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Empirical evidence of predictive adaptive response in humans: systematic review and meta-analysis of migrant populations

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Original Article

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Abstract

Meta-analysis is used to test a variant of a Developmental Origins of Adult Health and Disease (DOHaD)'s conjecture known as predictive adaptive response (PAR). According to it, individuals who are exposed to mismatches between adverse or constrained *in utero* conditions, on the one hand, and postnatal obesogenic environments, on the other, are at higher risk of developing adult chronic conditions, including obesity, type 2 diabetes (T2D), hypertension and cardiovascular disease. We argue that migrant populations from low and middle to high-income countries offer a unique opportunity to test the conjecture. A database was constructed from an exhaustive literature search of peer-reviewed papers published prior to May 2021 contained in PUBMED and SCOPUS using keywords related to migrants, DOHaD, and associated health outcomes. Random effects meta-regression models were estimated to assess the magnitude of effects associated with migrant groups on the prevalence rate of T2D and hypertension in adults and overweight/obesity in adults and children. Overall, we used 38 distinct studies and 78 estimates of diabetes, 59 estimates of hypertension, 102 estimates of overweight/obesity in adults, and 23 estimates of overweight/obesity in children. Our results show that adult migrants experience higher prevalence of T2D than populations at destination (PR 1.48; 95% CI 1.35–1.65) and origin (PR 1.80; 95% CI 1.40–2.34). Similarly, there is a significant excess of obesity prevalence in children migrants (PR 1.22; 95% CI 1.04–1.43) but not among adult migrants (PR 0.89; 95% CI 0.80–1.01). Although the total effect of migrant status on prevalence of hypertension is centered on zero, some migrant groups show increased risks. Finally, the size of estimated effects varies significantly by migrant groups according to place of destination. Despite limitations inherent to all meta-analyses and admitting that some of our findings may be accounted for alternative explanations, the present study shows empirical evidence consistent with selected PAR-like conjectures.

Introduction

PAR conjecture

The predictive adaptive response (PAR) conjecture tested in this paper is a cornerstone of the Developmental Origins of Adult Health and Disease (DOHaD). Although under a different name, its foundation was first laid down in the work of Barker and colleagues.[1–7] The original idea is that the embryonic and fetal developmental plan is modulated and adjusted in response to cues in the placental environment triggered by maternal conditions. When confronted with adverse nutritional challenges and stress signals, the program is fine-tuned, and energy supply to different physiological systems is rerouted with a strong bias toward growth of the heart and brain. Although this may result in constrained growth of some organs and increased risks of adult chronic conditions, it does optimize short-term chances of the organism's survival.

More recently, a rapidly growing body of research spearheaded by Gluckman, Hanson and colleagues[8,9] builds on the original idea of fetal programming and incorporates recent advances in developmental biology, epigenetics, and evolutionary biology.[10–14] According to this line of thought, humans and other mammals evolved strategies other than homeostasis and fetal programming to maximize fitness under changing environmental conditions. There is significant empirical evidence of more nuanced responses whereby early developmental adjustments are made not just in response to cues from current environmental factors but as plastic accommodations of developmental plans to assessments of future conditions. In mammals, the maternal and placental environments generate cues that operate as sensors and

allow the fetus to "read" conditions that might be encountered postnatally. Shifts in those readings promote the selection of alternative developmental paths. When the fidelity of the sensing mechanism is high, the resulting phenotype will possess enhanced fitness. When the prediction is inaccurate, the organism's fitness will be compromised. Of interest is a special class of mechanisms that modulate fetal growth and developmental plans in response to external signals that predict post-birth environments characterized by poor nutrient supply or stressful conditions that may threaten survival. These are referred to as PARs.[15–16]

Although PAR-related responses to nutritional (or other) stresses are more plastic and efficacious than homeostatic adjustments, most are irreversible and can backfire when predictions of future environments are incongruous with those encountered after birth. This type of mismatch is common in modern populations of low- and middle-income countries (LMICs), where ancestral environments of parents (and grandparents) are characterized by scarcity and harsh conditions while their offspring are born into a world of caloric abundance and obesogenic conditions. In these cases, future environments are incorrectly predicted *in utero* but individuals *who survive* to adulthood carry with them inappropriate adjustments that increase the risks of adult chronic conditions. The best documented cases of mismatches in humans involve pathways between fetal nutritional environments, adult obesity, type 2 diabetes (T2D), metabolic syndrome, hypertension, and cardiovascular disease.[17–20]

Importantly, there is strong empirical evidence from animal studies and from human populations exposed to extreme conditions, that epigenetic processes are an important component of the suite of responses to exposures during early stages of development.[17]

Empirical evidence for PAR

Despite its theoretical soundness and appeal, it has been difficult to find empirical evidence that falsifies hypotheses from DOHaD in humans. A robust test of the PAR conjecture requires randomized control trials that compare the prevalence of adult chronic conditions in two, otherwise identical, populations that differ only in the presence (absence) of mismatches between prenatal and postnatal environment. The conditions for such a randomized control trial are, however, strict, and unlikely to be satisfied anywhere except in animal experiments. The bulk of empirical evidence for PAR and related mechanisms among humans is drawn from studies of adult health outcomes in individuals who survive to adulthood after being exposed early in life to episodic or long-lasting exogenous shocks that caused deprivation and stress such as wars,[21,22] natural disasters,[23] famines,[24] pandemics,[25] and economic crisis.[26] Much of the empirical evidence gathered thus far shows effects, albeit small, consistent with PAR. An important drawback that limits the inferential power of these studies is that they are vulnerable to sample selection, measurement problems, and omitted variable biases.

Why study migrant populations?

An alternative research strategy for testing DOHaD hypotheses is to identify populations that approximately satisfy strict requirements of randomized trials. Under proper conditions, a comparison of migrant populations from LMIC and native populations in high-income countries (HICs) might fulfill, albeit imperfectly, some of the randomized trial criteria[a]. Most migrants from LMIC experience sharp contrasts between their ancestral environments and those that prevail at destination and are, therefore, more likely to be exposed to mismatches that increase the risk of chronic conditions. Furthermore, offspring of the first cohort of migrants will also experience the clash between their ancestral (parental and grandparental) and current environments during critical periods of growth and development.

There is an additional, but mostly neglected, set of conditions that makes the study of modern migrants from LMIC a potentially powerful tool for testing PAR conjectures. The bulk of adult populations residing in LMIC countries experienced an unprecedentedly rapid mortality decline that began in earnest after 1945–1950. Unlike HICs, these improvements in survival were driven less by amelioration of standards of living than by the diffusion of new medical technology (sulfa, antibiotics, pesticides, etc).[27,28] Under this emerging mortality regime, children who experienced hardship and adverse early conditions that would have been lethal under the old mortality regime, are able to survive to adulthood. They will thus increase the fraction of modern adult populations in LMIC scarred by early experiences and primed to manifest delayed adult responses. When there is a strong correlation between the severity of early deprivation and child mortality levels, the size of the adult population at risk of expressing delayed effects is reduced. When these two phenomena are decoupled, as happened under mortality declines experienced by modern LMIC, delayed effects and the manifestation of PAR mechanisms are more likely to be observed.

Although a comparison between these modern migrant and native populations is very distant from a rigorous randomized control trial, it can generate useful empirical evidence. Over the past ten years or so, a growing number of studies have focused on the health status of migrant populations and in some cases compared them with those of the native populations. Although most of these do not directly address PAR conjectures, all include potentially valuable empirical evidence. To harness the latent power of this evidence, we carry out a rigorous meta-analysis of selected studies. It is well known that inferences from meta-analysis can be as strong or stronger that those from individual studies.[29–31]

Hypotheses

To parse the meta-analysis into well-defined components and to organize the data analysis, it is most useful to formulate expected empirical findings in the form of four precisely stated hypotheses:

i. The prevalence of obesity, T2D, and hypertension is higher among adult migrants compared to the adult native populations.
ii. The prevalence of obesity is higher among children of adult migrants born either in the country of origin or of destination, compared to native children in the population at destination.
iii. There should be no differences between adult migrants and adult native populations in health outcomes not directly implicated by PAR.
iv. Differences between migrant populations and populations of stayers with similar ancestry in the country of origins should be at least as large as those in (i).

[a]This is not an original idea. It was suggested by several researchers, among them by Gluckman and Hanson.[19]

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Method

Search strategy and selection criteria

The systematic review and meta-analysis were conducted using the PRISMA guidelines as reference (Table S1).[32] Search was carried out in PUBMED and SCOPUS databases for studies published prior to May 2021, reporting health outcomes associated with DOHaD and/or migrants, without language restrictions. In addition, we used reference lists and relevant reviews to identify additional studies of interest. Terms used in the search are in Table S2. The initial selection was narrowed down to a reduced number of health outcomes and contrast groups identified in our hypotheses. The final database includes original observational (cohort and cross-sectional) studies that at least meet the following inclusion criteria (see full set of evaluation criteria in Supplementary Text S1): (1) reports estimated effects (and their standard errors) on either prevalence or odds of diabetes, hypertension, or obesity/overweight[b]; (2) unambiguously defines the LMIC migrant group and the contrast reference group. The latter must be either the native HICs host population and/or the population at origin; (3) the sample sizes of migrants and reference populations are adequate, and 4) the models employed to estimate effects on prevalence or odds ratios, *include full controls for age, sex, and SES/education*. Controls for age and sex are essential for these studies to produce useful inferences. A control of socioeconomic status (SES) (and/or education) is necessary as socioeconomic condition is a potent confounding factor associated with both migrant status and health outcomes. All studies focused on well-defined subpopulations of first- and second-generation migrant children (up to 10 years of age) and adults. We excluded studies with coarse, broad, or ill-defined immigrant or ethnic groups, those that focused on health outcomes not included as our chosen targets, those that did not use a native population from HICs as a contrast, and those with very small and/or nonrepresentative samples. Finally, we excluded studies limited to maternal or perinatal outcomes as well as those that report estimated effects on *continuously* measured BMI, blood pressure, or glucose tolerance.

The database search resulted in 22,635 articles of which 22,324 were duplicates or considered not relevant based on title and abstract. An additional 48 studies were identified in citations, resulting in 359 articles which were categorized by outcome and migrant origin and destination to identify unique studies that approximately satisfy PAR conditions (29 reviews were excluded at this stage). One hundred ninety-nine full-text articles were assessed for eligibility (12 could not be retrieved), of which 38 met the inclusion criteria (Fig. 1). Three of these included minority populations as part of the host contrast group and were only used in sensitivity analyses. Table 1 summarizes the characteristics of included studies. A narrative synthesis is in Supplementary Material Table S3.

In studies reporting estimates of prevalence in the reference group but only estimated effects on odds ratios, an approximation was employed to compute effects on prevalence.[33] This allows pooling studies that only reported odds ratios with those that utilized outcomes' prevalence[c]. Altogether, 38 studies and 272 unique effects were included in the main analyses.

Data analysis

All analysis were completed using STATA (version 17.0) and R (version 4.1.2) packages METAFOR (version 4.1.3), DMETAR (version 0.0.9000), and META (version 5.2-0). Studies with prevalence estimates of conditions (obesity, T2D, hypertension, other) were pooled into separate groups to obtain estimates of effects associated with a migrant group on the prevalence rate of each of these health outcomes[d]. With a few exceptions noted in the text, analyses are confined to contrasts between a migrant group and the native population. The latter excludes migrants from Western Europe and/or the USA and Canada as well as minority populations residing in the place of migrants' destination. We estimated random effects (RE) models by subgroups (and/or with moderators) and generated summary estimates of effects sizes and corresponding 95% CI's. Observations to compute estimates of effect sizes for a single outcome include multiple estimates associated from the same study[e].

Between-study heterogeneity was assessed using the I^2 statistic. To partially account for between-study heterogeneity we use group-specific estimation, and differences by region of origin and/or destination and by baseline contrast group were evaluated. Parameter estimation is extended to models that include region of origin as a moderator. The statistic to assess heterogeneity, I^2, has well-known flaws[34,35] and, to partially circumvent them, we used the range of study-specific estimates, a more informative measure of between-study heterogeneity. This is justified because in most cases the estimated effects from different studies are of the same sign and their ranges center quite a distance away from the null or no-effect values. Finally, several sensitivity tests were implemented to verify the robustness of findings. These are described in Supplementary Materials (Section II).

Results

Table 2 displays a global estimate of effects for migrant excess risk with host population as contrast regarding all outcomes. Tables 3–7 do the same according to region of origin. Finally, Tables 8–16 display results of meta-analyses in subgroups defined by region of origin and by combination of origin and destination. The first set of results pertains to estimation of effects of migrant status on the prevalence of T2D in studies in which the samples included population aged 18+ and the contrast group was the host population. Fig. 2 shows that study effects for T2D are consistently large and statistically significant. Effects sizes are, on average, of the order of logPR 0.40 (95% CI: 0.30-0.50), with fairly narrow

[b]An ideal study is one that generates estimates of the relative risks of an outcome. The only way for a study to retrieve these estimates is to be based on longitudinal information. Most studies are cross-sectional, and we focused on those reporting estimates of effects of migrant status on prevalence of conditions relative to in a baseline group. A few studies only provide effects on odds ratios of prevalence (rather than effects on prevalence). In these cases, we transformed estimates of effects on odds ratios into estimates of effects on prevalence relative to a baseline group (see text). We first analyzed these studies separately and then pooled them together with the rest. Because inferences were similar, we only discuss results from the pooled analysis.

[c]Six studies that reported odds ratio did not include enough information to transform the effects into prevalence ratios.

[d]Some studies do not specify whether the term "diabetes" refers to type I, type II, or both. Because type I diabetes is not associated with PAR, including these studies in the pool consisting of studies with well-specified T2D, will lead to understate the association between PAR responses and migrant status.

[e]For example, a study may report estimates of effects of migrant status on obesity for multiple migrant groups or for both genders or migrants to different destination or, lastly, retrieved from different waves of the single study.

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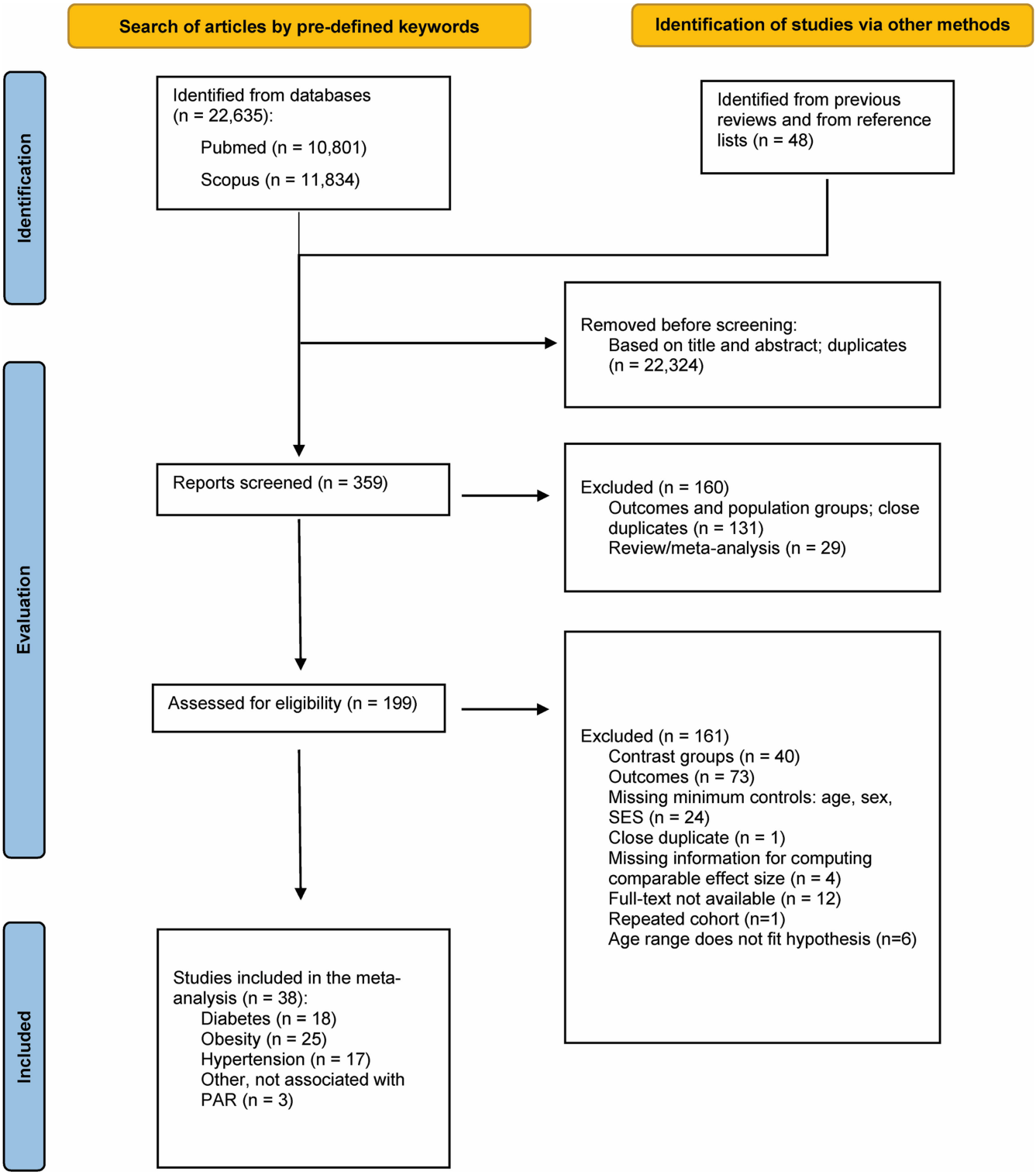

Figure 1. Study selection.

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Table 1. Study characteristics

First author, year	Dates	Effects	Origin	Arrival	*N*	Outcomes	Reference group (migrant generation)*	Age (mean)†	Adjustments
Agyemang, (2016)[36]	2012–2015	16	Africa (Ghana)	Europe (UK, Germany, Amsterdam), Africa (Urban Ghana)	5659	OB/T2D	Rural population at origin (1)	25–70 (45–48)	Age, education
Alkerwi (2012)[37]	2007–2008	1	Europe (Portugal)	Europe (Luxembourg)	843	OW[a]	Native at destination (1 + 2 pooled)	18–69 (31–48)	Age, sex, education
Alves (2015)[38]	1999–2006	3	Europe (Portugal)	Europe (Switzerland)	1938	OB/Diabetes/ HT	Population at origin (1)	35–65 (44–51)	Age, sex, education, smoking
Argueza (2020)[39]	2013–2016	1	Asia	North America (USA)	609	OB[a d]	Native ethnic counterpart at destination (2)	2–11 (7)	Age, sex, family income
Bennet (2015)[40]	2010	1	Asia (Iraq)	Europe (Sweden)	2155	T2D onset[c]	Native at destination (1)	30–75 (45–46)	Age, sex, family health history, education, height
Besharat Pour (2014a)[41]	1994–1996	2	All	Europe (Sweden)	2517	OW	Native at destination (2)	2, 12	Sex, maternal and perinatal characteristics
Besharat Pour (2014b)[42]	1994–1996	5	South America, Europe, Africa, Asia, Other	Europe (Sweden)	2589	OW[a]	Native at destination (2)	8	Sex, parental education, diet, physical activity
Bodewes (2021)[43]	2009–2010	4	Oceania (Indonesia)	Europe (Netherlands)	60,852	Diabetes[a]	Native at destination (1, 2)	40–60, 60+	Age, area-SES, urbanization
Brown (2017)[44]	2003–2014	4	Africa	North America (USA)	5033	HT[a]	Native ethnic counterpart at dest / Newly arrived migrant (1)	22–79 (44–45)	Age, sex, SES, smoking, physical activity, BMI
Cohen (2017)[45]	nr	2	Africa (Cameroon)	Europe (France), Africa (Urban Cameroon)	627	OB[b]	Rural population at origin / Newly arrived migrant (1)	18–65 (37–46)	Age, sex, education, lifestyle and body image preferences
Commodore-Mensa (2018)[46]	2010–2016	48	South America, Mexico, Central America, Caribbean, Asia, Middle East, Africa, SEA, Russia	North America (USA)	41,717	OW/Diabetes/ HT	European migrants to USA	18+ (41–54)	Age, SES, duration of US residence and doctor visits
Diemer (2020)[47]	2011–2015	4	South America (Suriname-South Asian and African descent)	Europe (Netherlands)	7971	HT [a d]	Native at destination (1 + 2 pooled)	18–70 (43–48)	Age, BMI, WC, educational level, physical activity, smoking

Table 1. (*Continued*)

Gibson (2013)[48]	2005–2006	1	Oceania (Tonga)	Oceania (New Zealand)	638	HT[a]	Population at origin (1 + 2 pooled)	19–48 (33–34)	Age, sex, marital status, SES (and SES in origin)
Guo (2015)[49]	2006–2008	12	Europe, Asia (LMICs and SEA)	Oceania (Australia)	263356	OW/HT	Native at destination (1)	45+ (59–65)	Age, SES, marital status, region of residence
Jackson (2012)[50]	born 1998–2002	8	All	North America (USA), Europe (UK)	19,250	OW/Other [a b]	Native at destination (2)	5	Ethnicity, maternal education, family SES
Kirchengast (2006)[51]	1994–2003	8	Europe (Yugoslavia), Asia (Turkey)	Europe (Austria)	1786	OW[a]	Native at destination (2)	6, 15	All from low class schools to control for class
Koochek (2008)[52]	nr	6	Asia (Iran)	Europe (Sweden)	476	OB/Diabetes/HT[a]	Native at destination (1)	60–84 (71)	Age, education, marital status
Labree (2015)[53]	2008–2009	4	Asia (Turkey), Africa (Morocco), LMICs	Europe (Netherlands)	1943	OW[a]	Native at destination (2)	8–9	Age, sex, parental education, BMI, diet, physical activity
Lindström (2005)[54]	1994	10	LMICs, North Africa, Middle East, Europe (Poland, Yugoslavia), HICs	Europe (Sweden)	3788	OW[a]	Native at destination (1)	21–80 (select birth years)	Age, education
Menigoz (2016)[55]	2011	24	All, Africa (Sub-Sahara, North), Middle East, Americas, Asia (LMICs), Europe, Oceania	Oceania (Australia)	13,047	OW[a]	Rural population at origin / Newly arrived migrant (1)	18+ (nr, most between 35–64)	Age, SES
Miranda (2011)[56]	2007–2008	3	South America (Peru)	South America (Peru)	989	OW/T2D/HT[b]	Rural population at origin (1)	30+ (48)	Sex, age, socioeconomic deprivation, parental education
Motlhale (2019)[57]	2015	4	All, Africa (South Africa, rural Gauteng)	Africa (South Africa, Gauteng province)	28,007	Diabetes/HT[a]	Native at destination (1)	18+ (nr, more young, mayority under 50)	Years in destination, age, sex, race, SES and diet
Oh (2021)[58]	2019	3	All	North America (USA)	2554	OB/Other[b]	Native at destination (1)	18+ (nr, 45% between 45–64)	Age, sex, race/ethnicity, SES
Oyebode (2015)[59]	2007–2010	18	Africa (Ghana, South Africa), Asia (China, India, Russia), Mexico	Africa (Ghana, South Africa), Asia (China, India, Russia), Mexico	39,436	OW/Diabetes/HT	Rural population at origin (1)	18+ (50–63)	Age, sex, marital status, SES
Palarino (2021)[60]	2000–2018	9	Africa, non-Hispanic White, Mexico	North America (USA)	570675	OB/Diabetes/HT[a]	Native non-Hispanic Black at destination (1)	18+ (31–55)	Race/ethnicity and duration in USA, sex, SES
Piao (2020)[61]	2009–2015	1	Asia	Asia (South Korea)	2680495	T2D incidence[b]	Native at destination (1)	20+ (nr, 88% under 45 in migrant group)	Age, sex, SES, BMI, smoking, alcohol use, physical activity

(*Continued*)

Table 1. (*Continued*)

First author, year	Dates	Effects	Origin	Arrival	*N*	Outcomes	Reference group (migrant generation)*	Age (mean)†	Adjustments
Raza (2017)[62]	2012–2013	3	Asia (Pakistan)	Europe (Netherlands)	7372	OB/Diabetes/ HT[a]	Native at destination (1)	19+ (40–64% under 40)	Age, sex, educational level
Reuven (2016)[63]	2002–2012	12	Asia (Russia), Africa (Ethiopia)	Asia (Israel)	58,901	OB/Diabetes/ HT[a]	Native at destination (1)	35+ (51)	Age, sex, BMI, smoking, SES
Salinas (2008)[64]	2000–2001	2	Mexico	North America (USA)	4170	HT[a]	Ethnic native counterpart at destination (1)	50+ (77-78)	Age, education, obesity, smoking
Shamshirgaran (2013)[65]	2006–2009	19	Africa, Americas, Asia, Middle East, Europe, Oceania	Oceania (Australia)	262233	T2D[a]	Native at destination (1)	45+ (nr)	Age, sex, country of birth, SES
Shiue (2014)[66]	2009–2010	12	All, non-Hispanic White, South America, Mexico	North America (USA), Europe (UK)	55,304	Diabetes/ Other[b]	Native at destination (1)	20+ (nr)	Age, sex, marital status, BMI, SES
Simchoni (2020)[67]	2016	2	Africa (Ethiopia)	Asia (Israel)	121997	T2D onset[c]	Native at destination (1, 2)	16–20 (mean follow-up 10–14 years)	Birth year, education level, cognitive score, BMI
Singh and DiBari (2019)[68]	2012–2014	17	All, South America, Central America, Mexico, Oceania, Asia, North America (Indian Nation), Africa, non-Hispanic White	North America (USA)	10431092	Prepregnancy OW [a d]	Native non-Hispanic White at destination (1)	Reproductive age	Race, age, marital status, maternal education
van der Linden (2019)[69]	2012–2015	8	Africa (Ghana)	Europe (UK, Germany, Amsterdam), Africa (Urban Ghana)	5659	HT	Rural population at origin (1)	25–70 (45–48)	Age, level of education, physical activity, smoking
Veenstra (2016)[70]	2001–2013	6	LMICs (SEA)	North America (Canada)	618722	Diabetes/HT/ Other[a]	Native non-Hispanic White at destination (1)	25+ (nr)	Age, educational attainment, household income
Verstraeten (2018)[71]	2012–2013	6	South America (Brazil)	Europe (Netherlands)	339114	OB/Diabetes/ HT [b d]	Native at destination / Population at origin (1)	19–65 (nr)	Age, marital status, educational level, employment
Will (2005)[72]	2002	3	All	Europe (Germany)	525	OW	Native at destination (2)	6–7	Effects by SES, sex
Zulfiqar (2019)[73]	2004–2014	4	LMICs, HICs	Oceania (Australia)	2389	OW[a]	Native at destination (2 + 3 pooled)	4–5, 10–11	Breastfeeding, birthweight, family SEP

OW = overweight (includes obesity); OB = obesity; T2D = type II diabetes; Diabetes = unspecified type I or type II; HT = hypertension; Other = outcomes not associated with PAR (predictive adaptive responses): asthma, cancer, and mental disorders. LMICs = low- and middle-income countries; HICs = high-income countries; SEA = South-East Asia; BMI = body mass index; SES = socioeconomic status; Nr = not reported.
Original estimated effect.
[a]Odds ratio/beta.
[b]Odds ratio; without sufficient information for transforming to prevalence ratios.
[c]Hazard ratio.
[d]Inversed reference group.
*All include both genders except study by Simchoni (2020) (male sample only).
†Rounded to one full year or whole number. Range of mean age when results are presented separately for males/females or different age groups.

Table 2. Estimates for migrant excess risk with host population as contrast

	T2D	Adult obesity	Hypertension	Child obesity	Other
STATISTIC					
Theta(logPR)	0.39	−0.11	0.07	0.20	−0.47
95% CI	[0.30; 0.50]	[−0.21; 0.01]	[−0.10; 0.15]	[0.04; 0.36]	[−0.74; −0.20]
Z	7.75	−2.07	1.71	2.45	−3.44
Prob>	0.0000	.0.039	0.0873	0.0143	0.0006
I^2	95%	99%	96%	40.3%	91%
Q statistic test *Q*	1271	43,583	861	36.87	83.19
SL	.0000	.0000	.0000	0.0245	.0000
N	59	75	36	23	10

"Other" includes outcomes not directly invoked in DOHaD as a result of exposures to early conditions: asthma ($n = 5$), cancer ($n = 3$), and mental disorders ($n = 2$).

Table 3. T2D by subgroup of origin (migrants vs. host)

	Statistic					
			Q statistic			
Group	Theta	95% CI	*Q*	SL	I^2	*N*
African	0.49	[0.30–0.68]	197	.000	97%	14
Asian	0.48	[0.32–0.65]	673	.000	94%	24
SA + Mx	0.37	[0.16–0.58]	24.8	.000	79%	7
Other	0.18	[−0.01–0.37]	135.9	.000	96%	14

Table 4. Obesity by subgroup of origin (migrants vs. host)

	Statistic					
			Q statistic			
Group	Theta	95% CI	Q	Prob	I^2	*N*
African	−0.134	[−0.350; 0.082]	6658	.000	99%	14
Asian	−0.362	[−0.509; −0.135]	1915	0.000	97%	26
SA + Mx	0.144	[−0.023; 0.310]	842	0.000	99%	10
Other	0.054	[−0.048; 0.156]	6658	0.000	99%	25

Table 5. Hypertension by subgroup of origin (migrants vs. host)

		Statistic				
			Q			
Group	Theta	95% CI	Q	Prob	I^2	*N*
African	0.150	[0.007; 0.292]	98.1	0.000	.92	8
Asian	0.090	[−0.021; 0.202]	384.8	0.000	.92	16
SA + Mx	0.069	[−0.010; 0.149]	83.3	0.000	.92	9
Other	−0.194	[−0.378; −0.010]	9.69	0.008	.98	3

Table 6. Child obesity by subgroup of origin (migrants vs. host)

	Statistic					
			Q statistic			
Group	Theta	95% CI	*Q*	Prob	I^2	*N*
African	0.39	[−0.30; 1.15]	0.84	0.36	0	2
Asian	0.47	[0.04; 0.90]	7.07	0.070	58%	4
SA + Mx	NA	NA	NA	NA	NA	1
Other	0.11	[−0.094; 0.317]	20.58	0.038	32%	16

Table 7. Other by subgroup of origin (migrants vs. host)

		Statistic				
Group	Theta	95% CI	Q statistic		I^2	*N*
African	NA	NA	NA	NA	NA	0
Asian	0.059	[−0.176; 0.294]	1.64	.201	39%	2
SA + Mx	NA	NA	NA	NA	NA	0
Other	−0.661	[−0.858; −0.464]	17.7	0.013	74%	8

SA + Mx = South America and Mexico.
"Other" includes outcomes not directly invoked in DOHaD as a result of exposures to early conditions: asthma ($n = 5$), cancer ($n = 3$), and mental disorders ($n = 2$).

Table 8. T2D estimates with contrasts in origin population

		Statistic				
			Q statistic			
Group	Theta	95% CI	*Q*	SL	I^2	*N*
All	0.59	[0.34; 0.85]	59.14	0.000	72%	19
African	0.93	[0.69; 1.16]	17	0.049	47%	10
Asian	0.09	[−0.24; 0.43]	5.66	0.226	29%	5
SA + Mx	0.18	[−0.13; 0.49]	2.22	.330	10%	3
Other	NA	NA	NA	NA	NA	1

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Table 9. T2D estimates with contrast origin population and ignoring size effects > 1

	Statistic					
			Q statistic			
Group	Theta	95% CI	*Q*	SL	I^2	*N*
All	0.15	[−0.17; 0.46]	21.03	0.004	45%	13
African	0.64	[0.44; 1.84]	1.15	0.886	47%	5
Asian	0.09	[−0.24; 0.43]	5.66	0.226	31%	5
SA + Mx	0.18	[−0.13;0.49]	0.02	0.899	NA	2

Table 10. T2D estimates by origin and destination combination (migrant vs. host)

	Statistic					
			Q statistic			
Group	Theta	95% CI	*Q*	SL	I^2	*N*
African_to_EU	0.96	[0.66; 1.27]	10.82	0.000	.54%	6
African_to_NA	0.20	[−0.24; 0.64]	110.1	0.000	.93%	5
Asian_to_EU	0.46	[0.17; 0.76]	25.46	0.001	.82%	8
Asian_to_NA	0.44	[0.17; 0.71]	73.65	0.000	.89%	10

Table 11. Obesity estimates with contrasts in origin population

	Statistic					
			Q statistic			
Group	Theta	95% CI	*Q*	SL	I^2	*N*
All	0.75	[0.40; 1.09]	507.5	0.000	96%	27
African	1.50	[1.04; 1.95]	135.46	0.000	55%	12
Asian	0.05	[−0.23; 0.33]	8.30	0.050	55%	5
SA + Mx	0.54	[−0.63; 1.71]	52.95	0.000	98%	3
Other	0.09	[−0.11; 0.28]	7.49	000	20%	7

Table 12. Obesity estimates with contrast origin population and ignoring size effects>1

	Statistic					
			Q statistic			
Group	Theta	95% CI	*Q*	SL	I^2	*N*
All	0.12	[0.00; 0.25]	32.8	0.000	54%	17
African	0.43	[0.23; 0.62]	57	0.000	NA	3
Asian	0.05	[−0.23; 0.33]	8.30	0.050	55%	5
SA + Mx	−0.04	[−0.17; 0.09]	43	0.000	NA	2

Table 13. Obesity estimates by origin and destination combination (migrant vs. host)

	Statistic					
			Q statistic			
Group	Theta	95% CI	*Q*	SL	I^2	*N*
African_to_EU	1.267	[1.05; 2.20]	49.59	0.000	91%	9
African_to_NA	0.085	[−0.004; 0.18]	33.49	0.0613	88%	6
Asian_to_EU	0.428	[−0.03; 0.88]	3.03	0.0640	36%	3
Asian_to_NA	−0.368	[−0.70; −0.03]	1857	0.000	99%	14

Table 14. Hypertension estimates with contrasts in origin population

	Statistic					
			Q statistic			
Group	Theta	95% CI	*Q*	SL	I^2	*N*
All	0.30	[0.141; 0.450]	158.1	0.000	86%	23
African	0.43	[0.26; 0.60]	52.43	0.000	77%	13
Asian	0.03	[−0.32; 0.39]	12.55	0.000	68%	5
SA + Mx	0.49	[0.30; 0.68]	62	0.000	NA	3
Other	−0.04	[−0.30; 0.21]	3.35	0.000	70%	2

Table 15. Hypertension estimates by origin and destination combination (migrant vs. host)

	Statistic					
			Q statistic			
Group	Theta	95% CI	*Q*	SL	I^2	*N*
African_to_EU	0.67	[0.585; 0.753]	2.57	0.767	NA	6
African_to_NA	0.02	[−0.131; 0.176]	30.93	0.0001	74%	9
Asian_to_EU	0.50	[0.156; 0.838]	.66	0.720	NA	3
Asian_to_NA	0.11	[0.024; 0.202]	2.50	0.0125	77%	10

Table 16. Child obesity estimates by origin and destination combination (migrant vs. host)

		Statistic				
			Q statistic			
Group	LogPR	95% CI	*Q*	Prob	I^2	*N*
African_to_EU	0.393	[−0.360; 1.145]	.84	0.361	0	2
African_to_NA	NA	NA	NA	NA	NA	0
Asian_to_EU	0.468	[0.038; 0.898]	7.07	0.0700	58%	4
Asian_to_NA	NA	NA	NA	NA	NA	0

SA + Mx = South America and Mexico; EU = Europe; NA = North America.
Tables 8–16 do not include "other" migrant as the combination of origin destination leads to an unfeasible large number of groups.
A table for child obesity with contrast to origin populations could not be estimated because there are no observations.

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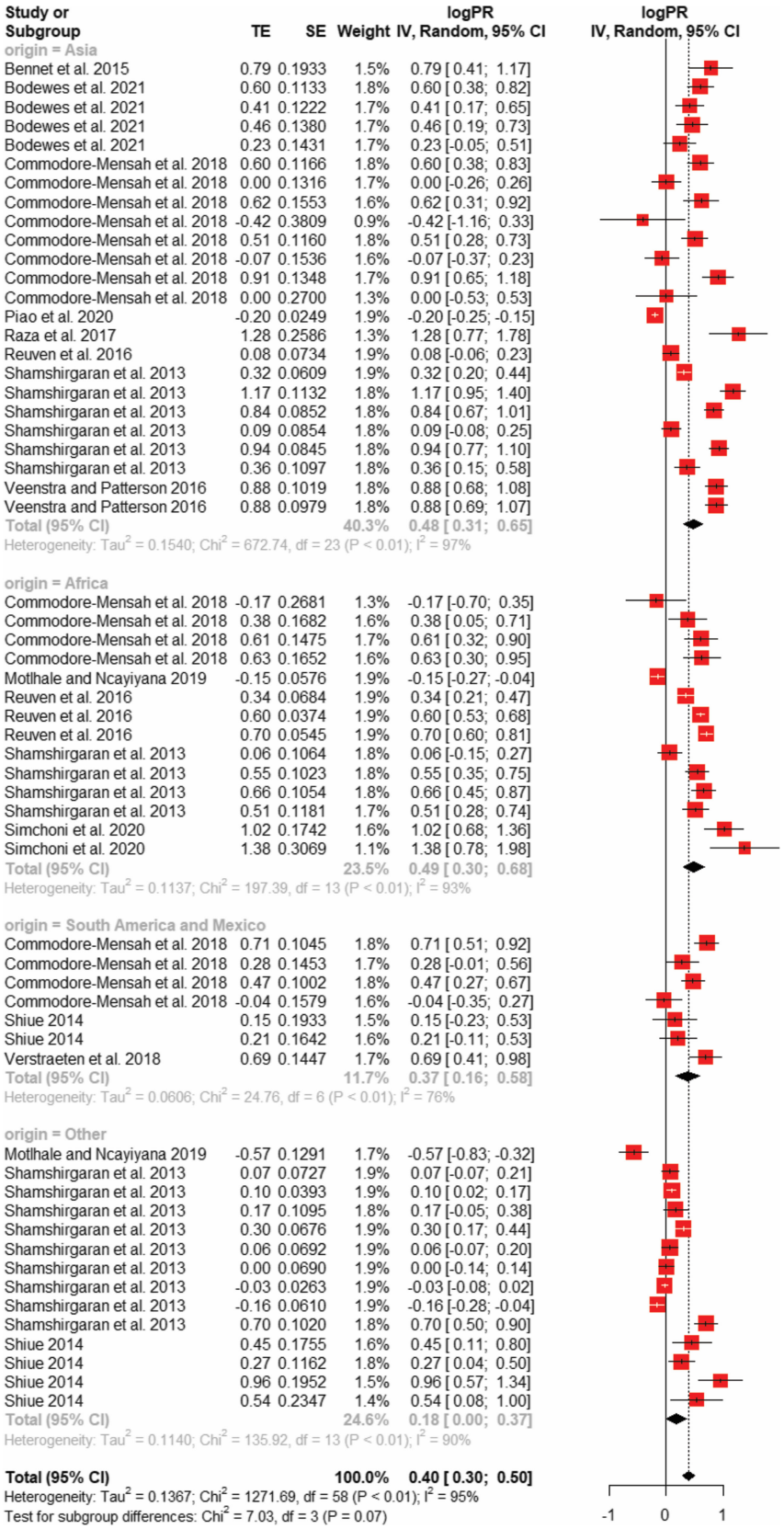

Figure 2. Diabetes risk of migrants vs. host population (by place of origin).

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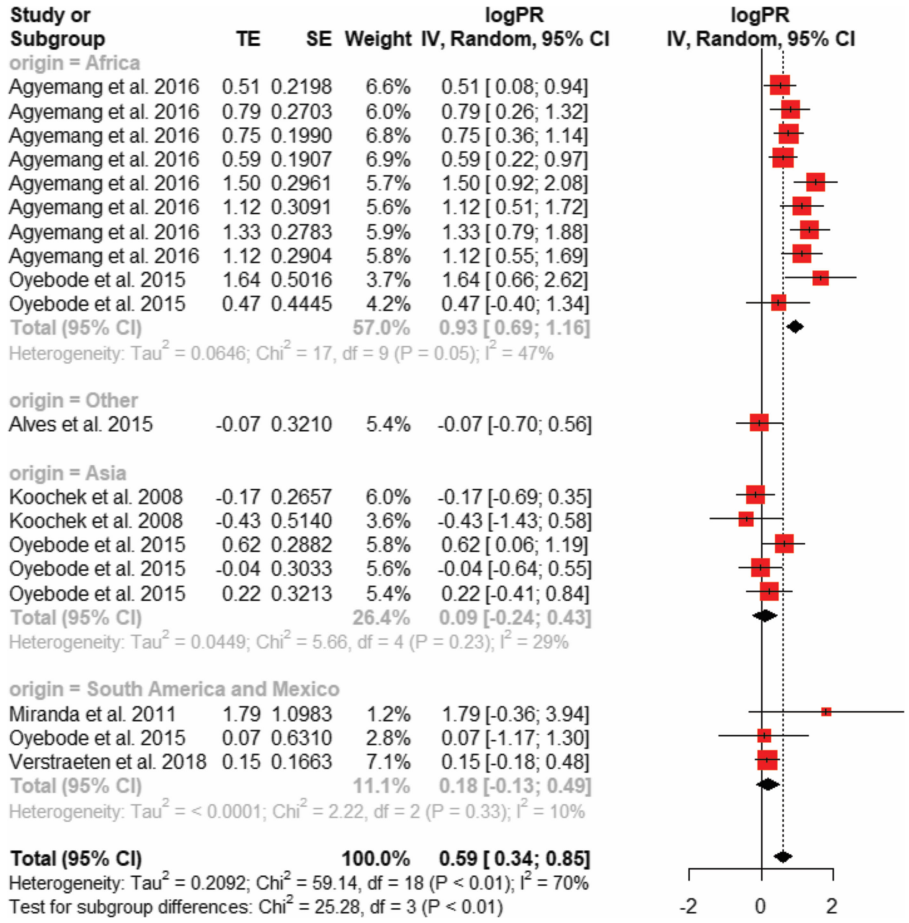

Figure 3. Diabetes risk of migrants vs. peers-in-origin (by place of origin).

confidence intervals. This implies that adult migrants experience T2D risks about 48% larger than the native populations. Subgroup analyses defined by region of origin suggests that African, Asian, and South American migrants fare worse than the contrast populations. The effect sizes range between logPR 0.37 and logPR 0.49, with African migrants exhibiting the worst profile. Significantly, and as expected, migrant groups originating in neither of these regions (mostly European migrants) do not experience excess risks.

To address Hypothesis 4 requires knowing whether migrants from a region experience worse conditions than those who stayed behind with whom they share similar ancestry. We estimate models in which the contrast group is always the stayers' population at origin. Fig. 3 shows that, on average, migrants experience excess risks of T2D close to twice (logPR 0.59 [95% CI: 0.34–0.85]) as large as their those residing in regions of origins, their ancestral populations. The bulk of the burden, however, is borne by African migrants who experience risks nearly three times as large. In contrast, the difference between Asian and South American (plus Mexican) migrants and their peers at origins are centered around 0 (Table 8). Alternative results drawn from a sample of studies that excludes all those in which the effect sizes exceeded 1 are presented in Table 9. Although the total effect becomes statistically insignificant, it is still the case that African migrants are at higher risk than their nonmigrant counterparts and by a large margin.

We also investigate whether *the combination of place of origin and destination* matters as much or more than the place of origin. This is a more direct test of the idea that it is the degree of dissonance between migrants' current and ancestral environments that matters. Table 10 displays estimates of models that shed some light on this conjecture. These models were estimated using results from studies in which effect sizes are measured for African and Asian migrants who migrated to North America and Europe[f]. The results suggest that Asian migrants fair worse and by a large margin, pointing to excess T2D risks that top 58% (logPR 0.46 [95% CI: 0.17–0.76]) of those in the host populations, both in Western Europe and North America. Only African migrants to Europe (but not to North America) perform equally bad or worse, with excess risks of the order of 200% or more. An explanation for this result can be deduced from the PAR conjecture: if the effect of mismatches is equally powerful among migrants to either Western Europe or the USA, it should be more visible in the former as the overall levels of T2D in the native population are much lower than in North America. Another explanation is that there is stronger migrant selection into North America than to Europe and much less so among Asians in both places of destination[g].

[f]A similar analysis with South American (plus Mexican) is not possible due to small sample sizes

[g]Whereas Asian migrants in the USA, for example, include a broad range of voluntary migrants and refugees, this is not the case for African migrants. With a few recent exceptions (migrants or refugees from Ethiopia, Somalia, and Eritrea) these may have been subjected to stronger selection, acting as a sieve to screen out perhaps the most at risk African populations. In contrast, African migrants to Europe are likely to be less selected than are those who choose the USA or Canada as destination.

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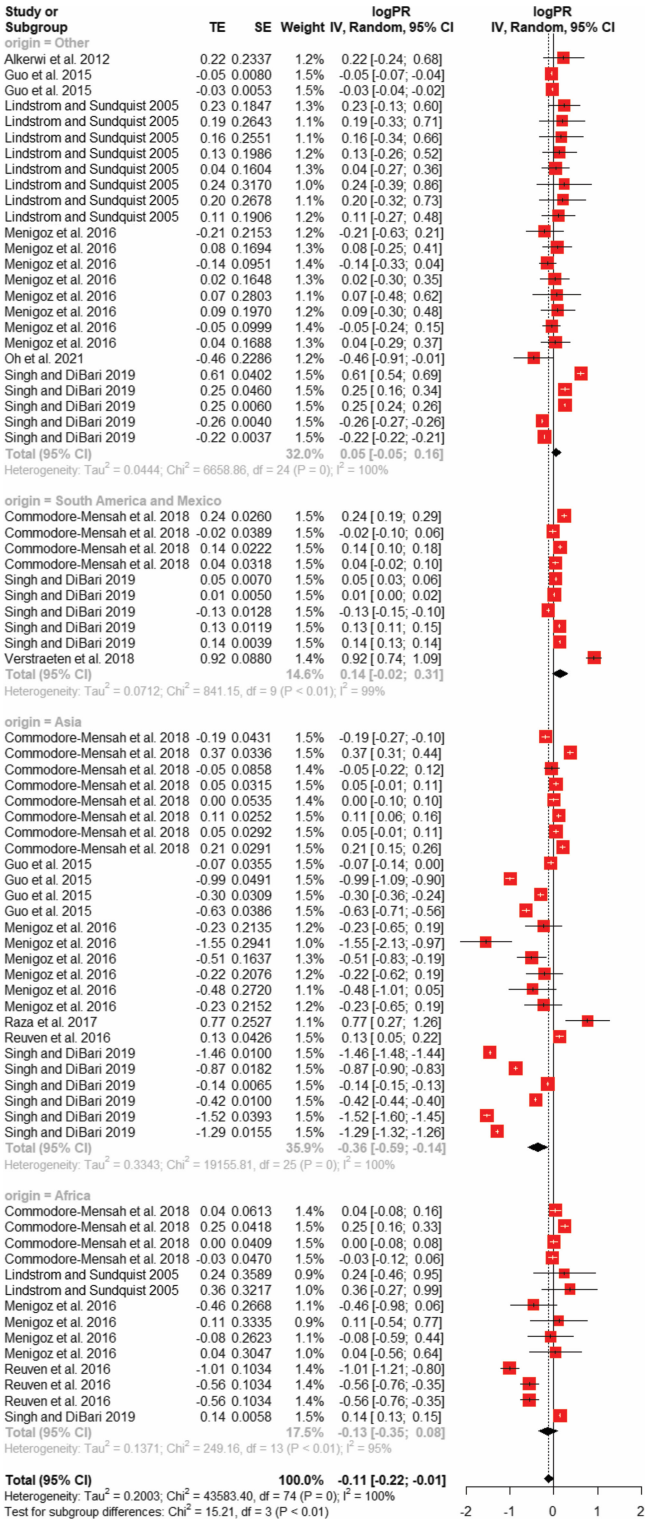

Figure 4. Adult obesity risk of migrants vs. host population (by place of origin).

Findings for adult obesity are less sharp than those for T2D. Column 2 of Table 2 shows that the migrant effect on obesity prevalence is negative and with a confidence interval whose upper bound is 0 (logPR −0.11 [95% CI: −0.21–0.01]. Furthermore, subgroup analysis in Fig. 4 suggests that the average effect is similar across all migrant groups. Note that the effect associated with Asian migrants is significantly different from 0 but negative, for example, Asian migrants experience less obesity than native populations. Although this result is consistent with empirical findings regarding Asian migrants in general,[74] it is inconsistent with studies showing that Asians of Indian origin fare much worse than native populations.[75] Fig. 5 reveals a startling result: the migrants' pooled sample experience twice as large a prevalence of obesity (logPR 0.75 [95% CI: 0.40−1.09]) as their peers left behind (Table 11). This excess is reduced to logPR 0.12 [95% CI: 0.00−0.25] when we exclude all studies that report size effects larger than 1 (see Table 12). Although this is consistent with the PAR conjecture, other explanations are possible. Thus, for example, strong migrant assimilation effects could produce similar patterns even in the absence of mismatches. This latter argument, however, relies on the assumption that African migrants are much more sensitive to assimilation effects than Asians, something we cannot verify with these data.

As in the case of T2D, Table 13 reveals that African migrants exhibit higher levels of obesity that native populations but only if their region of destination is Western Europe, not North America. As before, this finding could be explained by invoking the PAR conjecture or could be accounted for the fact that the average prevalence of obesity is much larger in North America than in Europe. It can also be dismissed altogether as an outcome of differential migrant selection by place of destination.

Table 2, column 3 shows that the total effect of migrant status on prevalence of hypertension is centered on zero (logPR 0.07 [95% CI: −0.10–0.15] and it is only significant among migrants originating in Africa (Fig. 6). Note that migrants from "other" regions fare better than natives, as they are likely not at risk of PAR (as are Africans and Asians). Fig. 7 and Table 14 show that African and South American (plus Mexican) migrants are particularly prone to hypertension when compared with populations of origin, and that African and Asian migrants to Western Europe fair worse than native host populations. Only Asians suffer a higher risk with respect to North American host population (Table 15).

The rationale for Hypothesis 2 is that, under conditions regulated by PAR, young children born in the country of origin or destination should be more likely to be exposed to contrasts between "current" and ancestral environments. It is, after all, the population of children that experiences the full blow of disharmony between ancestral and current conditions during a most sensitive period of growth and development, either *in utero*, infancy, early childhood, or combinations these.

Because the number of unique effects including children younger than 10 years of age is small (23 effects, from 7 studies of migrants to Western Europe), our inferences are tentative. Estimates in Table 2 (column 4) indicate that, on average, child obesity prevalence among migrants is about 22% higher than among natives (logPR 0.20 [95% CI: 0.04–0.36]. Fig. 8 and Table 16, however, suggest that not all migrant groups are equal: only the children of Asian migrants experience statistically significant excesses. Prevalence of child obesity among African migrants is higher as well, but the magnitude of the excess is not statistically significant[h].

According to Hypothesis 3 migrant groups should not experience worse conditions than populations at destination *when the health outcome is not one influenced by PAR conditions*.

[h]Findings for African populations, however, are quite weak since the number of eligible studies is very small.

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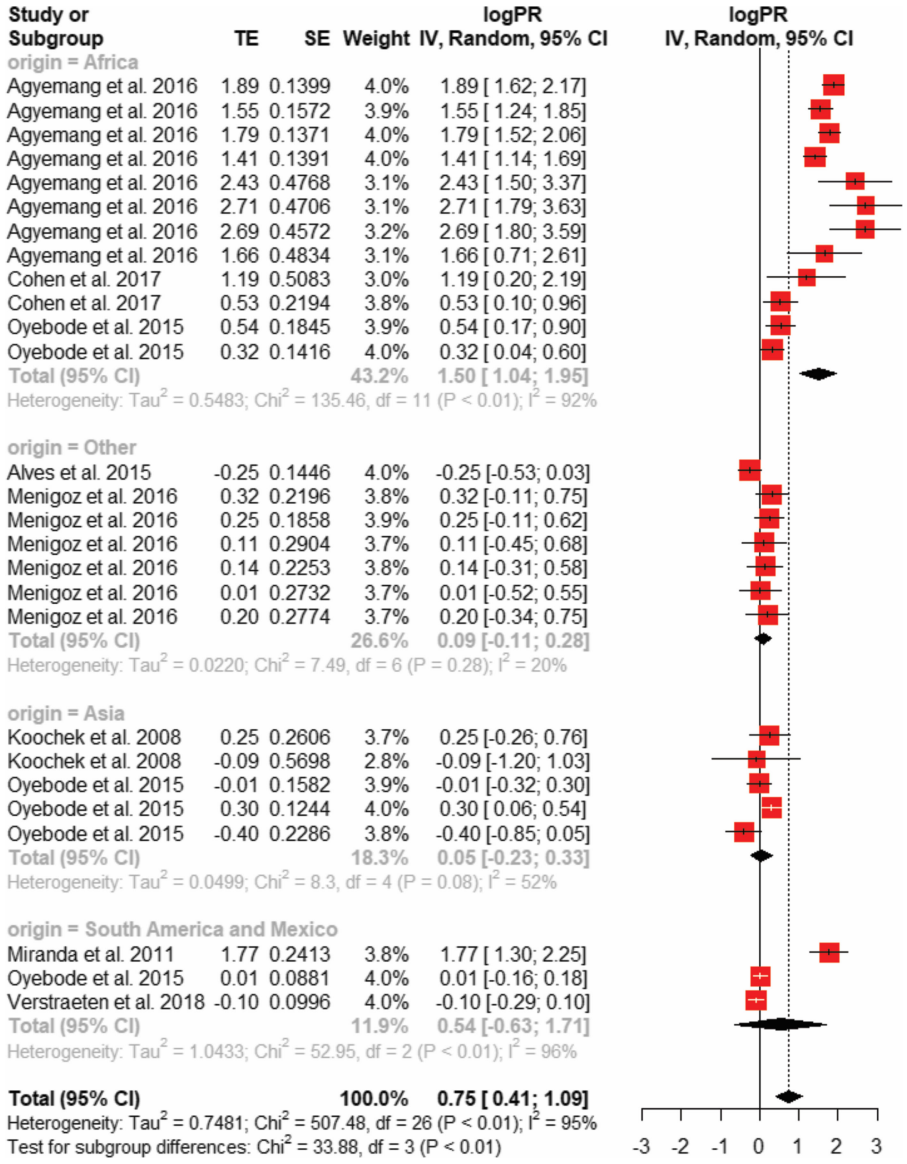

Figure 5. Adult obesity risk of migrants vs. peers-in-origin (by place of origin).

Unfortunately, there are just 10 effects from only three studies that account for non-PAR-related health outcomes. From these, five effects referred to asthma, three to cancer, and two to mental disorders. They do not include observations of African or South American (plus Mexican) migrant populations. Estimates in Table 2 (column 5) and Fig. 9 show that migrants from other regions and from Asia experience risks that are between 50 and 60% percent lower than populations at destination. This is consistent with Hypothesis 3.

Discussion

Results from the meta-analysis lead to five inferences. First, we find abundant support for the part of Hypotheses 1 and 4 that refers to T2D. All migrant groups, irrespective of origin or destination experience substantially higher risks of T2D than either native populations at destination or peer populations at origins. Second, less robust is the evidence for the part of Hypotheses 1 that refers to obesity and hypertension. Indeed, although we find either no or negative migrant effects (in the case of Asians) for obesity and hypertension, we uncover significant contrasts in the expected direction when comparing African (obesity and hypertension) and Asian (hypertension) migrants with the European host populations. Third, with respect to Hypothesis 4, migrants show substantially higher risks of obesity and hypertension in comparison with their populations at origin, but this effect is driven by African migrants. Fourth, although based on a smaller sample of studies, we find support for Hypothesis 2 as there are large excesses of child obesity among all migrants, particularly among those from Asian origins. Fifth, and as expected by

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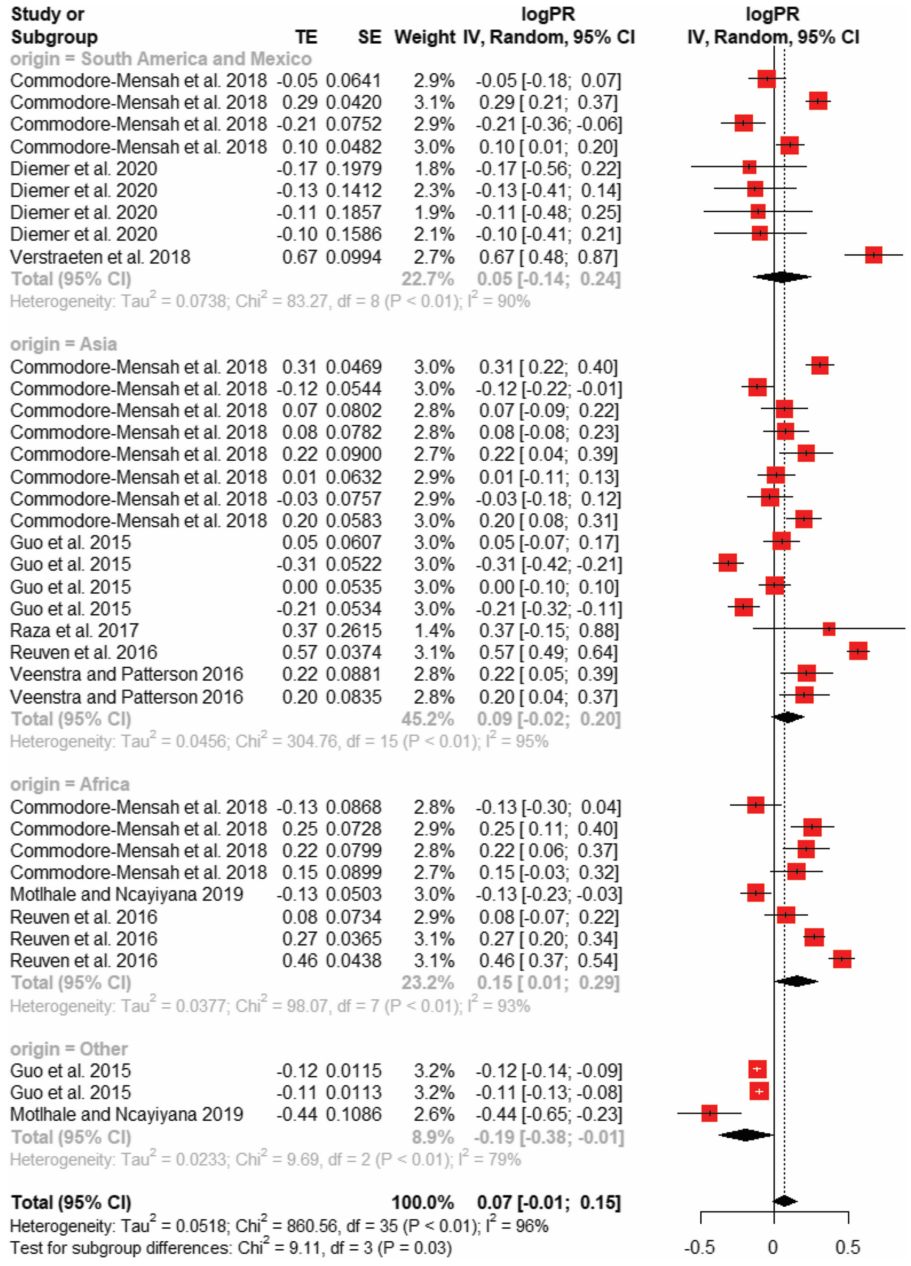

Figure 6. Hypertension risk of migrants vs. host population (by place of origin).

Hypothesis 3, we found no migrant effects for other health outcomes unrelated to the PAR conjecture.

Despite satisfactory performance of multiple robust sensitivity tests to detect flaws in model estimation (see Supplementary Material, Section II), our study shares limitations inherent to all meta-analyses. First because we do not have access to the original data, we cannot always ensure that proper controls for confounding variables were always introduced or are comparable across studies. Our protocol only required controls for age, gender, and educational attainment or other measures of SES. Similarly, the studies' statistics we used are selected and may not always coincide with the whole suite that could be employed to test the PAR conjecture. We only used those required by meta-analytic models that were available in the publications, for example, obesity rather than BMI. Second, some findings may be accounted for alternative explanations. A particularly important one is related to migrants' assimilation and selection. Because most studies do not control for duration since migration, the influence of assimilation is unaccounted for. However, although this may play a role in comparisons involving migrants and population at origins, it is

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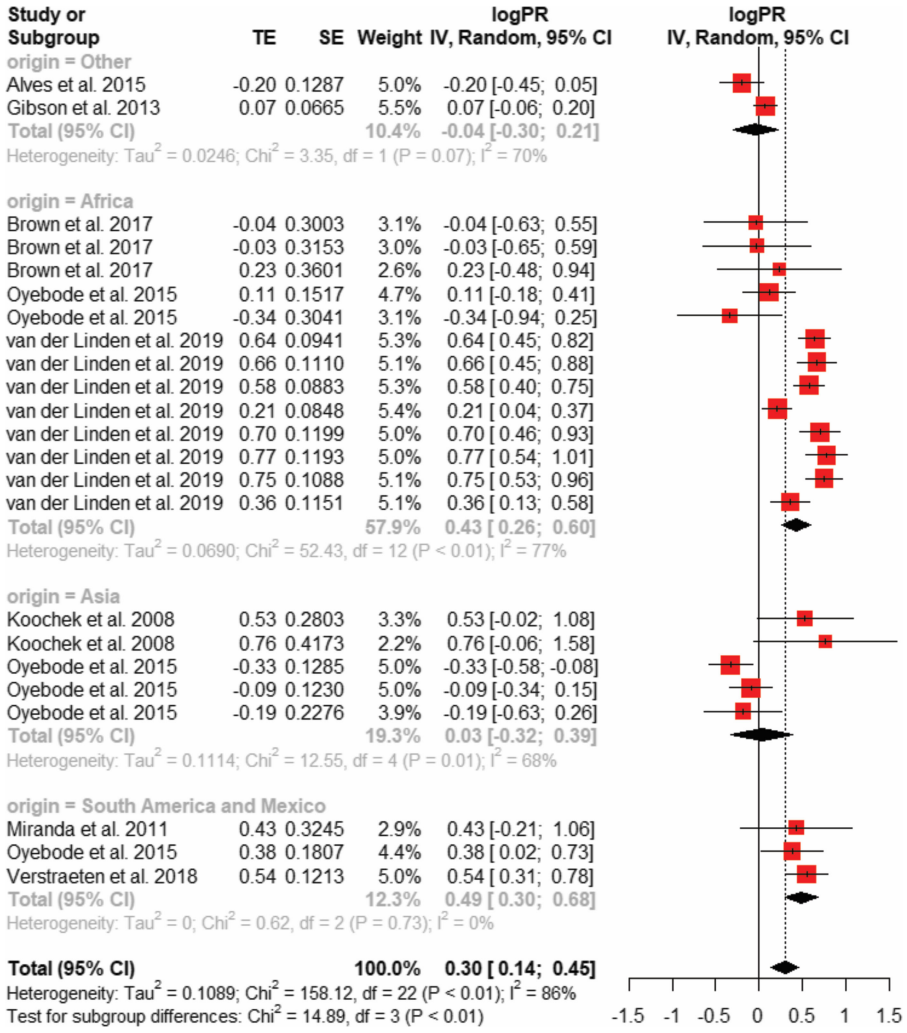

Figure 7. Hypertension risk of migrants vs. peers-in-origin (by place of origin).

irrelevant to account for differences between migrants and population at destination. In fact, because duration distributions are likely to be left skewed and mismatches are more likely to be manifested at longer durations, our estimates might be biased downward, not upward. A limitation unique to our study is that we are not able to distinguish more sharply between migrants from one region and the chosen destination. Thus, our findings regarding obesity and associated excesses among migrants to Europe (but not to North America) is not unambiguous support for PAR as it could be accounted by differential migrant health selection.[i] Despite these limitations, the present study shows important empirical evidence consistent with selected PAR-like conjectures.

Two classes of implications can be drawn from our study. The first is substantive and relates to the strength of findings. Results of our meta-analyses are uniformly consistent with the most important hypotheses derived from the PAR conjecture. Patterns of contrasts between migrants and nonmigrants (at origin and destination) regarding T2D, hypertension, and child obesity constitute an evidentiary corpus superior to that embedded in each of the individual studies separately. Some of the effects sizes, such as for T2D, are substantial and, very likely, underestimated. The non-finding associated with health outcomes not implicated by PAR offers an important complement to the positive evidence for the other outcomes.

The second implication is for future research based on migrant populations and targeting DOHaD hypotheses. As anticipated by Gluckman and Hanson,[19] studies of migrant populations are highly valuable for they can produce empirical evidence that, albeit in a very limited way, has at least some of the merits of randomized trials. To maximize their inferential power, however, they should clearly identify migrants at origin and destination, not just the latter as is normally done. To maximize the robustness of each study and any meta-analysis including them, these studies should follow a common template guiding their sampling plan, study design, and content. Our paper demonstrates that inferences generated with pooled studies of this kind can be powerful, all the more so if they are articulated *ex ante*.

[i]The so-called healthy migrant conjecture is relevant here. There is empirical evidence showing that migrants from LMIC experience lower mortality that host populations. An explanation for this regularity is that migrants are selected in terms of health status. If this applied across migrant populations, our estimates of effects sizes are downwardly biased.

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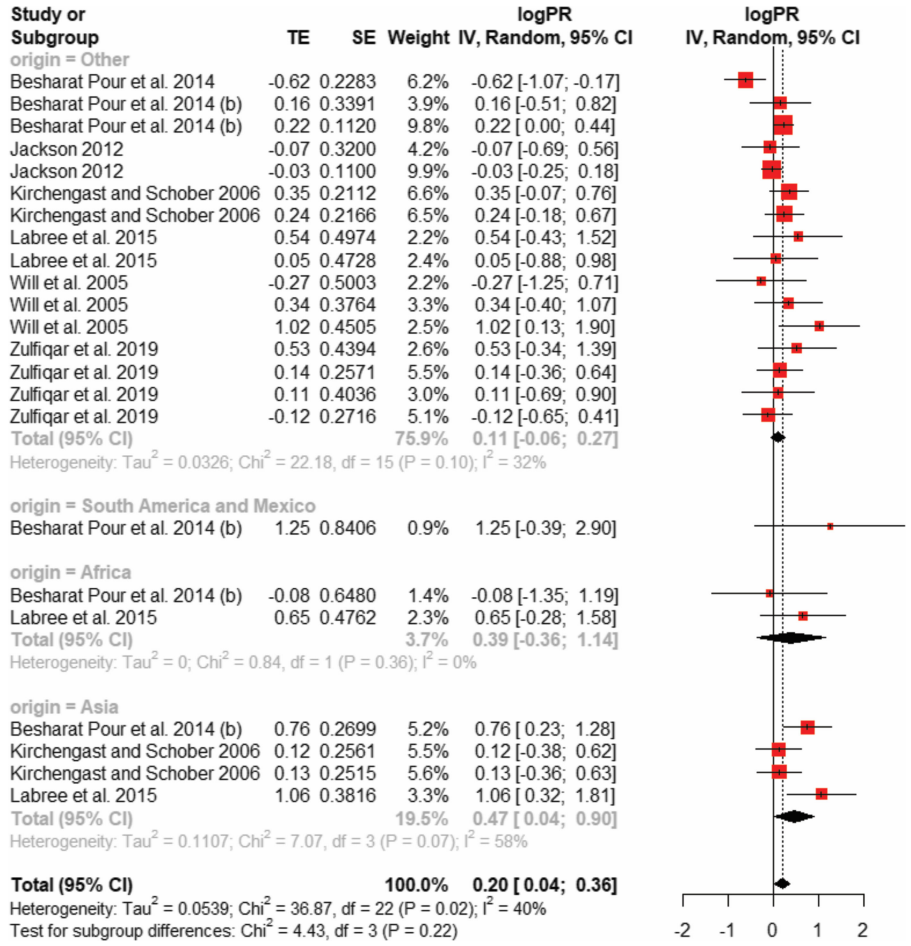

Figure 8. Risk of obesity among migrant children/first generation children vs. host population (by place of origin).

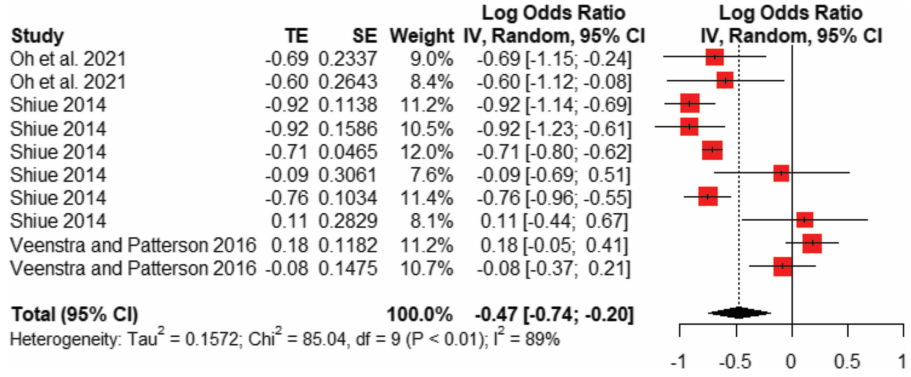

Figure 9. Risk of non-PAR-related health problems in migrants vs. host population.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S2040174423000429.

Data availability statement. Data extracted from the published studies included in our analyses and the statistical code for our main model and select subgroup and sensitivity analyses will be made available online at https://github.com/palloni/metaanalysis.

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Competing interests. None.

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