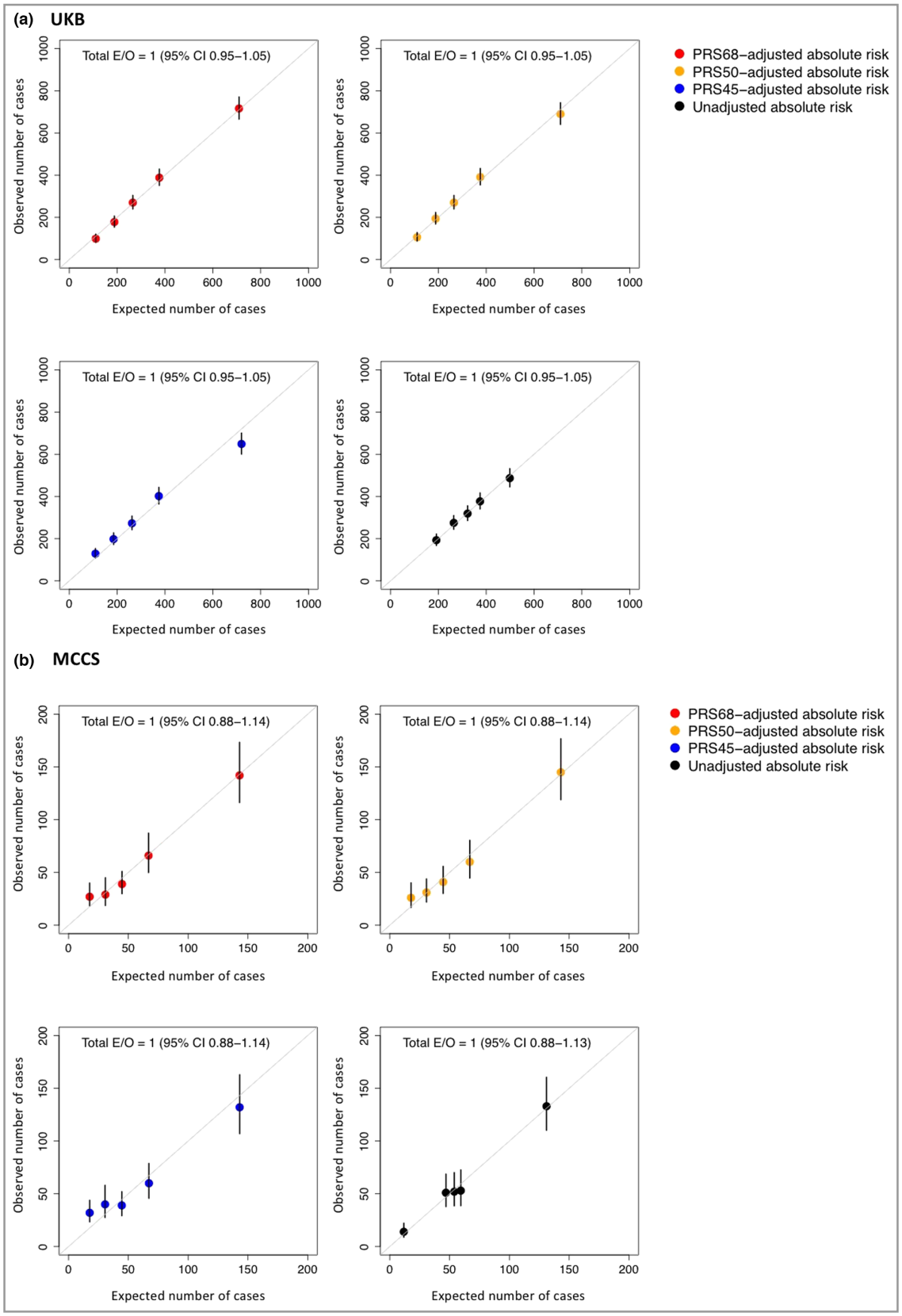

Figure 2 Calibration of absolute melanoma risks after rescaling to expected/observed (E/O) = 1 in (a) the UK Biobank (UKB) and (b) the Melbourne Collaborative Cohort Study (MCCS), by risk quintile. Bars show 95% confidence intervals (CIs).

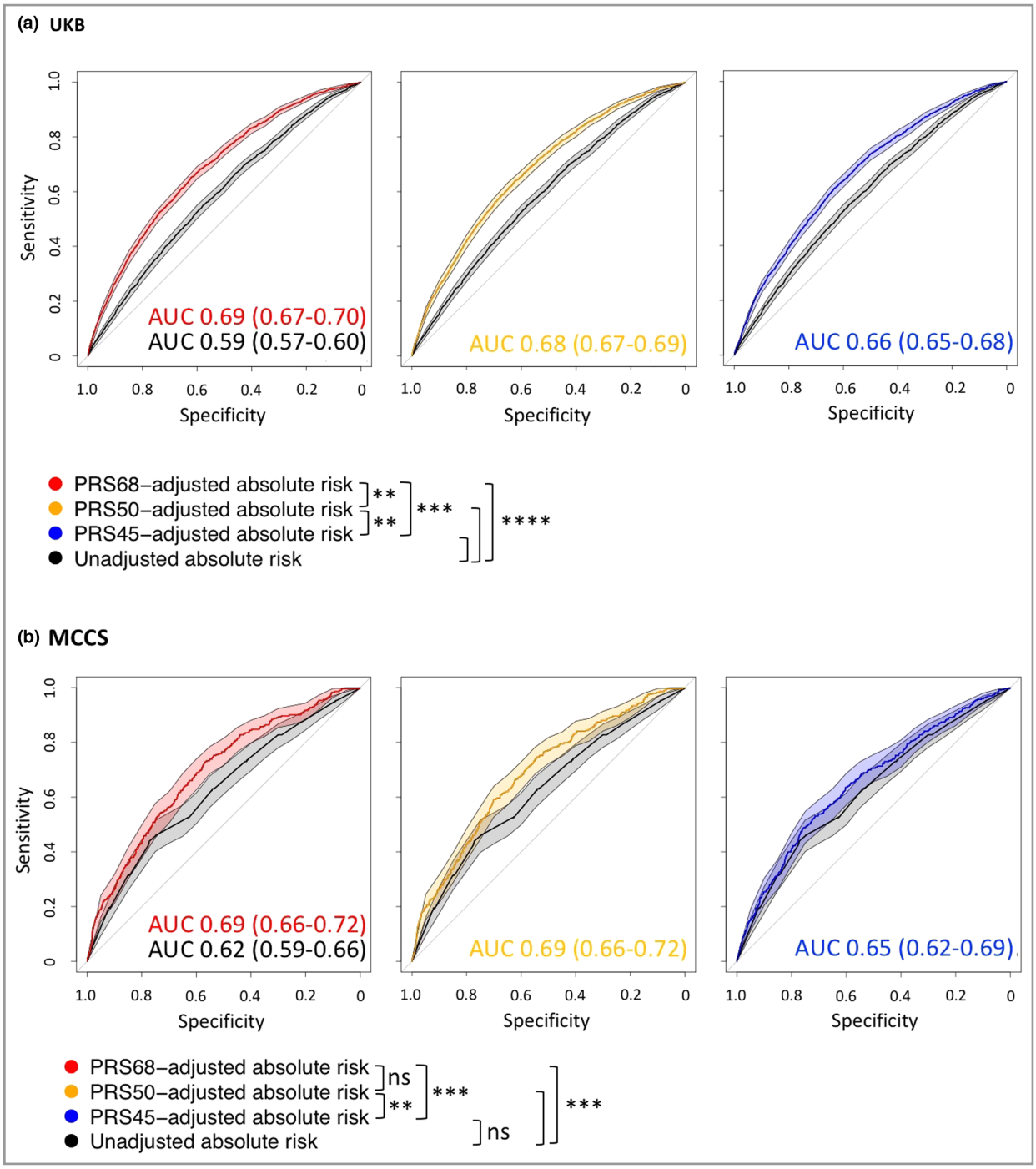

Figure 3 Polygenic risk score (PRS) adjustment improves the discriminative ability of absolute melanoma risks in (a) the UK Biobank (UKB) and (b) the Melbourne Collaborative Cohort Study (MCCS). Shaded areas indicate 95% confidence intervals. Absolute risks were calculated based on population-level cancer registry data, age and sex, with and without PRS adjustment. The straight diagonal line (grey) represents the line of no discrimination. AUC, area under the receiver operating characteristic curve (with 95% confidence interval). ns, $P > 0{\cdot}05$; **$P < 0{\cdot}001$; ***$P < 0{\cdot}0001$; ****$P < 10^{-10}$.

overdiagnosis in more health-seeking participants, as participants from both cohorts are more likely to have greater health literacy than the general population.[25] Melanoma incidence in the UKB was higher for participants with higher socioeconomic status, so over-representation of participants with higher socioeconomic status in the cohorts[25] could also contribute to the higher incidence than in the general population.

Comparing the three PRSs, we found that PRS68 performed slightly better than PRS50 in the UKB, as expected given that UKB data contributed to the meta-analysis from which PRS68

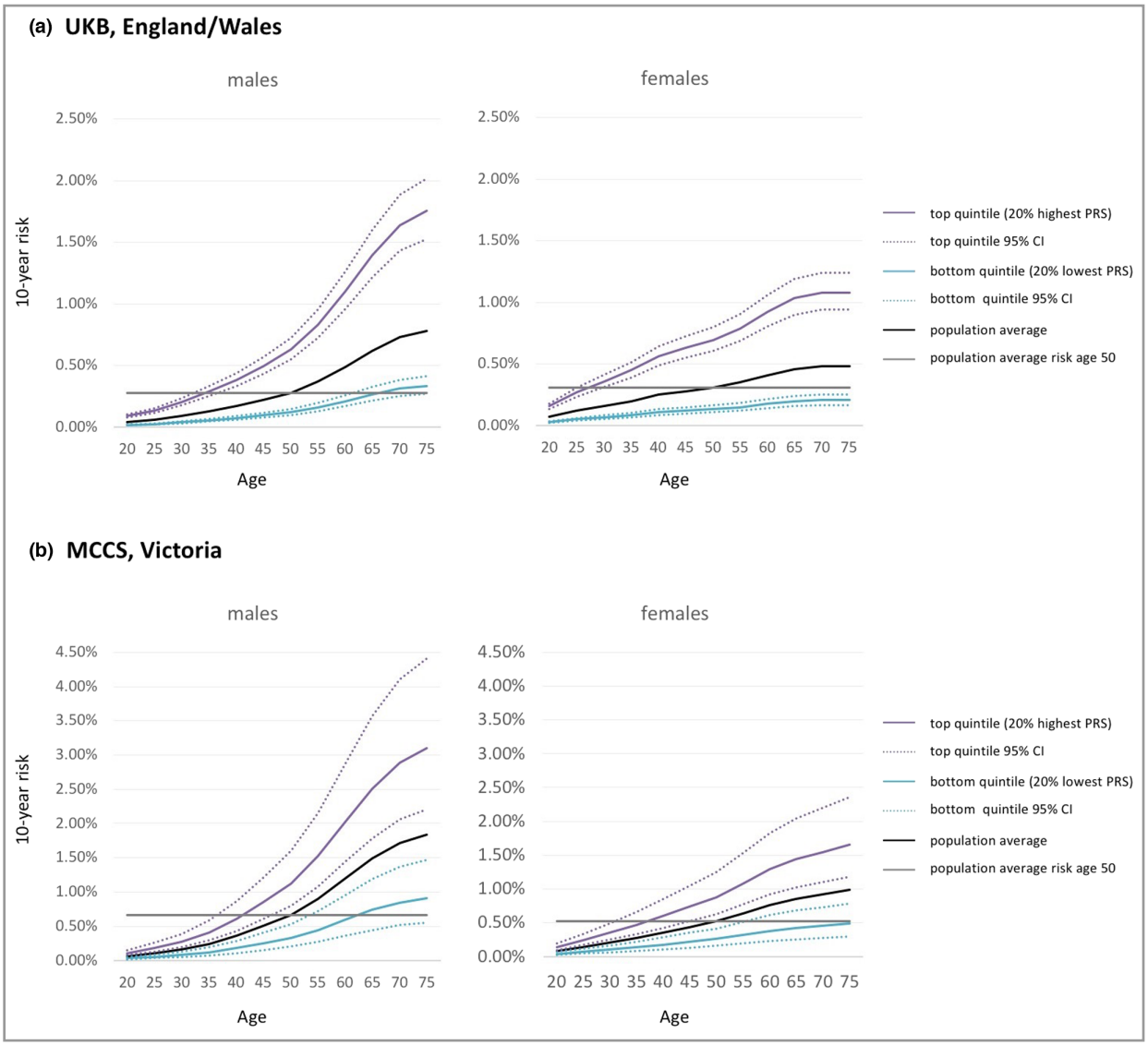

Figure 4 Estimated 10-year absolute melanoma risks and 95% confidence intervals (CIs) by the top or bottom PRS50 quintile and age based on data from (a) the UK Biobank and population-wide data for England/Wales, and (b) the Melbourne Collaborative Cohort Study and population-wide data for Victoria, Australia. (a) The estimated population-average 10-year risk of invasive melanoma for 50-year old men in England/Wales was 0·28%, which is estimated to be reached 15 years earlier and 15 years later for men in the top and bottom PRS50 quintiles, respectively. Similarly, the estimated population-average 10-year risk of melanoma for 50-year-old women in England/Wales was 0·31%, estimated to be reached more than 20 years earlier for those in the top PRS50 quintile, and not before age 80 years for those in the bottom quintile. The results were similar for Scotland. (b) For Victoria, the estimated population-average 10-year risk for 50-year-old men was 0·67%, estimated to be reached about 10 years earlier and 10 years later for those in the top and bottom quintiles, respectively. For women, the population-average 10-year risk at age 50 years was 0·52%, estimated to be reached 10 years earlier and not before age 80 years for those in the top and bottom PRS50 quintiles, respectively.

was derived. We did not see a difference in performance between PRS68 and PRS50 in the MCCS. This highlights the importance for independence between PRS construction and validation data.[24] To our knowledge, this is the first evaluation of the risk prediction performance of the PRS68 and PRS50 melanoma risk scores. A previous evaluation[12] of the PRS45 score in UK and Australia case–control studies, and a Southern European study[26] of a 204-variant score including non-genome-wide-significant variants based on pre-2020 data, found similar or slightly weaker associations of PRS with melanoma incidence. Other studies[27,28] evaluating melanoma PRS used smaller sets of variants (16–24) known prior to 2020. A 55-variant PRS based on the 2020 meta-analysis PRS has also been associated with melanoma risk (hazard ratio 1·46 per SD) in Australians aged ≥70 years,[15] but no assessment of calibration was performed.

Considering any melanoma risk models, a recent systematic review identified 46 different models from 40 publications, commonly using naevi (78% of models), but with little

consistency regarding other risk factors included.[29] Notably, only five publications assessed AUC using independent validation data. In four of five risk models with external validation, the 95% CIs for the validation AUC in the original publication or a later study overlapped the AUC estimates of 0·68–0·69 for the PRS50-adjusted absolute risks reported here (Appendix S1). Only one risk model incorporating clinically assessed factors had a higher external validation AUC (0·73, 95% CI 0·70–0·75; Appendix S1).[30] Thus, the discrimination of the models based on genomic risk factors, age and sex examined here is similar to externally validated phenotype-based risk models. Incorporating genomic risk information into the best available phenotype-based risk models might further improve risk prediction in the future.[12]

The PRS68 and PRS50 scores were based on a larger meta-analysis than the older studies underlying PRS45, and performed better than the PRS45, especially in the more ethnically diverse MCCS. The 2020 meta-analysis had improved representation of southern European populations compared with previous large-scale melanoma GWASs, which could improve melanoma risk predictions for countries with more diverse European ancestry such as Australia. Previous research[31,32] demonstrates the importance of increasing diversity of participants in genetic association studies that are used to construct PRSs, and failure to do so could lead to widening health disparities when PRSs are used in practice.

Our work has several limitations. We only included participants of European ancestry, so the results cannot be extrapolated to different populations. In the MCCS data, self-reported ethnicity could also reflect differences in migration status; for example, those selecting Australian ethnicity were perhaps more likely to be born in Australia and thus have higher underlying risk due to higher ambient ultraviolet radiation. The results from the MCCS had more uncertainty due to a smaller sample size.

Our work also has multiple strengths. We used data from two large prospective cohorts, ensuring that the evaluations of melanoma PRSs were valid in different settings. Moreover, we calculated absolute risks that include competing mortality risks, which is important to not overestimate melanoma risks for older age groups.[33] The results were reported according to best practice for PRS reporting,[34] and details for the PRS have been deposited in the Polygenic Score Catalog[35] to enable reuse. We also conducted thorough sensitivity analyses to verify the robustness of our results.

In conclusion, newer melanoma PRSs derived from a larger meta-analysis have better risk prediction performance than an earlier PRS, and could be used to tailor melanoma prevention and early detection strategies to different risk levels. Recalibration of 10-year absolute risks may be necessary when applied to specific populations. Ensuring that risk prediction models are well calibrated and that they can be applied to diverse populations remain key aspects for future research.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1 Supplementary methods and results.

Figure S1 Distribution of melanoma polygenic risk scores.

Figure S2 Association between melanoma polygenic risk score quintiles or deciles and melanoma incidence.

Figure S3 Relative increase in 10-year absolute melanoma risks calculated from cancer registry and population data for England/Wales and Scotland.

Figure S4 Calibration of absolute melanoma risks (by risk quintile) for male participants.

Figure S5 Calibration of absolute melanoma risks (by risk quintile) for female participants.

Figure S6 Calibration of absolute melanoma risks by risk quintile and Townsend Deprivation Index quartile in the UK Biobank.

Table S1 Variants included in the polygenic risk scores, with odds ratios and allele frequencies.

Table S2 Characteristics of UK Biobank and Melbourne Collaborative Cohort Study participants included in sensitivity analyses (three sets each).

Table S3 Associations between melanoma polygenic risk score and participants' characteristics.

Table S4 Associations between melanoma polygenic risk score and participants' characteristics: results of multivariable and univariable sensitivity analyses.

Table S5 Subhazard ratios for association between polygenic risk score quintiles or deciles and melanoma incidence.

Table S6 Calibration of age-and-sex-specific 10-year melanoma risks in the UK Biobank based on population-wide data from different periods.

Table S7 Sensitivity, specificity, positive likelihood ratio and negative likelihood ratio based on polygenic risk score-adjusted absolute risk thresholds.

Table S8 Variance (R^2) on the liability scale explained by the polygenic risk score (PRS) relative risk, as well as the unadjusted and PRS-adjusted absolute risks.

Video S1 Author video.