Table 2. Odds ratios with 95% confidence intervals for congenital abnormalities, low birth weight, and premature birth in children fathered by men treated with azathioprine, cyclosporine, methotrexate, or mycophenolate mofetil within the last 90 d before *and* after conception

	Exposed n/N (%)	Unexposed n/N (%)	Crude OR (95% CI)	*P*-Value	Adjusted OR[1] (95% CI)	*P*-Value
Any immunosuppressants						
Congenital abnormality	34/480 (7.1)	31,204/417,154 (7.5)	0.94 (0.67–1.34)	0.740	0.94 (0.66–1.35)	0.751
Low birth weight (<2,500 g)	23/480 (4.8)	22,066/417,154 (5.3)	0.90 (0.59–1.37)	0.626	0.87 (0.56–1.35)	0.543
Preterm birth (<37 wk)	25/480 (5.2)	18,947/417,154 (4.5)	1.15 (0.77–1.73)	0.484	1.13 (0.74–1.71)	0.581
Azathioprine						
Congenital abnormality	21/335 (6.3)	32,217/417,229 (7.5)	0.83 (0.53–1.29)	0.400	0.85 (0.55–1.33)	0.486
Low birth weight (<2,500 g)	18/335 (5.4)	22,071/417,229 (5.3)	1.02 (0.63–1.64)	0.945	1.04 (0.64–1.70)	0.867
Preterm birth (<37 wk)	18/335 (5.4)	18,954/417,229 (4.5)	1.19 (0.74–1.92)	0.466	1.13 (0.68–1.87)	0.642
Cyclosporine						
Congenital abnormality	7/67 (10.5)	31,231/417,567 (7.5)	1.44 (0.66–3.16)	0.358	1.45 (0.66–3.19)	0.350
Low birth weight (<2,500 g)	<3/67 (not shown)	22,087/417,567 (5.3)	0.55 (0.14–2.25)	0.407	0.58 (0.14–2.39)	0.454
Preterm birth (<37 wk)	4/67 (6.0)	18,968/417,567 (4.5)	1.34 (0.493.67)	0.575	1.40 (0.51–3.85)	0.520
Methotrexate						
Congenital abnormality	6/81 (7.4)	31,232/417,553 (7.5)	0.99 (0.43–2.27)	0.980	0.85 (0.34–2.10)	0.718
Low birth weight (<2,500 g)	3/81 (3.7)	22,086/417,553 (5.3)	0.69 (0.22–2.18)	0.526	0.43 (0.11–1.77)	0.244
Preterm birth (<37 wk)	4/81 (4.9)	18,968/417,553 (4.5)	1.09 (0.40–2.98)	0.864	1.13 (0.41–3.10)	0.813
Mycophenolate mofetil						
Congenital abnormality	0/6 (0.0)	31,238/417,628 (7.5)			not applicable	
Low birth weight (<2,500 g)	0/6 (0.0)	22,089/417,628 (5.3)				
Preterm birth (<37 wk)	0/6 (0.0)	18,972/417,628 (4.5)				

Abbreviations: CI, confidence interval; OR, odds ratio.
[1]Adjusted for mother's age (below 25 y, 25–29 y, and 30 y or more), parity (1 or more than 1), maternal smoking (yes/no), and sex of the child in a logistic regression model.

statistical analysis. They provided administrative, technical, or material support. All authors supervised the study.

***Alexander Egeberg*[1,*], *Gunnar H. Gislason*[2,3,4] *and Alexander Nast*[5]**

[1]*Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark;* [2]*Department of Cardiology, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark;* [3]*The Danish Heart Foundation, Copenhagen, Denmark;* [4]*The National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark; and* [5]*Division of Evidence based Medicine (dEBM), Department of Dermatology, Venerology und Allergy, Charité—Universitätsmedizin Berlin, Berlin, Germany*
[*]*Corresponding author e-mail: alexander.egeberg@gmail.com*

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at http://dx.doi.org/10.1016/j.jid.2017.03.030.

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Association between Body Mass Index, C-Reactive Protein Levels, and Melanoma Patient Outcomes

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Abbreviations: BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; DFS, disease-free survival; HR, hazard ratio; MSS, melanoma-specific survival; OS, overall survival; SNP, single-nucleotide polymorphism

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TO THE EDITOR

Obesity is a known risk factor for cancer development (Arnold et al., 2016; Basen-Engquist and Chang, 2011; Renehan et al., 2015) and death

Table 1. Relationship of demographic and clinical factors with body mass index in 1,186 patients with melanoma

Characteristic	Total (N = 1,186)	Correlation with BMI	
		Pearson r^2	P-value[1]
BMI, median (IQR), kg/m^2	28.2 (25.2–32.1)	–	–
Age at diagnosis, median (IQR), y	52.4 (42.4–62.7)	0.11	**0.0002**
Sex, n (%)			
Female	471 (39.7)		**<0.0001**
Male	715 (60.3)		
Tumor thickness, median (IQR), mm	1.10 (0.61–2.20)	0.07	
Stage at diagnosis, n (%)			
I/II	893 (75.3)		0.1118
III/IV	293 (24.7)		
Time from diagnosis to blood draw, median (IQR), y	0.64 (0.11–2.03)	–	–
CRP, median (IQR), mg/l[2]	1.71 (0.69–4.40)	0.35	**<0.0001**
Follow-up time from diagnosis to disease relapse or censoring, median (IQR), y	7.6 (3.81–10.11)	–	–
Follow-up time from diagnosis to death or censoring, Median (IQR), y	8.3 (5.95–10.64)	–	–
Recurrence among all patients, n (%)	334 (28.2)	–	–
Recurrence among stage I/II patients, n (%)	197/893 (22.1)	–	–
Death from all causes, n (%)	325 (27.4)	–	–
Death from melanoma, n (%)	224 (18.9)	–	–

Abbreviations: BMI, body mass index; CRP, C-reactive protein; IQR, interquartile range.
[1]*P*-value from the Student *t* test for the association between categorical variables and BMI.
[2]Correlation measured using BMI and logarithmic CRP levels.

(Calle et al., 2003). Obesity has been associated with an increased risk of developing melanoma in men (Sergentanis et al., 2013) and with thicker primary melanomas (Skowron et al., 2015). The inflammatory adipokine leptin promotes melanoma progression in mice (Amjadi et al., 2011; Brandon et al., 2009; Gogas et al., 2008); elevated leptin levels may predict melanoma sentinel node metastasis (Oba et al., 2016). We hypothesized that elevated body mass index (BMI) would be associated with decreased melanoma patient survival through chronic inflammation, as indicated by levels of C-reactive protein (CRP). We also evaluated whether obesity-related genetic variants (single-nucleotide polymorphisms [SNPs]) play a role in melanoma patient outcomes.

Among 1,804 patients with melanoma enrolled from 1998 to 2008, BMI information was available for 1,186 patients, and 725 underwent CRP determination (Supplementary Methods and Figure S1 online). A total of 2.65 million SNPs were available. The median BMI was 28.2 kg/m^2, obtained at a median of 0.10 years after diagnosis (Table 1). The median CRP level was 1.71 mg/l. The raw CRP distribution was skewed (skewness = 8.06, kurtosis = 99.40, data not shown), but was close to normally distributed after log transformation (skewness = −0.01, kurtosis = 0.40, data not shown). Therefore, we used the log-transformed CRP (log[CRP]) in our analysis. Blood samples were obtained a median of 0.64 years after diagnosis, and the median follow-up duration was 8.3 years.

Increased BMI was weakly associated with older age, increased tumor thickness, and increased log[CRP] (Table 1).

Elevated BMI was associated with shorter overall survival (OS) (hazard ratio [HR] = 1.20 per 5 kg/m^2 increase in BMI, 95% confidence interval [CI] 1.11–1.29, $P < 0.0001$). In the multivariable analysis, after adjustment for age, sex, and stage, increased BMI remained associated with poorer OS (HR = 1.14, 95% CI 1.06–1.23,

Table 2. Association between body mass index and patient outcome in 1,186 patients with melanoma[1]

	Melanoma-specific survival				Overall survival			
	Per 5 kg/m^2 increase in BMI		Categorical BMI (≥30 kg/m^2 versus <30 kg/m^2)		Per 5 kg/m^2 increase in BMI		Categorical BMI (≥30 kg/m^2 versus <30 kg/m^2)	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Univariate analysis								
BMI	1.20 (1.09–1.31)	**0.0002**	1.65 (1.27–2.16)	**0.0002**	1.20 (1.11–1.29)	**<0.0001**	1.56 (1.25–1.94)	**<0.0001**
Multivariable analysis								
BMI	1.15 (1.05–1.26)	**0.0037**	1.47 (1.12–1.91)	**0.0049**	1.14 (1.06–1.23)	**0.0005**	1.45 (1.16–1.81)	**0.0010**
Age	1.02 (1.01–1.03)	**0.0007**	1.02 (1.01–1.03)	**0.0004**	1.04 (1.03–1.05)	**<0.0001**	1.04 (1.03–1.05)	**<0.0001**
Sex: male versus female	1.29 (0.97–1.72)	0.0833	1.27 (0.95–1.69)	0.1052	1.31 (1.03–1.67)	**0.0272**	1.29 (1.02–1.65)	**0.0374**
Stage: III/IV versus I/II	4.63 (3.54–6.04)	**<0.0001**	4.57 (3.50–5.97)	**<0.0001**	2.91 (2.33–3.64)	**<0.0001**	2.89 (2.31–3.60)	**<0.0001**
Multivariable analysis adjusted for CRP[2]								
BMI	1.08 (0.96–1.21)	0.2268	1.33 (0.96–1.85)	0.0858	1.08 (0.97–1.19)	0.1531	1.32 (1.01–1.73)	**0.0455**
Logarithmic CRP	1.26 (1.12–1.41)	**0.0002**	1.26 (1.12–1.41)	**0.0002**	1.21 (1.10–1.34)	**0.0001**	1.21 (1.10–1.34)	**0.0001**
Age	1.01 (1.00–1.03)	**0.0334**	1.01 (1.00–1.03)	**0.0261**	1.04 (1.03–1.05)	**<0.0001**	1.04 (1.03–1.05)	**<0.0001**
Sex: male versus female	1.56 (1.11–2.21)	**0.0115**	1.56 (1.10–2.20)	**0.0122**	1.61 (1.20–2.15)	**0.0014**	1.60 (1.20–2.14)	**0.0015**
Stage: III/IV versus I/II	3.67 (2.65–5.10)	**<0.0001**	3.67 (2.65–5.09)	**<0.0001**	2.27 (1.73–2.97)	**<0.0001**	2.26 (1.73–2.97)	**<0.0001**

Abbreviations: BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio.
[1]Cox proportional hazards analyses.
[2]725 patients with CRP data available.

$P = 0.0005$) (Table 2). However, when log[CRP] was included, elevated CRP remained an independent predictor of poorer OS (HR = 1.21 per unit increase in log[CRP], 95% CI 1.10−1.34, $P = 0.0001$), but BMI was no longer associated with OS (HR = 1.08, 95% CI 0.97−1.19, $P = 0.1531$) (Table 2).

We also observed associations between BMI and melanoma-specific survival (MSS) in both univariate (HR = 1.20, 95% CI 1.09−1.31, $P = 0.0002$) and multivariable (HR= 1.15, 95% CI 1.05−1.26, $P = 0.0037$) analyses (Table 2). In addition, we found associations between BMI and disease-free survival (DFS) in patients with stage I/II melanoma (HR = 1.17, 95% CI 1.05-1.30, $P = 0.0033$ in univariate analysis; HR = 1.10, 95% CI 0.98−1.23, $P = 0.0994$ in multivariable analysis) (Supplementary Table S1 online). As in our OS analysis, after incorporation of log[CRP], BMI was no longer associated with MSS (HR = 1.08, 95% CI 0.96−1.21, $P = 0.2268$) (Table 2) or DFS (HR = 0.99, 95% CI 0.86−1.13, $P = 0.8623$) (Supplementary Table S1).

We further evaluated BMI by dichotomizing the variable at the standard cutoff for obesity, 30 kg/m^2. Patients with a BMI $\geq$ 30 kg/m^2 had poorer OS (HR = 1.56, 95% CI 1.25−1.94, $P < 0.0001$; Table 2) and MSS (HR = 1.65, 95% CI 1.27−2.16, $P = 0.0002$; Table 2) than did patients with a BMI < 30 kg/m^2. Patients with stage I/II melanoma and BMI $\geq$ 30 kg/m^2 had poorer DFS (HR = 1.48, 95% CI 1.11−1.96, log-rank $P = 0.0077$; Supplementary Table S1). The associations between BMI and the three outcome measures were weaker after adjustment for age, sex, and stage (OS: HR = 1.45, 95% CI 1.16−1.81, $P = 0.0010$; MSS: HR = 1.47, 95% CI 1.12−1.91, $P = 0.0049$; DFS: HR = 1.29, 95% CI 0.97−1.72, $P = 0.0836$ [nonsignificant]) (Table 2, Supplementary Table S1). When log[CRP] was incorporated, the association between BMI and OS became weaker (HR= 1.32, 95% CI 1.01−1.73, $P = 0.0455$), and the relationships between BMI and MSS (HR = 1.33, 95% CI 0.96−1.85, $P = 0.0858$) and BMI and DFS (HR = 1.12, 95% CI 0.79−1.59, $P = 0.5304$) lost significance (Table 2, Supplementary Table S1).

We next excluded patients whose first BMI measurement or blood draw was performed more than 1 year after diagnosis and again assessed the relationship between BMI and melanoma outcomes for the remaining 760 patients. We observed the same pattern of associations as in the full patient cohort (Supplementary Tables S2 and S3 online).

Although underweight patients in our population tended to have a lower risk of death than did normal-weight patients (HR close to 0, likely because sample size was small; Supplementary Table S4 online), overweight patients had a trend toward an elevated risk of disease recurrence and death. These risks were significantly increased in patients who were obese ($P < 0.05$).

Previously validated BMI-associated SNPs were assessed for association with melanoma risk and patient outcomes. None of the 82 examined SNPs significantly predicted any outcome after correction for multiple testing ($P = 0.05/82 = 6.10 \times 10^{-4}$) (Supplementary Table S5 online). Fifteen SNPs from different gene regions reached nominal significance ($P < 0.05$) in predicting BMI. In addition, several BMI-associated SNPs were associated with melanoma risk or outcome ($P < 0.05$). In particular, the C allele in the rs17782313 SNP (within *MC4R*, the melanocortin 4 receptor) was nominally associated with increased BMI (beta coefficient = 0.65, $P = 0.0249$), showed a trend toward association with elevated CRP (beta coefficient = 0.13, $P = 0.0653$), and was associated with poorer OS (HR = 1.11, 95% CI 1.00−1.23, $P = 0.0422$) and poorer MSS (HR = 1.16, 95% CI 1.03−1.30, $P = 0.0135$), but not DFS (HR = 1.08, 95% CI 0.95−1.22, $P = 0.237$), among patients with stage I/II melanoma (Supplementary Table S5).

To our knowledge, this investigation is the first to report associations between elevated BMI and poorer melanoma patient outcomes after adjustment for sex, age, and stage. A previous population-based cohort study detected no association between elevated BMI and melanoma mortality (Calle et al., 2003), but that study was small, did not assess melanoma stage or recurrence, and did not include biomarker data. Furthermore, because prior investigations have identified strong associations between obesity and elevated levels of inflammatory markers, including CRP (Ellulu et al., 2016; Oba et al., 2016), our finding that the outcome associations identified in the current investigation were weakened or became insignificant after adjustment for CRP suggests that systemic inflammation and/or metabolic syndrome may be involved in BMI-associated melanoma progression. Finally, our data suggest that genetic variations underlying elevated BMI and CRP might also contribute to poorer melanoma patient survival. Further investigation is needed to confirm these findings and to determine whether control of body weight and/or interventions to reduce chronic inflammation and metabolic syndrome could be beneficial to patients with melanoma.

All individuals gave written informed consent to participate under an Institutional Review Board-approved protocol.

CONFLICT OF INTEREST

JEG claims a consulting role for Merck. JW claims roles for the following companies: Honoraria for Dava Oncology, H. Lee Moffitt Cancer Center and Research Institute; Consulting or Advisory Role for Genentech, GlaxoSmithKline, Novartis; Speakers' Bureau for Illumina, Bristol-Myers Squibb, Dava Oncology; Research Funding for Genentech, GlaxoSmithKline, Bristol-Myers Squibb; Travel, Accommodations, Expenses for Bristol-Myers Squibb, JP Morgan. All other authors state no conflict of interest.

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Shenying Fang[1,], Yuling Wang[1], Yifang Dang[1], Andrew Gagel[1], Merrick I. Ross[1], Jeffrey E. Gershenwald[1], Janice N. Cormier[1], Jennifer Wargo[1], Lauren E. Haydu[1], Michael A. Davies[2], Jennifer L. McQuade[2], Dawen Sui[3], Roland L. Bassett[3], John D. Reveille[4],*

Qingyi Wei[5], Christopher I. Amos[6] and Jeffrey E. Lee[1,*]

[1]Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA; [2]Department of Melanoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA; [3]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA; [4]Division of Rheumatology and Clinical Immunogenetics, The University of Texas Health Science Center at Houston, Houston, Texas, USA; [5]Department of Medicine, Duke University School of Medicine, Durham, North Carolina, USA; and [6]Community and Family Medicine, Geisel College of Medicine, Dartmouth College, Lebanon, New Hampshire, USA

*Corresponding author e-mail: sfang@mdanderson.org or jelee@mdanderson.org

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at http://dx.doi.org/10.1016/j.jid.2017.04.007.

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See related commentary on pg 1619

Postzygotic Mutations in Beta-Actin Are Associated with Becker's Nevus and Becker's Nevus Syndrome

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TO THE EDITOR

Becker's nevus is a cutaneous hamartoma affecting approximately 1 in 200 individuals (Tymen et al., 1981). Becker's nevus appears in childhood as a unilateral tan patch, increasing in thickness, pigmentation, and hair growth during adolescence (Becker, 1949; Glinick et al., 1983) (Figure 1a). Histologically, epidermal acanthosis is accompanied by irregularly dispersed ectopic smooth muscle bundles and increased terminal hair follicles (Figure 1b). In rare cases, termed Becker's nevus syndrome, nevi can be associated with musculoskeletal abnormalities, unilateral breast hypoplasia, mental retardation, developmental delay, and cardiomyopathy (Danarti et al., 2004; Dasegowda et al., 2014; Happle and Koopman, 1997). Although most Becker's nevi are innocuous, rapid onset during adolescence presents significant cosmetic distress. Despite prevalence of Becker's nevi, the pathogenesis remains unknown.

A 13-year-old girl presented with hyperpigmented patches overlying her arms, legs, torso and back, and unilateral left breast and pectoralis muscle hypoplasia (Figure 1c). Lesional skin biopsy revealed epidermal acanthosis with flat-tipped rete ridges, basilar hyperpigmentation, and smooth muscle hypertrophy (Figure 1d). Her presentation was characteristic of Becker's nevus syndrome. To identify genetic alterations underlying her condition, biopsies from a pigmented patch and adjacent nonlesional skin were subjected to exome-sequencing, along with seven independent biopsies of nonsyndromic Becker's nevi, and an additional adjacent nonlesional skin (Supplementary Materials and Methods online; Supplementary Tables S1–S4 online). This study was approved by the institutional review board of Stanford University. Patients and parents of minors signed consent for skin biopsies performed for this study, and provided verbal consent for publication of photos. For research conducted on preexisting paraffin-embedded samples, signed consent was waived by Stanford institutional review board.

Our analysis identified an *ACTB* point mutation (c.C439T, p.R147C) in the index case absent from adjacent normal skin. An additional five of seven nonsyndromic Becker's nevi contained a point mutation affecting the same codon resulting in *ACTB* c.C439T, p.R147C or c.C439A, p.R147S (Figure 2a, Supplementary Table S1). These variants

Abbreviation: Hh, Hedgehog

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