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Severe malnutrition or famine exposure in childhood and cardiometabolic non-communicable disease later in life: a systematic review

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ABSTRACT

Introduction Child malnutrition (undernutrition) and adult non-communicable diseases (NCDs) are major global public health problems. While convincing evidence links prenatal malnutrition with increased risk of NCDs, less is known about the long-term sequelae of malnutrition in childhood. We therefore examined evidence of associations between postnatal malnutrition, encompassing documented severe childhood malnutrition in low/middle-income countries (LMICs) or famine exposure, and later-life cardiometabolic NCDs.

Methods Our peer-reviewed search strategy focused on 'severe childhood malnutrition', 'LMICs', 'famine', and 'cardiometabolic NCDs' to identify studies in Medline, Embase, Global Health, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases. We synthesised results narratively and assessed study quality with the UK National Institute for Health and Care Excellence checklist.

Results We identified 57 studies of cardiometabolic NCD outcomes in survivors of documented severe childhood malnutrition in LMICs (n=14) and historical famines (n=43). Exposure to severe malnutrition or famine in childhood was consistently associated with increased risk of cardiovascular disease (7/8 studies), hypertension (8/11), impaired glucose metabolism (15/24) and metabolic syndrome (6/6) in later life. Evidence for effects on lipid metabolism (6/11 null, 5/11 mixed findings), obesity (3/13 null, 5/13 increased risk, 5/13 decreased risk) and other outcomes was less consistent. Sex-specific differences were observed in some cohorts, with women consistently at higher risk of glucose metabolism disorders and metabolic syndrome.

Conclusion Severe malnutrition or famine during childhood is associated with increased risk of cardiometabolic NCDs, suggesting that developmental plasticity extends beyond prenatal life. Severe malnutrition in childhood thus has serious implications not only for acute morbidity and mortality but also for survivors' long-term health. Heterogeneity across studies, confounding by prenatal malnutrition, and age effects in famine studies preclude firm conclusions on causality. Research to improve understanding of mechanisms linking postnatal malnutrition and NCDs is needed to inform policy and programming to improve the lifelong health of severe malnutrition survivors.

Key questions

What is already known?

- Many countries face a large 'double burden' of malnutrition: high prevalence of child undernutrition combined with a growing epidemic of overweight/obesity and associated cardiometabolic non-communicable diseases (NCDs).
- Convincing evidence for the Developmental Origins of Health and Disease hypothesis links prenatal malnutrition with increased long-term NCD risk, but less is known about the effects of severe malnutrition in childhood on NCD risk.

What are the new findings?

- Our review identified 57 studies examining NCD outcomes among survivors of historical famines (n=43) and severe childhood malnutrition (n=14).
- Severe malnutrition and famine exposure in childhood were consistently associated with increased risk of cardiovascular disease, impaired glucose metabolism, and metabolic syndrome (MetS). Some sex-specific effects were observed, with famine-exposed women at higher risk of glucose metabolism disorders and MetS.
- Heterogeneity across studies, uncontrolled confounding by prenatal malnutrition, and inadequate statistical adjustment for age effects in some famine studies were key limitations.

INTRODUCTION

Severe malnutrition (undernutrition) in childhood and adult non-communicable diseases (NCDs) are two of the world's most urgent public health problems.[1] In all its forms, malnutrition accounts for some 45% of all mortality in children under 5 years.[2] Severe malnutrition, particularly wasting, threatens the survival of an estimated 47 million children under 5 in low/middle-income countries (LMICs).[1] In contrast, obesity-related NCDs are emerging as a

Key questions

What do the new findings imply?

- Preventing and treating severe malnutrition in children are not only important in their own right but also play a potentially important role in preventing NCDs. This is especially important in the context of impending global hunger related to the COVID-19 pandemic.
- Further research into mechanisms linking severe malnutrition in childhood with NCDs is needed to inform policy, programming, and patient management strategies that support long-term health in survivors of early-life malnutrition.

leading cause of death in these settings, with nearly three quarters of all NCD deaths occurring in LMICs (28 million) including most premature deaths (82%).[3] While convincing evidence for the Developmental Origins of Health and Disease (DOHaD) hypothesis links prenatal malnutrition with increased NCD risk later in life, less is known about the long-term sequelae of severe malnutrition during postnatal periods of developmental plasticity such as childhood and adolescence. However, it is biologically plausible that malnutrition during these crucial periods of postnatal growth and development may also have lasting effects on survivors' health.[4]

At present, efforts to address severe childhood malnutrition are focused on community-based management with ready-to-use therapeutic foods along with inpatient treatment of complicated cases to prevent short-term mortality.[5] As these efforts reduce case-fatality rates and global child mortality declines, considering the long-term health consequences of severe malnutrition and effects of therapeutic foods is increasingly important.[6 7] Tackling NCDs is a priority under Sustainable Development Goal 3 (Good health and well-being), which aims to 'reduce by one third premature mortality from NCDs through prevention and treatment' by 2030.[8] As LMICs face the financial and social penalties of the increasing NCD burden, it is imperative to prioritise NCD prevention. This area of research is especially topical as early evidence suggests that severe malnutrition in childhood may be linked with increased NCD risk for survivors.[9 10]

While a narrative review examining evidence of differences in cardiometabolic risk between marasmus and kwashiorkor survivors was conducted by Boyne *et al* in 2017, no systematic review examining evidence on NCD outcomes following severe malnutrition or famine exposure in childhood currently exists in the literature.[11] As more children survive severe malnutrition globally, greater knowledge in this area is key to informing improved policy and programming around severe childhood malnutrition that reduce NCD risk. This review brings together evidence from studies of survivors of documented severe childhood malnutrition in LMICs or famines to present a synthesis of current knowledge on this topic.

Table 1 Country and setting of included studies

Country	Setting	No. of studies
Documented severe malnutrition studies		
Jamaica	Tropical Metabolism Research Unit, Kingston	3
Senegal	Urban nutritional rehabilitation units, Thiès and Dakar	2
Malawi	Nutrition ward at central hospital, Blantyre	2
Uganda	Infantile Malnutrition Research Unit, Kampala	2
Mexico	Paediatric hospitals, Mexico City	2
Ethiopia	Urban health centres, Jimma and Gondar	1
Gambia	Medical Research Council field station, West Kiang	1
Kenya	Rural hospital, Kijabe	1
Total		**14**
Famine studies		
China	Great Chinese Famine (1959–1961)	30
The Netherlands	Dutch Hunger Winter (1944–1945)	4
Russia	Siege of Leningrad (1941–1944)	3
England	German occupation of Channel Islands (1944–1945)	2
Ukraine	Holodomor famine (1932–1933)	2
Bangladesh	Post-monsoon famine (1974–1975)	1
Nigeria	Biafran civil war (1967–1970)	1
Total		**43**

METHODS

Protocol and registration

This review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[12] The protocol was registered on PROSPERO (ID: CRD42019145683).

Search strategy

A peer-reviewed search strategy focused around 'severe childhood malnutrition, 'LMICs', 'famine', and 'cardiometabolic NCDs' was used to identify studies in Medline, Embase, Global Health, and CINAHL databases (search strategy in online supplemental file 1). Reference lists of studies identified through database searching were hand-searched for additional studies. All final searches were run on 31 July 2019.

Eligibility criteria

Human studies published in English were assessed for eligibility against the following criteria:

Population: older children and adults who survived an episode of documented severe malnutrition in LMICs or famine exposure in childhood and adolescence (defined as 0–18 years of age).

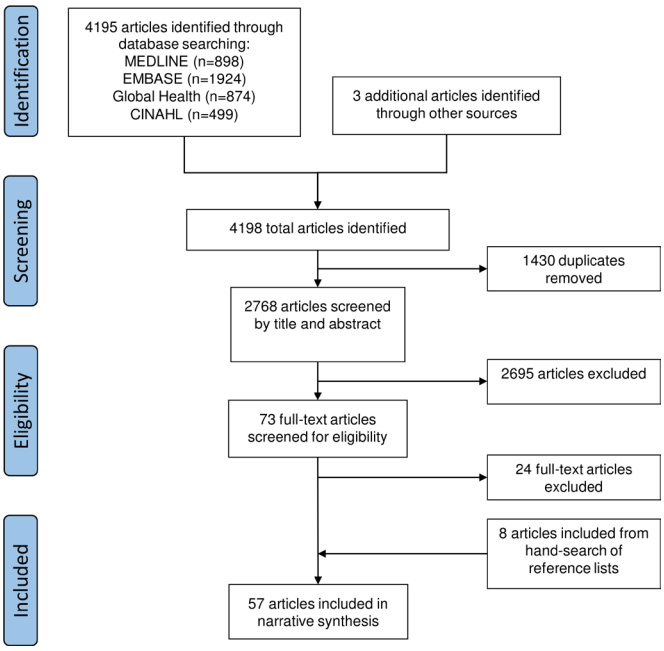

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the study selection process.

Exposure: exposure definitions included two closely related groups: (1) documented severe malnutrition in childhood defined according to standard classifications based on low weight-for-height, low weight-for-age (WFA), low mid-upper arm circumference (MUAC), or nutritional oedema, or (2) famine conditions defined by severe food insecurity in the local area or country setting. Although severe stunting is a form of severe malnutrition, we excluded studies that considered stunted children alone as the association between stunting and increased NCD risk has been described elsewhere.[13]

Comparators: a comparison group unexposed to documented severe malnutrition or famine in childhood was preferred but not required.

Outcomes: a range of cardiometabolic NCD outcomes (eg, impaired glucose metabolism, dyslipidaemia, hypertension) was considered if they were based on an objective clinical outcome measured at least 1 year after exposure to severe malnutrition or famine. All study designs were eligible. Grey literature and unpublished studies were excluded.

Screening and selection

Studies were screened for inclusion by a single author (KG) using a two-step process. First, potentially relevant studies were identified by screening titles and abstracts against the eligibility criteria. The full-text articles of identified studies were then reassessed to confirm their suitability for inclusion.

Risk-of-bias assessment

A risk-of-bias assessment at study level was conducted using the appraisal checklist for quantitative studies reporting correlations and associations from the UK National Institute for Health and Care Excellence. This 16-item checklist facilitates assessment of a study's internal and external validity (EV) based on key aspects of study design, including characteristics of study participants, definition of independent variables, outcomes assessed, and analytical methods.[14] Each study is assigned an overall quality grade for internal validity and another for EV as follows: (••) all or most of the checklist criteria have been fulfilled, where they have not been fulfilled the conclusions are very unlikely to alter, (•) some of the checklist criteria have been fulfilled, where they have not been fulfilled, or not adequately described, the conclusions are unlikely to alter, or (–) few or no checklist criteria have been fulfilled and the conclusions are likely or very likely to alter.

Data extraction, analysis, and reporting

Data were extracted using a standardised Microsoft Excel (2016) template that was piloted and adapted during the review process. The data extracted included: publication year, study design, study population, exposure definition, time since exposure, control group characteristics, outcomes, analytical methods, and key findings.

Due to the wide range of included NCD-related outcomes, meta-analysis was impossible. Therefore, a narrative synthesis was carried out for each outcome with a focus on any differential effects of exposure between subgroups where data allowed (eg, sex-specific or age-specific differences). Effect sizes for similar outcomes were compared across studies to identify areas of agreement or inconsistency in the results. Data from studies of famine survivors and documented severe childhood malnutrition were analysed separately to account for the different nature of the exposures.

Patient and public involvement

Neither patients nor the public were involved in this research.

RESULTS

Search results

The search yielded 2765 articles after removing duplicates. Three articles identified by senior authors were included for a total of 2768 articles for screening by title and abstract, which resulted in 73 articles for full-text appraisal. Another 24 articles were then excluded as they did not meet inclusion criteria. Eight eligible articles were identified from hand-searching reference lists for a total of 57 included articles (figure 1).

Study characteristics

A total of 57 articles published between 1968 and 2019 were included, with 31 (54%) published between 2015 and 2019. Among these studies, 14 (25%) examined NCD outcomes among survivors of documented severe childhood malnutrition in LMICs and 43 (75%) studied famine survivors. Famine studies were predominantly retrospective cohorts (n=31; 72%), followed

by prospective cohorts (n=7; 16%) and cross-sectional studies (n=5; 12%). Studies of documented severe malnutrition survivors were prospective cohorts (n=12; 86%) or case-control studies (n=2; 14%).

Study population and context

The studies represent findings from 15 countries; however, most were conducted among survivors of the Great Chinese Famine (n=30; 53%; table 1).

Participants in studies of documented severe childhood malnutrition were selected from clinic records of treatment for severe childhood malnutrition. However, in two case-control studies examining the exposure history of patients with diabetes, participants were recruited from outpatient clinics.[15 16]

Famine studies were conducted with participants exposed to famines between 1932 and 1970 (table 1). Participants in these studies were usually drawn from cross-sectional surveys or cohorts initiated for other studies. In some cases, participants were selected from physical examination records at health facilities or registries of patients with diabetes or siege survivors. In the Nigerian study, participants were recruited from central markets.[17]

In studies of documented severe childhood malnutrition, sample sizes ranged from 15 to 320 (median: 52; IQR: 34–100), whereas sample sizes varied between 62 and 105 374 for famine studies (median: 3548; IQR: 705–5920). For two of the famine studies, the number of cases and controls was not reported, and so the total number of participants was taken as the sample size.[18 19] Gender balance among participants varied across studies from 30% to 83% female; however, three studies had male-only samples, six studies had only female participants and information on participant gender was unavailable for three studies.[20–22]

Definitions of exposure to severe childhood malnutrition and famine

Various criteria were used to define severe malnutrition exposure, with admission to nutritional rehabilitation units based on WHO, Wellcome and Gomez classifications being the most common. Three studies used clinical diagnosis of marasmus or kwashiorkor without precise definitions,[20 23 24] and two used self-reports of severe childhood malnutrition.[15 16] In the study by Moore *et al* (2001), childhood WFA z-scores for all participants were analysed against NCD outcomes regardless of whether they classified as malnourished.[25]

Famine exposure was most frequently defined according to participants' birthdates and residency in famine-affected areas during childhood. However, five studies used individual self-reports of famine exposure.[26–30] Excess mortality was often used to approximate levels of famine severity in different locations. Due to the different nature of the exposures, study characteristics have been presented separately for famine studies (table 2) and documented severe malnutrition studies (table 3) along with the results of the risk-of-bias assessment. Detailed tables containing effect sizes and *p*-values can be found in online supplemental file 2. An alternative version of table 2 categorising famine studies by study design is in online supplemental file 3.

Outcomes assessed

Included studies examined the impact of severe childhood malnutrition or famine exposure on one or more cardiometabolic NCD outcomes, including: glucose metabolism, cardiovascular disease (CVD), dyslipidaemia, non-alcoholic fatty liver disease (NAFLD), blood markers of cardiometabolic disease (eg, acute phase proteins, cortisol), physical capacity, metabolic syndrome, chronic kidney disease, epigenetic profile, telomere length, thyroid function, and anthropometry. Outcomes were assessed between 2 and 70 years post exposure in studies of documented severe malnutrition and 28–70 years post exposure in famine studies.

Results by outcome

Because many of the studies presented in tables 2 and 3 reported findings on various outcomes, the results are summarised by outcome for clarity:

Cardiovascular outcomes

Famine studies

Famine exposure during childhood and adolescence was associated with increased risk of CVD (eg, myocardial infarction, coronary artery calcification) in 7/8 studies from the UK, China, Russia and the Netherlands,[22 27 29–33] with only one study of Leningrad Siege survivors finding no difference in the prevalence of CVD.[34] A sex-specific effect was noted in 2/3 studies; one study reported increased risk of peripheral arterial disease among women exposed to the Dutch Hunger Winter in adolescence, and another found higher mortality from cerebrovascular disease and ischaemic heart disease in men exposed to the Leningrad Siege at ages 9–15 years and 6–8 years, respectively.[31 33]

There was also consistent evidence of positive association between famine exposure and elevated blood pressure (BP) and hypertension in 8/11 studies from China, Nigeria and Russia.[17 32 33 35–39] However, three Chinese studies found no difference in BP or hypertension risk between unexposed controls and those exposed to famine in infancy, early childhood, and late childhood, respectively.[30 40 41] While the findings primarily indicate that famine exposure during infancy and childhood are associated with increased BP in adulthood, the two studies that included adolescents found positive associations between adolescent famine exposure (9–15 years) and increased BP.[32 33]

Documented severe malnutrition studies

Cardiovascular outcomes examined in studies of severe childhood malnutrition survivors largely focused on BP. These studies found mixed effects on BP outcomes, with one Jamaican study finding higher diastolic blood pressure (dBP) (d=4.3 mm Hg; p=0.007), but no differences in sBP, in survivors compared with controls at ~30 years, while a Mexican study found lower dBP (p=0.001) and sBP

Table 2 Summary of studies examining effects of early life famine exposure on non-communicable diseases (NCDs) outcomes

Study	Country and population	Exposure age group in years (sample size)	Outcome(s)	Key findings*	Risk-of-bias score (IV/EV)†
Great Chinese Famine (1959–1961)					
Chen *et al*[63]	China, adults>40 years	0–9 years (n=1799) 10–37 years (n=1064)	Visceral adipose dysfunction (VAD)	↑ VAD (women 0–9 years)	• / •
Huang *et al*[35]	China, women~50 years	0–1.5 years (n=1035) 1.5–2.5 years (n=743)	Hypertension, body mass index (BMI)	↑ Hypertension (0–1.5 years) ↑ BMI (1.5–2.5 years)	• / •
Li *et al*[44]	China, adults~45 years	0–2 years (n=1654) 3–5 years (n=1588) 6–8 years (n=1673)	Hyperglycaemia, type 2 diabetes (T2D)	↑ Fasting plasma glucose ↑ Hyperglycaemia (6–8 years)	• / •
Li *et al*[58]	China, adults~45 years	0–2 years (n=1654) 3–5 years (n=1588) 6–8 years (n=1673)	Metabolic syndrome (MetS)	↑ MetS (0–2 years)	• / •
Liu *et al*[19]	China, adults 35–74 years	0–9 years (n=n/r) 10–17 years (n=n/r)	Obesity	↑ Obesity	– / •
Liu *et al*[40]	China, adults 45–53 years	0–3 years (n=455)	Hypertension	↔ Hypertension	– / –
Meng *et al*[51]	China, adults~45 years	1–3 years (n=31 363)	T2D, obesity	↔ T2D, obesity ↓ Abdominal obesity	• / •
Shi *et al*[36]	China, adults~55 years	0–2 years (n=1149) 3–5 years (n=1217) 6–8 years (n=1250)	Cardiovascular disease (CVD)	↑CVD (with hypertension and famine exposure)	• / •
Sun *et al*[48]	China, adults~55 years	1–3 years (n=1297) 4–6 years (n=1476) 7–10 years (n=1499)	Hyperglycaemia, T2D	↑ Hyperglycaemia (women) ↓ T2D (men 1–3 years, 7–10 years)	– / –
Wang *et al*[45]	China, adults~60 years	1–3 years (n=1932) 3–5 years (n=1712) 5–7 years (n=1953)	T2D, hyperglycaemia	↑ T2D, hyperglycaemic (women 3–5 years, 5–7 years)	• / –
Wang *et al*[46]	China, adults 52–93 years	0–9 years (n=1911) 10–37 years (n=1188)	T2D	↑ T2D (women, 0–9 years)	• / ••
Wang *et al*[97]	China, adults 52–93 years	0–9 years (n=1778) 10–37 years (n=1076)	Non-alcoholic fatty liver disease (NAFLD)	↑ NAFLD (women, 0–9 years)	•/••
Wang *et al*[47]	China, adults 52–77 years	0–9 years (n=1140) 10–33 years (n=706)	T2D	↑ T2D (0–9 years)	•/••
Wang *et al*[59]	China, adults 52–93 years	0–9 years (n=1776) 10–37 years (n=1053)	MetS	↑ MetS (women, 0–9 years)	•/••
Wang *et al*[98]	China, women 52–93 years	0–9 years (n=1679) 10–37 years (n=1003)	Chronic kidney disease (CKD)	↔ CKD	•/••
Wang *et al*[37]	China, adults~50 years	0–2 years (n=3126)	Hypertension, obesity	↑ Hypertension ↔ Obesity	•/••
Wang *et al*[37]	China, adults~50 years	1–3 years (n=4563)	Overweight, obesity	↑ Weight/BMI (women) ↑ Obesity (women)	– / –

Continued

Table 2 Continued

Study	Country and population	Exposure age group in years (sample size)	Outcome(s)	Key findings*	Risk-of-bias score (IV/EV)†
Wang *et al*[38]	China, adults~50 years	0–1 years (n=338) 2–6 years (n=457)	Hypertension	↑ Hypertension (0–1 years)	• / •
Wang *et al*[56]	China, adults~50 years	0–1 years (n=536) 2–6 years (n=597)	Dyslipidaemia	↑ Low-density lipoprotein cholesterol (women)	– /•
Wang *et al*[60]	China, adults~50 years	0–1 years (n=269) 2–6 years (n=717)	MetS	↑ MetS (0–1 years)	– /•
Woo *et al*[30]	China, adults>65 years	Age in childhood n/s (n=2222)	NCDs, blood pressure, BMI	↑ BMI, myocardial infarction ↔ T2D, hypertension	•/ –
Xin *et al*[57]	China, adults,~60 years	3–12 years (n=2132) 13–20 years (n=1140)	Dyslipidaemia	↑ Dyslipidaemia	– / –
Yao *et al*[55]	China, adults,~60 years	2–4 years (n=206)	Dyslipidaemia	↔ Dyslipidaemia	– / –
Yu *et al*[39]	China, adults~60 years	0–3 years (n=2115) 3–5 years (n=1941) 5–7 years (n=2248)	Hypertension	↑ Hypertension	• / –
Yu *et al*[61]	China, adults~60 years	0–3 years (n=1940) 3–5 years (n=1741) 5–7 years (n=2010)	MetS	↑ MetS (women)	• / –
Zhang *et al*[49]	China, adults~55 years	0–3 years (n=1582)	Hyperglycaemic, T2D	↑ Hyperglycaemia (women)	• / •
Zheng *et al*[99]	China, adults~55 years	0–2 years (n=1344)	MetS	↑ MetS (women)	• / –
Zheng *et al*[62]	China, women~55 years	0–2 years (n=2403)	NAFLD	↑ NAFLD	• / –
Zheng *et al*[41]	China, adults~55 years	0–2 years (n=95)	Thyroid function	↓ Free thyroxine ↑ Thyroid stimulating hormone	– / –
Zhou *et al*[50]	China, adults 45–60 years	0–2 years (n=160) 3–5 years (n=173) 6–8 years (n=141)	NCDs	↑ T2D (0–2 years, 3–5 years) ↑ Hypercholesterolaemia (0–2 years)	– / –
Dutch Hunger Winter (1944–1945)					
Idris *et al*[29]	Netherlands, women~70 years	0–9 years (n=93) 10–18 years (n=54)	Coronary artery calcifications, valve calcification	↑ Coronary calcium score (10–18 years) ↔ Valve calcification	• / –
Portrait *et al*[31]	Netherlands, adults 60–76 years	0–1 years (n=81) 1–5 years (n=293) 6–10 years (n=244) 11–14 years (n=181)	Heart diseases, peripheral arterial diseases (PAD), T2D	↑ T2D, PAD (women, 11–14 years)	• / •
van Abeelen *et al*[27]	Netherlands, women 49–70 years	0–9 years (n=n/r) 10–17 years (n=n/r)	T2D	↑ T2D (0–9 years)	• / •
van Abeelen *et al*[28]	Netherlands, women 49–70 years	0–9 years (n=2196) 10–17 years (n=1773)	Coronary heart disease (CHD), stroke	↑ CHD (10–17 years) ↓ Stroke	• / •
Siege of Leningrad (1941–1944)					

Continued

Table 2 Continued

Study	Country and population	Exposure age group in years (sample size)	Outcome(s)	Key findings*	Risk-of-bias score (IV/EV)†
Koupil *et al*[33]	Russia, adults 40–70 years	1–5 years (n=81) 6–8 years (n=287) 9–15 years (n=739) 16–25 years (n=813)	CVD risk factors and mortality	↑ Hypertension (men 6–25 years) ↑ Ischaemic heart disease mortality (men 6–8 years) ↑ Cerebrovascular disease mortality (men 9–15 years)	• / •
Rotar *et al*[34]	Russia, adults 64–81 years	0–1 years (n=50) 1–10 years (n=210)	Cardiovascular health, telomere length	↔ CVD, organ damage ↓ Telomere length	• / –
Sparen *et al*[32]	Russia, men 64 – 83 years	6–8 years, 9–15 years, 16–26 years (total n=1406)	CVD risk factors and mortality	↑ BP (9–15 years) ↑ Ischaemic heart disease mortality, stroke (9–15 years)	•• / •
German occupation of Channel Islands (1944–1945)					
Head *et al*[22]	England, adults~70 years	8–22 years (n=225)	CVD	↑ CVD	– / –
Head *et al*[54]	England, adults~70 years	8–22 years (n=87)	Cholesterol levels	↔ Cholesterol levels	– / –
Holodomor famine (1932–1933)					
Khalangot *et al*[26]	Ukraine, adults>44 years	Age in childhood n/s (n=62)	Glucose tolerance	↓ T2D	• / •
Vaiserman *et al*[18]	Ukraine, adults~70 years	0–3 years (n=n/r)	T2D	↔ T2D	• / •
Post-monsoon famine in Bangladesh (1974–1975)					
Finer *et al*[21]	Bangladesh, adults~30 years	1–2 years (n=81)	Glucose tolerance, epigenetics	↔ Glucose tolerance ↕ Epigenetics	• / •
Biafran civil war (1967–1970)					
Hult *et al*[17]	Nigeria, adults~40 years	0–3 years (n=246)	Hypertension, glucose tolerance, BMI	↑ Blood pressure ↔ Glucose tolerance, BMI	• / –

Acceptable IV and EV | Poor IV or EV | Poor IV and EV.

*Symbols for effect direction: ↑ increased; ↓ decreased; ↕ mixed (indicate statistically significant results were reported, defined as p<0.05); ↔ none (indicates no statistically significant result was reported). If no age group is indicated beside the finding, then all age groups were affected.

†The scoring system used in the risk-of-bias assessment is described in the Methods section.

Table 3 Summary of studies examining effects of documented severe malnutrition in childhood on non-communicable disease (NCD) outcomes

Study	Setting and population	Type/timing of severe malnutrition (SM) exposure	Outcomes	Key findings*	Risk-of-bias score (IV/EV)†
Case-control studies					
Chege[15]	*Cases*: patients with diabetes 61.8±10.9 years, Kenya (n=45) *Controls*: age and sex-matched non-diabetics from same area attending outpatient clinics (n=45)	Self-reported episode of SM in childhood Exposure age not specified	T2D risk factors	↑ Childhood SM among diabetics	– / –
Fekadu *et al*[16]	*Cases*: insulin-requiring diabetics 18–40 years, Ethiopia (n=107) *Controls*: age and sex-matched patients attending other hospital clinics (n=110)	Self-reported episode of childhood SM Exposure age not specified	Insulin-requiring diabetes risk factors	↑ Childhood SM in diabetics	•/ –
Prospective cohort studies					
Benefice *et al*[65]	*Ex-malnourished*: children 5.5±0.5 years, Senegal (n=52) *Chronic controls*: chronically undernourished children (n=54) *Well-nourished controls (WN)*: age-matched, well-nourished children (n=33)	Marasmus Median age: 14 months	Motor fitness, anthropometry	↓ Handgrip in post-SM versus chronic controls ↓ Height/weight for age versus WN controls ↓ Distance throw, jump, agility/shuttle run versus WN controls ↔ Endurance run	•/ –
Boulé *et al*[52]	*Ex-malnourished*: young men 22.0±3.6 years, Mexico (n=26) *Controls*: young men 26.5±2.1 years with no history of SM (n=27)	Marasmus, kwashiorkor Age at admission: ≤1 years	Insulin sensitivity, abdominal obesity	↓ Insulin sensitivity w/ high abdominal fat versus fat-matched controls	• / –
Bourdon *et al*[77]	*Ex-malnourished*: children 9.6±1.6 years, Malawi (n=69) *Sibling controls*: closest in age to case child with no history of SM (n=44) *Community controls*: age and sex-matched (n=37)	Marasmus and kwashiorkor Median age at admission: 21.5 months	Cardiometabolic disease markers	↔ Metabolites	• / –
Cook[23]	*Ex-malnourished*: children 6.7–14.9 years, Uganda (n=31) *Controls*: children raised in similar environment as cases with no history of SM (n=21)	Kwashiorkor Mean age at admission: 1.9 years	Carbohydrate tolerance	↓ Glucose clearance ↑ Blood glucose 2 hours post oral glucose tolerance test (OGTT)	• / –

Continued

Table 3 Continued

Study	Setting and population	Type/timing of severe malnutrition (SM) exposure	Outcomes	Key findings*	Risk-of-bias score (IV/EV)†
Francis-Emmanuel *et al*[53]	*Ex-malnourished*: adult marasmus survivors (MS) (n=42) and kwashiorkor survivors (KS) (n=38) 17–50 years, Jamaica *Community controls*: age, sex, BMI-matched (n=70) *Birthweight-matched controls*: age-matched (n=40)	Marasmus and kwashiorkor Age at admission: 6–18 months	Glucose metabolism	↔ Fasting plasma glucose ↑ Glucose intolerance (MS versus KS) ↓ Insulin sensitivity (MS versus KS) ↔ Insulin sensitivity (MS versus controls) ↓ Insulinogenic and oral disposition indices (MS vs all groups)	•• / –
Gonzalez-Barranco *et al*[42]	*Ex-malnourished*: young men 20.2±3.6 years, Mexico (n=52) *Controls*: young men with no history of SM (n=50)	Marasmus, kwashiorkor Mean age at admission: 4.5 months	Glucose metabolism, lipid profile, blood pressure (BP)	↑ Areas under the curves of glucose and insulin ↓ Insulin sensitivity, BP ↔ Fasting blood glucose, lipid profile	•• / –
Idohou-Dossou *et al*[20]	*Ex-malnourished*: children 6–8 years, Senegal (n=24) *Sibling controls (SC)*: closest in age to case child with no history of SM (n=24) *Well-nourished controls (WN)*: age-matched healthy children from wealthier area (n=19)	Marasmus Age at admission: 1–3 years	Biochemical nutritional indicators, growth factors, anthropometry	↓ Apolipoprotein A↔ versus WN controls, no difference between post-SM and SC ↓ Lean mass in post-SM and SC associated with low IGF-↔	• / –
Kajubi[24]	*Ex-malnourished*: adolescents 11–19 years, Uganda (n=15) *Controls*: adolescents with no history of SM (n=11)	Kwashiorkor Age at admission: 1.5–3 years	Pancreatic function	↔ Blood glucose post-OGTT ↓ Fasting plasma insulin	•/–
Lelijveld *et al*[9]	*Ex-malnourished*: children 9.6±1.6 years, Malawi (n=320) *Sibling controls (SC)*: closest in age to case child with no history of SM (n=217) *Community controls (CC)*: age and sex-matched with no history of SM (n=184)	Marasmus, kwashiorkor Median age at admission: 24 months	Blood markers of NCDs, physical capacity, anthropometry	↔ Glucose tolerance, glycosylated haemoglobin, blood lipids, salivary cortisol ↑ Diastolic BP in post-SM versus SC ↓ Handgrip strength versus CC/SC ↓ Lean mass versus CC but similar to SC	••/–

Continued

Table 3 Continued

Study	Setting and population	Type/timing of severe malnutrition (SM) exposure	Outcomes	Key findings*	Risk-of-bias score (IV/EV)†
Moore *et al*[25]	Rural adults (mean age 35.8 years), Gambia (n=145)	Low weight-for-age z-score (WAZ) WAZ measured at 18 months	Cardiovascular disease (CVD) risk factors	↓ Fasting plasma insulin in lower WAZ quartiles ↔ Fasting blood glucose, blood glucose or insulin post-OGTT, cortisol, BP	••/–
Sheppard *et al*[84]	*Ex-malnourished*: adult survivors of kwashiorkor (KS) 29.82±9.03 years (n=21) or marasmus (MS) 25.02±5.69 years (n=23), Jamaica	Marasmus, kwashiorkor Mean age at admission: 11 months	Epigenetic profile in muscle tissue	↕ Differences in DNA methylation of 63 genes related to, body size/composition, glucose metabolism, musculoskeletal growth, cardiovascular pathways between MS and KS	•/–
Tennant *et al*[43]	*Ex-malnourished*: adult survivors of childhood kwashiorkor (n=62) 27.2±7.8 years and marasmus (n=54) 29.2±8.4 years, Jamaica *Community controls*: age and sex matched with no history of SM (n=45)	Marasmus, kwashiorkor Mean age at admission: 12 months	Cardiovascular structure/function	↓ Left ventricular outflow tract parameter, stroke volume, cardiac output, pulse wave velocity ↑ Diastolic BP ↔ Systolic BP ↑ Systemic vascular resistance ↑ Heart rate in MS versus KS ↔ Large vessel, cardiac remodelling	••/–

Acceptable IV and EV . Poor IV or EV . Poor IV and EV .

*Symbols for effect direction: ↑ increased; ↓ decreased; ↕ mixed (indicate statistically significant results were reported, defined as p<0.05); ↔ none (indicates no statistically significant result was reported). If no age group is indicated beside the finding, then all age groups were affected.

†The scoring system used in the risk-of-bias assessment is described in the Methods section.

T2D, type 2 diabetes.

(p<0.0001) in survivors at ~20 years.[42 43] Among Malawian survivors at ~9 years, dBP was higher than sibling controls (d=1.91 mm Hg, p=0.03).[9] Meanwhile, a Gambian study showed no association between decreasing WAZ in the malnourished range in childhood and sBP or dBP at ~36 years in women.[25]

The single study that examined cardiovascular structure and function found reduced left ventricular outflow tract, stroke volume, cardiac output, and pulse wave velocity, together with increased systemic vascular resistance in survivors versus controls.[43]

Glucose metabolism outcomes

Famine studies

The evidence shows a positive association between childhood famine exposure and impaired glucose metabolism, with 2/15 studies finding increased risk of hyperglycaemia and 7/15 showing increased diabetes risk.[28 31 44–50] The five studies that stratified analyses by sex found increased risk of glucose metabolism disorders in women only.[31 45 46 48 49]

Increased risk of hyperglycaemia in famine-exposed women was found in two Chinese studies. Both found similarly increased risk as a result of early childhood famine exposure (0–3 years; OR 1.48; 95% CI 1.15 to 1.9[48]; OR 1.55; 95% CI 1.10 to 2.19[49]), with one study finding further associations with exposure in mid-childhood (4–6 years; OR 1.38; 95% CI 1.06 to 1.79) and late childhood (7–10 years; OR 1.57; 95% CI 1.25 to 1.98).[48 49] By contrast, one of these studies found a decreased risk of diabetes in men exposed to famine in early (OR 0.65; 95% CI 0.49 to 0.86) and late childhood (OR 0.74; 95% CI 0.56 to 0.98) compared with controls.[48]

Increased diabetes risk was found in seven studies from China and the Netherlands (5/7 and 2/7, respectively) after childhood famine exposure,[28 31 44–47 50] with three studies reporting an effect in women only.[31 45 46] Increased diabetes risk was mainly observed among participants exposed to famine in early and late childhood (0–10 years); however, one Dutch study reported increased risk in the female adolescent exposure group (11–14 years) only.[31]

Of the remaining six studies, five reported null findings and one reported a negative relationship between famine exposure and impaired glucose metabolism in adulthood. Studies from Bangladesh, Nigeria, China and Russia found no association between childhood famine exposure and impaired glucose metabolism when outcomes were assessed between ~30 and 80 years.[17 18 21 41 51] Finally, one study of Ukrainian famine survivors reported reduced diabetes risk in childhood-exposed participants (OR 0.063; 95% CI 0.007 to 0.55) compared with unexposed controls.[26]

Documented severe malnutrition studies

The evidence indicates that severe childhood malnutrition is associated with impaired glucose metabolism in survivors, with 6/9 studies reporting a positive association with diabetes, reduced insulin sensitivity, or glucose intolerance.[15 16 23 42 52 53] Notably, a Jamaican study that differentiated between survivors of marasmus and kwashiorkor reported greater fasting insulin, increased glucose intolerance, and reduced insulin sensitivity in adult marasmus survivors only.[53] Conversely, a Ugandan study showed that glucose tolerance was impaired in kwashiorkor survivors compared with healthy controls.[23] In a Mexican study, insulin sensitivity was reduced in survivors with high levels of abdominal fat even when matched to controls with similar levels of abdominal obesity; however, when matched for low amounts of abdominal fat, survivors and controls had similar insulin sensitivity.[52] Severe childhood malnutrition was a risk factor for type 2 and insulin-requiring diabetes in case-control studies of patients with diabetes in Kenya and Ethiopia.[15 16]

The remaining 3/9 studies found no differences in glucose metabolism between severe malnutrition survivors and controls; however, these studies assessed outcomes in children, adolescents, and lean adults on a low-fat diet, respectively, which may have led to underestimation of the long-term effects of severe malnutrition.[9 24 25]

Lipid metabolism outcomes

Famine studies

Of eight studies that reported on lipid metabolism outcomes, four reported no difference in lipid profiles between famine-exposed participants and controls.[21 41 54 55] Three Chinese studies found increased risk of dyslipidaemia after childhood famine exposure between 0 and 12 years, with one also reporting an effect in the adolescent group (13–20 years).[50 56 57] A study of Leningrad Siege survivors found higher high-density lipoprotein (HDL) in exposed participants (p=0.008) but no difference in triglycerides compared with controls.[34] Only one Chinese study stratified analyses by sex and it found an increased risk of dyslipidaemia in women only.[56]

Documented severe malnutrition studies

Three studies of severe malnutrition survivors examined lipid metabolism, with two finding no differences between the lipid profiles of controls and survivors at ~9 years (Malawi) and ~20 years (Mexico), respectively.[9 42] One study found reduced apolipoprotein A1 in Senegalese marasmus survivors compared with well-nourished controls (p<0.05) but no difference compared with sibling controls.[20]

Metabolic syndrome outcomes

Famine studies

All five studies of metabolic syndrome (MetS) in Chinese famine survivors showed an increased risk in participants exposed between 0 and 9 years.[58–62] Four studies stratified analyses by sex and found increased risk exclusively in women.[59–62] Another Chinese study used a different method to assess MetS-related outcomes called the 'visceral adiposity index' (VAI), a sex-specific equation

based on waist circumference, BMI, and triglyceride and HDL levels. They found a positive association between childhood famine exposure (0–9 years) and VAI in women only.[63]

Obesity-related outcomes

Famine studies

Evidence on obesity-related outcomes in famine survivors showed mixed effects. Four Chinese studies reported increased BMI, obesity or overweight among those exposed to famine between 0 and 9 years and followed up in late adulthood.[19 30 35 64] Conversely, three studies found no association between famine exposure between 0 and 3 years and overweight, obesity, BMI or waist circumference.[17 37 41]

Documented severe malnutrition studies

In contrast with famine survivors, evidence on anthropometric outcomes in severe malnutrition survivors indicates that they remain thinner than unexposed controls through childhood to adulthood. Of six studies, five reported that survivors had lower BMI, WFA, MUAC or WAZ than controls when measured as older children or adults.[9 20 42 52 65] However, two studies noted that WFA and WAZ were lower in severe malnutrition survivors compared with well-nourished controls but observed no difference when compared with chronically malnourished or sibling controls, respectively.[20 65]

Results for outcomes with ≤3 studies reporting results can be found in online supplemental file 4, including NAFLD, physical capacity, chronic kidney disease, thyroid function, metabolomics, and epigenetic and genetic outcomes.

DISCUSSION

Summary of main results

We found evidence to support the hypothesis that exposure to severe malnutrition or famine during childhood increases long-term risk of cardiometabolic NCDs. The evidence was strongest for an association with CVD (myocardial infarction, coronary artery calcification, peripheral arterial disease, cerebrovascular disease, ischaemic heart disease, hypertension), impaired glucose metabolism (diabetes, hyperglycaemia) and MetS, while evidence for effects on lipid metabolism and obesity risk was less consistent. Where increased risk of NCDs in exposed groups was reported as an OR, effect sizes ranged from 1.11 to 5.50. Overall, these results suggest that childhood malnutrition may have a clinically, as well as statistically, significant effect on NCD risk in some survivors. Sex-specific differences were observed in some cohorts, with famine-exposed women at higher risk of glucose metabolism disorders and MetS than their male counterparts.

Interpretation of findings

Windows of developmental plasticity

Current literature suggests that developmental plasticity extends beyond prenatal life and that severe malnutrition in childhood exerts independent effects on NCD risk. Due to heterogeneity in exposure age across studies, it is difficult to conclude whether morbidity risk is higher among children exposed at specific ages. However, it appears that the window of plasticity could remain open beyond the first 1000 days of life, which is the focus of much current child health policy and programming.

Our results build on a narrative review of differences in cardiometabolic risk between marasmus and kwashiorkor survivors from Boyne *et al* (2017) by systematically identifying new evidence for an effect of severe malnutrition and famine exposure in childhood on NCD risk.[11] Building on the DOHaD hypothesis, these findings indicate that severe childhood malnutrition may not only have serious implications for short-term morbidity and mortality but also for survivors' long-term health. This concept is described by Wells' (2018) 'capacity-load model of NCD risk', which proposes that individuals develop physiological traits during early life that give them the capacity to maintain homeostasis in metabolism and cardiovascular function when challenged by a metabolic load.[66] Therefore, if postnatal malnutrition impairs development of metabolic capacity, then survivors are more vulnerable to NCDs in later life, especially in an increasingly obesogenic environment.

Mechanistic links between severe malnutrition or famine in childhood and NCDS

There is little mechanistic evidence linking severe malnutrition or famine in childhood and long-term NCD risk, with most studies speculating on mechanisms or extrapolating from findings on prenatal malnutrition. Commonly proposed mechanisms include:

Growth acceleration

There is strong evidence that periods of rapid postnatal weight gain increase obesity and CVD risk later in life, with observational and intervention studies showing that accelerated early growth is associated with later body fatness as well as increased BP, cholesterolaemia and insulin resistance.[67–71] Since rapid weight gain often follows episodes of severe childhood malnutrition, this may explain the increased CVD risk among those exposed to postnatal malnutrition followed by nutritional recovery.[72] While the mechanisms linking rapid weight gain with NCD risk are not fully understood, the evidence is strongest for increased visceral adiposity as the key causal factor in CVD and diabetes.[73–75]

Body composition in later life

Endocrine changes caused by malnutrition may influence body composition in adult survivors and affect their NCD risk.[11] Reduced growth factors (eg, IGF-1) and insulin, along with higher cortisol levels, may be conducive to stunting, reduced muscle mass, and a tendency towards obesity with high calorie intake.[76] In studies of older children who experienced severe malnutrition in early life, survivors had less lean mass and more stunting compared with community controls, which was associated with low IGF-1.[9 20 77] This phenotype may increase

NCD risk as skeletal muscle is the major site of insulin-induced glucose uptake and therefore protects against insulin resistance and MetS.[78 79]

Impaired pancreatic function

Animal studies have shown that postnatal malnutrition negatively impacts pancreatic β-cell function.[80 81] When malnutrition was induced in rats during lactation and the postweaning period using a low-protein diet, there were negative effects on insulin secretion leading to impaired glucose tolerance. On nutritional rehabilitation, the deleterious effects were reversed in the lactation-exposed group but not in the postweaning group, suggesting that postnatal malnutrition can permanently alter pancreatic function and lead to glucose metabolism disorders.[80]

Altered hypothalamic–pituitary–adrenocortical (HPA) axis

Exposure to stressors in utero and during childhood may alter the set-point of the HPA axis as an adaptation to cope with an anticipated high-stress environment in later life.[82] However, these changes in neuroendocrine mediators of the stress response may predispose to metabolic disease when the adult environment is mismatched for these adaptations as excess glucocorticoids have been associated with hypertension and glucose intolerance.[83]

Epigenetic changes

While literature on epigenetic effects of early-life malnutrition on NCD risk largely focuses on the antenatal period, postnatal malnutrition may also cause epigenetic changes that contribute to future cardiometabolic disease risk.[21 84 85] If epigenetic plasticity extends into postnatal life, then this may provide the mechanistic link between early-life malnutrition and later disease by 'programming' an adverse metabolic phenotype.[86 87] However, epigenetic studies on the effects of childhood malnutrition are limited, and this theory requires further supporting evidence.

Sex-specific effects

Women exposed to famine in childhood appear to be at higher risk of glucose metabolism disorders and MetS than famine-exposed men. This finding is supported by a recent meta-analysis examining the effect of early-life famine exposure on risk of MetS in adulthood that included 39 studies (n=81 504). Compared with a non-exposed group, early-life famine exposure significantly increased the risk of MetS in women only.[88] However, most studies were conducted in China where families may have preferentially allocated food and other resources to sons at the expense of daughters during the famine due to a culture of 'son preference'.[89] Malnutrition severity may thus explain increased NCD risk in women.[89] While hypothetically this would select for the healthiest female survivors, it would also improve the average welfare of males, leading to better long-term health.[89] Another explanation might be healthy survivor effect in boys as a recent review found that they are biologically more vulnerable to malnutrition and potentially only the healthiest survived.[90]

Review limitations and strengths

We acknowledge several limitations. Due to our broad scope, there was extensive clinical and methodological heterogeneity between studies, rendering it difficult to directly compare study findings. As all studies were observational, associations cannot be interpreted as causal. This makes it difficult to disentangle the effects of fetal and postnatal malnutrition. Few studies controlled for effects of foetal malnutrition as the proxy measure of birth weight was rarely available; however, four studies showed independent effects of postnatal malnutrition on NCD risk after controlling for birth weight.[22 42 52 53] Inadequately controlled age effects are another important confounder as most famine studies used birthdate to determine famine exposure. This was primarily an issue in Chinese studies as there were no truly unexposed areas during the Chinese famine, rendering it difficult to make comparisons with age-matched controls.[48] Because there was no overlap in the birth years of exposed and non-exposed participants, age adjustment in regression models alone will have no impact on risk estimate calculations.[91] Without an age-matched or age-balanced control group, age differences between groups may explain many of the effects on NCD outcomes attributed to famine exposure because ageing is a risk factor for NCDs and childhood-exposed groups were older than controls born post famine.[91 92]

Another limitation is the small sample size in some studies; thus, the children included may not represent the wider affected/at-risk population and chance observations are possible. We also note the risk of selection and information bias. Because severe childhood malnutrition is associated with high mortality, participants may represent the healthiest survivors and any effects observed in these populations may underestimate long-term health impacts of severe malnutrition.[9 93] Misclassification of famine exposure status is an important source of information bias. Most studies assigned exposure status and severity based on birth date and place relative to famine years and regions of excess mortality. This may have resulted in misclassification of participants into incorrect exposure groups because individual exposure data were not available; participants may have been exposed to varying degrees of famine severity or even entirely protected for circumstantial reasons.

Finally, we recognise the currently limited data sources on this topic; although we identified an important number of individual papers, many were from the same famine event and some had high risk of bias. However, even when studies with higher risk of bias were discounted from our analysis, we found that most studies from the Great Chinese Famine, Dutch Hunger Winter and Siege of Leningrad (the famine events for which there were >2 available studies) showed a positive association between famine exposure and NCD outcomes. Therefore, our

conclusions regarding the potential relationship between famine exposure and NCDs remain valid and all studies were included in the results so as to present a complete overview of available literature. We hope that future research in different settings might add further weight to our findings.

Our review has several strengths. To our knowledge, this is the only systematic review on this topic. It examines a highly topical subject; COVID-19 threatens to trigger food crises and famines worldwide, putting great numbers of children at risk of severe malnutrition.[94–96] The resulting potential increase in NCDs risks putting a major burden on already overstretched health systems in LMICs in coming decades. Finally, while all studies were observational, there was consistency in findings, strength of associations, biological plausibility, temporal progression between exposure and outcomes, and coherence between epidemiological and laboratory findings.[80 81]

Implications of findings and future research

If postnatal malnutrition influences long-term NCD risk as our results suggest, this is of global public health significance given the growing NCD epidemic in LMICs where there remains a large burden of severe childhood malnutrition.[3] Prevention of severe malnutrition should be prioritised as no child should have to suffer the short-term or long-term effects of malnutrition. While short-term mortality and morbidity are widely recognised outcomes of malnutrition, we hope that the case for prevention will be further strengthened once policymakers and funders appreciate the long-term sequelae highlighted in our review.

With over 80% of premature NCD-related deaths occurring in LMICs, where health systems already struggle with this massive disease burden, the need for interventions to prevent NCDs among severe malnutrition survivors is urgent. Our review highlights the limited evidence relevant to LMIC contexts, where severe malnutrition remains a threat to public health. Many of the highest quality studies we identified were conducted in settings where famine events were short lived and therefore may underestimate the effects of severe malnutrition in some contemporary contexts where malnutrition is endemic. There is a need for more high-quality studies in a wider range of contemporary LMIC settings to explore the potential links between severe malnutrition and NCDs.

There is reasonable strength and consistency in the findings and biological plausibility to indicate an association between severe malnutrition or famine exposure and increased NCD risk. However, the precise mechanisms underlying this association remain largely unclear. For instance, how do long-term outcomes differ by duration, intensity, and age at which a child experiences malnutrition and what are the biological processes leading to long-term adverse effects. Research in this area will be essential to inform policy and programming around prevention and management strategies for severe childhood malnutrition that promote long-term health in survivors as well as strategies to mitigate NCD risk among famine survivors. Recent predictions of major hunger following the COVID-19 pandemic make our review particularly timely.[94 95] Taking action to prevent and appropriately treat this hunger is not only vital to save child lives, but also matters for NCD prevalence in decades to come.

CONCLUSION

Our review indicates that severe malnutrition or famine exposure in childhood is associated with increased NCD risk later in life. The evidence on CVD, impaired glucose metabolism and MetS consistently shows deleterious effects of postnatal malnutrition on these chronic disease outcomes. Evidence for effects on lipid metabolism and obesity risk is less consistent.

Given that many countries with large burdens of child malnutrition also face NCD epidemics, understanding associations between severe childhood malnutrition and chronic diseases has major implications for preventing long-term morbidity and mortality. Increased global hunger resulting from the COVID-19 pandemic makes this link more important than ever. Efforts must be made to prevent and appropriately treat child malnutrition: not only to avoid short-term mortality, but to avoid escalating an already overwhelming NCD burden in decades to come. Better evidence is required from contemporary LMIC contexts where severe malnutrition may be inflicting long-lasting damage on public health.

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Online supplementary file 1
Severe malnutrition or famine exposure in childhood and cardiometabolic non-communicable disease risk later in life: a systematic review (Grey K et al., 2020)

SEARCH STRATEGY:
Database: Ovid MEDLINE(R) and In-Process & Other Non-Indexed Citations and Daily <1946 to July 30, 2019> Search Strategy:
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1. ((severe* or acute* or moderate*) adj3 (malnutrition or malnourished or undernutrition or undernourished or wasted or wasting)) (6321)
2. ((post natal or postnatal) adj3 undernutrition) (174)
3. kwashiorkor* (3005)
4. ((oedematous or edematous) adj2 malnutrition) (66)
5. (nutrition* oedema or nutrition* edema) (101)
6. marasm* (1152)
7. ((non oedematous or non edematous or nonoedematous or nonedematous) adj2 malnutrition) (10)
8. wasting (16802)
9. wasted (3224)
10. emaciat* (2371)
11. wasting syndrome* (3156)
12. ((protein or energy) adj2 malnutrition) (9757)
13. nutrition* depriv* (719)
14. underweight (9759)
15. starvation (32720)
16. famine* (2254)
17. (low adj1 (MUAC or mid upper arm circumference or weight for length or WFL or WLZ or weight for age or WFA or WAZ)) (265)
18. exp severe acute malnutrition/ (2753)
19. protein-energy malnutrition/ (7213)
20. wasting syndrome/ (1166)
21. starvation/ (9737)
22. (metabolic adj3 syndrome*) (53310)
23. dysmetabolic syndrome* (108)
24. insulin resistance syndrome* (1716)
25. glucose metaboli* disorder* (1083)
26. ((type 2 or type II or obes*) adj1 diabet*) (138876)
27. ((type 2 or type II or obes*) adj1 DM) (3464)
28. (diabetes adj2 (type 2 or type II)) (170899)
29. (adult adj2 diabet*) (2410)
30. ((maturity onset or late onset) adj1 diabet*) (2053)
31. glucose intoleran* (15708)
32. glucose toleran* (56836)
33. insulin resistan* (91557)
34. MODY (1193)
35. NIDDM (6899)
36. DMNID (9)
37. ((non insulin dependent or noninsulin dependent or non insulin?dependent or noninsulin?dependent) adj1 diabet*) (11252)
38. ((non insulin treated or noninsulin treated or non insulintreated or noninsulin?treated or non insulin or noninsulin) adj1 diabet*) (142)

39. hyperinsulin* (26197)
40. glucose homeostasis (12345)
41. glucose regulation (2383)
42. insulin sensitiv* (31712)
43. (fasting adj2 glucose) (38270)
44. hyperglyc?emi* (66898)
45. glycated h?emoglobin (38356)
46. HbA1c (29756)
47. (cardio metabolic disorder* or cardiometabolic disorder*) (550)
48. lipid metabolism (93948)
49. lipid* profile* (28445)
50. plasma lipid* (13195)
51. hypercholesterol?emia (43123)
52. dyslipid?emia* (34335)
53. hyperlipid?emia* (43311)
54. (non alcoholic fatty liver disease or nonalcoholic fatty liver disease) (18003)
55. NAFLD (11670)
56. fat* liver (38196)
57. (cardiovascular disease* or cardio vascular disease*) (241048)
58. coronary heart disease* (48413)
59. hypertension (462338)
60. blood pressure (427853)
61. atheroscleros* (119342)
62. ((cardiovascular or cardio vascular) adj2 (function* or structure* or risk*)) (100701)
63. (muscle adj1 (strength or function)) (40358)
64. physical capacity (1784)
65. grip strength (10168)
66. (hand adj2 strength) (14799)
67. exp diabetes mellitus, type 2/ (124121)
68. exp insulin resistance/ (78156)
69. exp hyperglycemia/ (34546)
70. exp dyslipidemias/ (76958)
71. hypertension/ (227123)
72. arteriosclerosis/ (56520)
73. cardiovascular diseases/ (139159)
74. (Africa or Asia or Caribbean or West Indies or South America or Latin America or Central America) (245079)
75. (Afghanistan or Albania or Algeria or Angola or Antigua or Barbuda or Argentina or Armenia or Armenian or Aruba or Azerbaijan or Bahrain or Bangladesh or Barbados or Benin or Byelarus or Byelorussian or Belarus or Belorussian or Belorussia or Belize or Bhutan or Bolivia or Bosnia or Herzegovina or Hercegovina or Botswana or Brasil or Brazil or Bulgaria or Burkina Faso or Burkina Fasso or Upper Volta or Burundi or Urundi or Cambodia or Khmer Republic or Kampuchea or Cameroon or Cameroons or Cameron or Camerons or Cape Verde or Central African Republic or Chad or Chile or China or Colombia or Comoros or Comoro Islands or Comores or Mayotte or Congo or Zaire or Costa Rica or Cote d'Ivoire or Ivory Coast or Croatia or Cuba or Cyprus or Czechoslovakia or Czech Republic or Slovakia or Slovak Republic or Djibouti or French Somaliland or Dominica or Dominican Republic or East Timor or East Timur or Timor Leste or Ecuador or Egypt or United Arab Republic or El Salvador or Eritrea or Estonia or Ethiopia or Fiji or Gabon or Gabonese Republic or Gambia or Gaza or Georgia Republic or Georgian Republic or Ghana or Gold Coast or Greece or Grenada or Guatemala or Guinea or Guam or Guiana or Guyana or Haiti

or Honduras or Hungary or India or Maldives or Indonesia or Iran or Iraq or Isle of Man or Jamaica or Jordan or Kazakhstan or Kazakh or Kenya or Kiribati or Korea or Kosovo or Kyrgyzstan or Kirghizia or Kyrgyz Republic or Kirghiz or Kirgizstan or Lao PDR or Laos or Latvia or Lebanon or Lesotho or Basutoland or Liberia or Libya or Lithuania or Macedonia or Madagascar or Malagasy Republic or Malaysia or Malaya or Malay or Sabah or Sarawak or Malawi or Nyasaland or Mali or Malta or Marshall Islands or Mauritania or Mauritius or Agalega Islands or Mexico or Micronesia or Middle East or Moldova or Moldovia or Moldovian or Mongolia or Montenegro or Morocco or Ifni or Mozambique or Myanmar or Myanma or Burma or Namibia or Nepal or Netherlands Antilles or New Caledonia or Nicaragua or Niger or Nigeria or Northern Mariana Islands or Oman or Muscat or Pakistan or Palau or Palestine or Panama or Paraguay or Peru or Philippines or Philipines or Phillipines or Phillippines or Poland or Portugal or Puerto Rico or Romania or Rumania or Roumania or Russia or Russian or Rwanda or Ruanda or Saint Kitts or St Kitts or Nevis or Saint Lucia or St Lucia or Saint Vincent or St Vincent or Grenadines or Samoa or Samoan Islands or Navigator Island or Navigator Islands or Sao Tome or Saudi Arabia or Senegal or Serbia or Montenegro or Seychelles or Sierra Leone or Slovenia or Sri Lanka or Ceylon or Solomon Islands or Somalia or South Africa or Sudan or Suriname or Surinam or Swaziland or Syria or Tajikistan or Tadzhikistan or Tadjikistan or Tadzhik or Tanzania or Thailand or Togo or Togolese Republic or Tonga or Trinidad or Tobago or Tunisia or Turkey or Turkmenistan or Turkmen or Uganda or Ukraine or Uruguay or USSR or Soviet Union or Union of Soviet Socialist Repu blics or Uzbekistan or Uzbek or Vanuatu or New Hebrides or Venezuela or Vietnam or Viet Nam or West Bank or Yemen or Yugoslavia or Zambia or Zimbabwe or Rhodesia) (3499931)

76. ((developing or less* developed or under developed or underdeveloped or middle income or low* income or underserved or under served or deprived or poor*) adj (countr* or nation? or population? or world)) (90208)
77. ((developing or less* developed or under developed or underdeveloped or middle income or low* income) adj (economy or economies)) (485)
78. (low* adj (gdp or gnp or gross domestic or gross national)) (231)
79. (low adj3 middle adj3 countr*) (12882)
80. (lmic or lmics or third world or lami countr*) (6290)
81. transitional countr* (154)
82. famine* (2254)
83. Dutch Hunger Winter (46)
84. Siege of Leningrad (30)
85. developing countries/ (72581)
86. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 (80392)
87. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 (1546841)
88. 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 (3644081)
89. 86 and 87 and 88 (1361)
90. limit 89 to (english language and humans) (898)

Online supplementary file 2
Severe malnutrition or famine exposure in childhood on cardiometabolic non-communicable disease risk later in life: a systematic review (Grey K et al., 2020)

Table 2. Detailed summary of studies examining effects of early life famine exposure on NCD outcomes

Lead author, year, study design	Population, setting, sample size (%female)	Timing of famine exposure	Years post-exposure	Outcome(s)	Key findings
Chen 2019[31] Retrospective cohort	Study population: adults>40y, SPECT China Survey (n=3569, ~57% across groups) Controls: conceived post-famine (n=1726)	Prenatal: n=706 Childhood: 0-9y, n=1799 Adolescent/adult: 10-37y, n=1064	~50y	Visceral adipose dysfunction (VAD)	-Positive association between childhood famine exposure and VAD in women (B=0.13;0.02-0.24; p<0.05) vs non-exposed women -No association in men PreN: Higher VAD in prenatal exposed women vs non-exposed (p<0.05) (BW: n/r)
Finer 2016[21] Retrospective cohort	Study population: adults ~30y, cross-sectional survey in rural Bangladesh (n=121, n/a) Epigenetics sub-sample (n=143) Controls: conceived post-famine (n=70) Older controls: exposed >16y (n=112), for comparison to a background population	Prenatal: n=40 Postnatal: 1-2y, n=81	~28y	Metabolic profile, DNA methylation of metastable epialleles (ME) sensitive to maternal nutrition	-No differences in BG post-OGTT, T2D, IFG, IGT, or fasting lipids between postnatal and unexposed group (all p>0.05) PreN: hypomethylation at 7 ME vs postnatal and control groups (p=0.0003) (BW: n/r)

Head 2008[22] Retrospective cohort	Study population: birth cohort attended by community midwife on Guernsey, UK (1923-37) (n=225, 52%) Controls: evacuated before German occupation (n=648)	Postnatal: 8-22y, n=225	~50y	CVD	-Higher CVD risk in postnatal group vs controls (HR2.52; 1.54-4.13) -Higher risk of CVD in urban parishes (more severe food deprivation) vs rural parishes (p=0.01) (BW: no association between BW and CVD (HR/kg increase BW:1.12; 0.70–1.78))
Head 2009[32] Retrospective cohort	Study population: birth cohort attended by community midwife on Guernsey, UK (1923-37) (n=87, 52%) Controls: evacuated before German occupation (n=309)	Postnatal: 8-22y, n=87	~30y	Cholesterol levels	No association between exposure to occupation (d=0.04mmol/; -0.26-0.33) for exposed group) and cholesterol levels (BW: no association between BW (d=0.08mmol/l per kg increase;0.17-0.34) and cholesterol levels)
Huang 2010[33] Retrospective cohort	Study population: women born 1957-63 from folic acid trial from 1993-96 in three Chinese provinces (n=19,719, 100%) n, rural=32,732 (more severe famine exposure) n, urban=2,293 Controls: conceived post-famine(n=15,306)	Prenatal: 1960,1961,1962 (n=6195) Postnatal: 1957, 1.5-2.5y, n=743 Postnatal: 1958,0-1.5y, n=1035	~30y	Hypertension, height, BMI	-Higher risk of HT in 1958 rural women 3.97x vs controls (log odds: 1.38; 0.17–2.59) -Reduced height in 1958 rural women (d=1.66cm; 0.63-2.69) due to exposure -Increased BMI in 1957 women (d=0.92 kg/m2; 0.32-1.51) due to exposure PreN: lost height in 1959 rural women (1.33cm; 0.46-2.19), reduced BMI in 1960 (-0.32kg/m2; -0.58, -0.08) and 1961 group (-0.30 kg/m2; -0.58, -0.02). No association w/ HT. (BW: n/r)
Hult 2010[17]	Study population: adults born in southeast Nigeria 1965-73 working in Enugu,	Fetal/infant: n=292	~40y	Hypertension, glucose tolerance (GT), overweight	-Higher risk of high BP (sBP>140mmHG) in overweight adults famine-exposed in childhood (OR=3.95; 1.88-9.04) vs controls

Prospective cohort	former Biafran capital (n=538, ~30% across groups) Controls: conceived post-famine (n=486)	Childhood: 0-3y, n=246			-No differences in GT, BMI in childhood exposed group vs controls PreN: Fetal-infant exposure associated w/ elevated sBP (p<0.001), dBP (p<0.001), BG (p<0.05), waist circumference (p=0.001), systolic HT (OR2.87; 1.90–4.34), IGT (OR1.65; 1.02–2.69) and overweight (OR1.41; 1.03–1.93) vs controls (BW: n/r)
Idris 2013[29] Retrospective cohort	Study population: post-menopausal women from Prospect-EPIC cohort (Utrecht, Netherlands 1993-97) (n=147, 100%) Controls: conceived post-famine (n=139)	Preadolescence: 0-9y, n=93 Adolescence: 10-18y, n=54	~60y	Coronary artery calcifications	-Higher risk for high coronary calcium score after severe famine in adolescence vs controls (OR4.62; 1.16-18.43) -No association between childhood famine exposure and valve or aortic calcification (OR1.66; 0.69-4.10) (BW: n/r)
Khalangot 2017[26] Cross-sectional	Study population: rural adults >44y from villages near Kyiv, Ukraine (2013-14) (n=62, ~75% across groups) Controls: born<1947, confirmed no starvation in family (n=11)	Born before famine (<1947), confirmed starvation (age at exposure unclear, n=62)	~67-80y (two famines)	Glucose tolerance, anthropometry	-Higher risk of T2D in controls vs childhood exposure group (OR=0.063; 0.007-0.55) -Negative association between adult height (OR0.86; 0.76-0.97), neck circumference (OR0.73; 0.54-0.97) and childhood exposure (BW: n/r)
Koupil 2007[60] Cross-sectional	Study population: men born 1916-35, women born 1910-40 living in St. Petersburg (formerly Leningrad) between 1975-82 (n=2011,	Early-childhood: 1-5y, n=81 Late-childhood: 6-8y, n=287	~40y	Cardiovascular risk factors and mortality	-Higher sBP in women exposed to peak of starvation in late childhood (d=8.8; 0.1–17.5mmHg) and men in puberty (2.9; 0.7–5.0mmHg) vs controls of same age

	~27% in late childhood, puberty, adolescence groups, 100% in early childhood and adulthood groups) Controls: unexposed to famine (n=3319)	Puberty: 9-15y, n=739 Adolescence: 16-25y, n=813 Adulthood: 26-31y, n=91			-Excess of HT in men exposed to famine at 6–25y (OR1.20; 1.03-1.39) -Higher mortality from ischaemic heart disease in men exposed in late-childhood (HR1.89; 1.18-3.01) and cerebrovascular disease w/ puberty exposure (HR1.27; 1.07-1.55) (BW: n/r)
Li 2010[34] Retrospective cohort	Study population: rural adults born 1954-64 from nationally representative CNNHS 2002 (n=5920, ~53% across groups) Controls: conceived post-famine (n=1954)	Prenatal: n=1005 Early-childhood: 0-2y, n=1654 Mid-childhood: 3-5y, n=1588 Late-childhood: 6-8y, n=1673	~40y	Hyperglycemia, T2D	-Higher FPG in early (p=0.037), mid- (p=0.059) and late childhood (p=0.008) w/ severe famine exposure -No consistent effects on hyperglycemia and T2D w/ childhood exposure PreN: Higher FPG (mean diff=0.20mmol/l, p=0.007) and hyperglycemia (OR3.92; 1.64-9.39) w/ severe prenatal exposure. No differences in less severely exposed areas. (BW: n/r)
Li 2011[35] Retrospective cohort	SP: rural adults born 1954-64 from nationally representative CNNHS 2002 (n=5920, ~53% across groups) Controls: conceived post-famine(n=1954)	Prenatal: n=1005 Early-childhood: 0-2y, n=1654 Mid-childhood: 3-5y, n=1588 Late-childhood: 6-8y, n=1673	~40y	MetS	-Higher risk of MetS w/ severe famine exposure in early childhood (OR2.85; 1.19-6.83, p=0.019) vs controls -No differences in less severely exposed areas (all p>0.05) PreN: Higher risk of MetS w/ severe prenatal famine exposure (OR3.12; 1.24-7.89, p=0.016) vs controls (BW: n/r)

Liu 2017[19] Retrospective cohort	Study population: adults 35-74y from two population-based surveys in Qingdao, China (2006, 2009) (n=8185*, 62%) Controls: conceived post-famine (n= n/r)	Prenatal/infant: n=n/r Childhood: 0-9y, n=n/r Adolescence: 10-17y, n=n/r	~50y	Obesity	-Higher risk of obesity in childhood (OR1.42; 1.11-1.82, p<0.01) and adolescence (OR1.86; 1.25-2.77, p<0.01) exposed vs controls -Higher risk of obesity at highest weight in childhood (OR1.24; 1.02-1.49) and adolescence (OR1.64; 1.40-1.93) exposed vs controls PreN: Higher risk of obesity in fetal/infant exposed (OR1.59; 1.24-2.03, p<0.001) vs controls (BW: n/r)
Liu 2017[36] Retrospective cohort	Study population: adult residents 45-53y in Chongqing City (n=754, ~46% across groups) Controls: conceived post-famine (n=470)	Fetal/infant: n=299 Childhood: 0-3y, n=455	~50y	Hypertension	No difference in HT risk after childhood exposure vs controls PreN: higher HT risk in fetal/infant group (OR1.79; 1.13-2.84) w/ stronger effect in women (OR2.34; 1.01-5.42) than men (OR1.67; 0.95-2.92) (BW: n/r)
Meng 2018[57] Prospective cohort	SP: non-diabetic participants born around famine years from China Kadoorie Biobank (n=50, 242, ~60% across groups) Controls: conceived post-famine (n=38,588)	Fetal: n=18,879 Early-childhood: 1-3y, n=31,363	~50y	T2D, obesity patterns	No association between early childhood exposure and risk of T2D (HR0.95; 0.67–1.36) vs controls PreN: Increased risk of T2D in fetal-exposed (HR1.25; 1.07–1.45) vs age-balanced controls. Association between abdominal obesity and T2D in fetal-exposed group (p for interaction=0.025), stronger in women (p=0.013) than men (p=0.699). (BW: n/r)

Portrait 2011[51] Retrospective cohort	Study population: adults from Longitudinal Aging Study Amsterdam, nationally representative Dutch cohort (n=278, 47% in exposed) Controls: from rural areas not exposed to famine (n=521, 57%)	Fetal/infant: 0-1y, n=81 Childhood: 1-5y, n=293 Pre-adolescence: 6-10y, n=244 Adolescence: 11-14y, n=181	~60y	Heart diseases, peripheral arterial diseases (PAD), T2D	Higher T2D risk in women (p=0.021) and PAD (p=0.018) exposed in adolescence vs controls. No association in men. (BW: n/r)
Rotar 2017[37] Retrospective cohort	Study population: siege survivors born 1930-43 registered with Petersburg Primorski District Society (n=278, 73%) Controls: age, sex-matched, not in Leningrad during siege (n=51)	Fetal: n=45 Newborn/infant: 0-1y, n=50 Childhood: 1-10y, n=210	~60y	Cardiovascular health, telomere length (TL)	-No differences in prevalence of CVD or target organ damage between groups (all p>0.05) -Shorter TL in survivors (p<0.0001), with clear association with the period of famine in early life. Newborn/infant group had longer TL (T/S ratio=0.63; 0.31-0.81) vs childhood (0.46; 0.23-0.62) and fetal group (0.44; 0.19-0.57) (p=0.023) -Survivors had lower height (p=0.007), weight (p=0.008) and higher HDL (p=0.008) (BW: n/r)
Shi 2018[39] Retrospective cohort	Study population: adults born 1954-64 from China Health and Retirement Longitudinal Study (CHARLS) baseline survey (2011-12) (n=4378, ~53% across groups) Controls: conceived post-famine (n=1394)	Fetal: n=762 Early-childhood: 0-2y, n=1149 Mid-childhood: 3-5y, n=1217 Late-childhood: 6-8y, n=1250	~50y	CVD	-Higher risk of CVD w/ HT in childhood-exposed groups: late (1.69; 1.06–2.72), mid- (2.35; 1.44–3.83), and early childhood (2.48; 1.49–4.11) vs unexposed -Risk gradient between HT and CVD across groups mainly in women, in urban areas, w/ central obesity

					PreN: Higher risk of CVD w/ HT in fetal group (3.35; 1.54–7.27) vs controls (BW: n/r)
Sparen 2014[58] Prospective cohort	Study population: men born 1916-35 living in St Petersburg randomly selected for health exams (1975-7), mortality followed until 1999 (n=1406, 0%) Controls: men of same age living in St Petersburg in 1975, no siege exposure (n=2499)	Early-childhood: 6-8y Puberty: 9-15y Young-adulthood: 16-26y (n=1406 all groups)	~33-60y	Cardiovascular risk factors, mortality	-Higher dBP (p=0.02) and sBP (p=0.0003) in puberty-exposed group -Higher mortality from ischaemic heart disease (RR1.39; 1.07-1.79), stroke (1.67; 1.15-2.43) including haemorrhagic stroke (1.71; 0.90-3.22) w/ puberty exposure. Effect on mortality partly mediated via BP but not any other measured biological, behavioural, or social factor. (BW: n/r)
Sun 2018[59] Retrospective cohort	Study population: adults born 1949-66 from CHARLS baseline survey (2011) (n=5661, ~54% across groups) Controls: conceived post-famine(n=1601)	Fetal: n=1389 Early-childhood: 1-3y, n=1297 Mid-childhood: 4-6y, n=1476 Late-childhood: 7-10y, n=1499	~50y	Hyperglycemia (HG), T2D	-Higher HG in women exposed in early (OR1.48; 1.15–1.90), middle (1.38; 1.06–1.79) and late childhood (1.57; 1.25–1.98). Association stronger in women who lived in rural areas <16y (more severe famine) -Lower T2D risk in men for early (0.65; 0.49–0.86) and late childhood (0.74; 0.56–0.98) exposure vs controls PreN: higher HG risk in fetal-exposed women (1.34; 1.04–1.74) (BW: n/r)
Vaiserman 2013[18] Retrospective cohort	Study populations: (1)T2D patients in 2000 born 1930-38 from four Ukraine regions exposed to	-Fetal: n= n/r -Childhood: 0-3y, n=n/r	~70y	T2D	-No association between childhood famine exposure and T2D

	severe famine (n=28,358*, 71%) (2)T2D patients in 2008 born 1920-64 in Ukraine regions with different famine histories (n=105, 374*, 67%) Controls: birth cohorts conceived post-famine (n= n/a)				-Higher prevalence of T2D in females than males overall (OR 1.48; 1.46-1.50), more pronounced in famine exposed PreN: increased T2D risk (OR1.5; p<0.001) in men and women conceived during peak famine vs pre- and post-famine cohorts (BW: n/r)
van Abeelen 2012[27] Retrospective cohort	Study population: women 49-70y from Prospect-EPIC cohort recruited 1993-97 exposed to Dutch famine between 0-21y (n=3572, 100%) Controls: women reported 'hardly' any hunger, weight loss during famine (n=3,572)	Childhood: 0-9y, n=n/r Adolescence: 10-17 y, n=n/r Young-adulthood: >18 y, n=n/r *n by degree of famine exposure: -Moderate (n=2,975) -Severe (n=1290)	~50y	T2D	-Higher risk of T2D w/ severe childhood famine (HR2.06; 1.37-3.10) -Dose-dependent T2D risk relative to unexposed women: moderate exposure (HR1.36; 1.09-1.70) and severe exposure (HR1.64; 1.26–2.14) (BW: n/r)
van Abeelen 2012[28] Retrospective cohort	Study population: women 49-70y from Prospect-EPIC cohort recruited 1993-97 exposed to Dutch famine between 0-21y (n=4268, 100%) Controls: women reported 'hardly' any hunger, weight loss during famine (n=3577)	Childhood: 0-9y, n=2196 Adolescent: 10-17y, n=1773 Young-adulthood: >18y, n= 299	~50y	Coronary heart disease, stroke	-Higher CHD risk after severe famine in adolescence (HR1.38;1.03-1.84) -Lower stroke risk in famine-exposed women (HR0.77;0.59-.99) (BW: n/r)

Wang, J 2016[40] Retrospective cohort	Study population: retirees 56-63y from Dongfeng Motor Corporation cohort in China (n=6863, 95% fetal, 85% early, 79% mid, 73% late childhood) Controls: conceived post-famine (n=938, 92%)	Fetal: n=1266 Early-childhood: 1-3y, n=1932 Mid-childhood: 3-5y, n=1712 Late-childhood: 5-7y, n=1953	~50y	T2D, hyperglycemia	-Higher T2D risk after mid- (OR1.55; 1.16-2.06) and late childhood (OR1.40; 1.05-1.87) exposure in women vs controls. No association in men. Similar associations for HG risk. PreN: No association between fetal famine and dysglycemia risk (BW: n/r)
Wang, N 2015[41] Retrospective cohort	Study population: men and women from SPECT-China 2014 survey (n=3844, ~58% across groups) Controls: conceived post-famine (40-51y, n=1808) and (<39y, n=1245)	Fetal: n=745 Childhood: 0-9y, n=1911 Adolescent/young-adult: 10-37y, n=1188	~55y	T2D	-Higher T2D risk in childhood-exposed women (OR2.81; 1.59–4.97) vs controls. No association in men. -Living in areas with high economic status increased diabetes risk in adulthood (OR1.46; 1.20–1.78) PreN: Higher T2D risk in fetal-exposed men (OR1.64; 1.04–2.59) (BW: n/r)
Wang, N 2016[42] Retrospective cohort	Study population: adults from SPECT-China survey (n=3566, ~57% across groups) Controls: conceived post-famine (n=1740)	Fetal: n=712 Childhood: 1-10y, n=1778 Adolescent/young-adult: 11-38y, n=1076	~50y	NAFLD	-Childhood-exposed women at higher risk of moderate-severe NAFLD (OR1.82; 1.35-2.46) vs controls. No association in men. -Association between increased alanine aminotransferase and famine in childhood-exposed women (p<0.05) PreN: Fetal famine increased risk of moderate-severe NAFLD (OR1.77; 1.22- 2.57) and increased alanine aminotransferase (p<0.05) (BW: n/r)

Wang, N 2017[43] Retrospective cohort	SP: adults in Anhui and Shanghai provinces from SPECT-China (n=2335, ~59% across groups,39% in severe adolescent exposed) Controls: conceived post-famine (n=1632)	Fetal: n=489 Childhood: 1-10y, n=1140 Adolescent/young-adult: 11-33y, n=706	~55y	T2D	Higher T2D risk after severe childhood exposure (OR1.44; 1.06-1.97) PreN: Higher T2D risk after severe fetal exposure (OR1.90; 1.12-3.21) (BW: n/r)
Wang, N 2017[44] Retrospective cohort	Study population: men and women from SPECT-China 2014 survey (n=3530, ~57% across groups) Controls: conceived post-famine (40-51y, n=1719) and (<39y, n=1196)	Fetal: n=701 Childhood: 0-9y, n=1776 Adolescent/young-adult: 10-37y, n=1053	~55y	MetS	Higher MetS risk in childhood-exposed women (OR1.80; 1.22-2.67) vs older controls. No association in men. PreN: Higher MetS risk in fetal-exposed women (OR1.47; 1.05-2.07) (BW: n/r)
Wang, N 2018[45] Retrospective cohort	Study population: women >40y from SPECT-China 2014-15 (n=3329, 100%) Controls: conceived post-famine (n=1795)	Fetal: n=647 Childhood: 1-10y, n=1679 Adolescent/young-adult: 11-38y, n=1003	~55y	Chronic kidney disease (CKD)	No association between childhood (OR1.23; 0.52-2.90) and adolescence (OR1.18; 0.39-3.59) exposure and CKD risk vs controls PreN: Fetal famine exposure associated with lower eGFR (B=−1.35; −2.67,−0.04) and increased CKD risk (OR2.42; 1.05-5.58) vs controls (BW: n/r)
Wang, P 2012[46] Retrospective cohort	Study population: men and women 46–53y from health survey (2010) in Guangdong, China (n=7193, 51%) Controls: conceived post-famine (n=4872)	Fetal: by trimester, n=1156 Infancy-only: 0-2y, n=3126 Fetal+infancy: n=2911	~50y	Hypertension, short stature, obesity	-Higher HT risk w/ exposure in infancy only (OR1.83; 1.61–2.08) and in fetal/infancy exposed group (OR1.31; 1.14–1.51) vs controls -Exposure to famine during infancy increased the risk of short stature (p<0.01) but not obesity.

					PreN: Higher HT risk w/ first trimester exposure only (OR1.36; 1.03–1.79). No difference if exposed during 1st and 2nd trimester only or all three trimesters without subsequent infancy exposure. (BW: n/r)
Wang, Y 2010[46] Retrospective cohort	Study population: adults born 1956–64 who had physical evaluations at public health centre of Chongqing Medical University, China (2006-08) (n=8619, ~25% in exposed groups) Controls: conceived post-famine (n=8,404, 48%)	Fetal: n=4,056 Early childhood: 1-3y, n=4,563	~50y	Overweight, obesity	-Higher weight and BMI, lower height in female toddler group than controls ($p<0.05$) -Higher risk of overweight in females in toddler group (OR1.48; 1.28–1.68) vs fetal group (OR1.26; 1.08–1.45) -Higher risk of obesity in females in toddler group (OR1.46; 1.28–1.68) vs controls -No impact of famine on adult body weight in males PreN: Higher weight/BMI, lower height in fetal group vs controls ($p<0.05$) (BW: n/r)
Wang, Z 2016[47] Retrospective cohort	Study population: men and women >45y from CHARLS baseline survey (2011-12) (n=1394, ~50% across groups) Controls: conceived post-famine (n=572)	Fetal: n=599 Infant: 0-1y, n=338 Pre-schoolers: 2-6y, n=457	~45y	Hypertension	-Higher sBP in infant-exposed and preschool-exposed cohorts ($p<0.05$). No difference in dBP ($p>0.05$). -Increased HT risk after severe famine exposure in infant group only (OR2.11; 1.18-3.77) vs controls -No consistent association in less severely affected areas or other exposed cohorts in severely affected areas

					(BW: n/r)
Wang, Z 2017[48] Retrospective cohort	Study population: men and women >45y from CHARLS baseline survey (2011-12) (n=1935, ~50% across groups) Controls: conceived post-famine (n=822)	Fetal: n=797 Infant: 0-1y, n=536 Pre-schoolers: 2-6y, n=597	~45y	Dyslipidemia	Increased LDL in women exposed to severe famine as infants (OR1.75; 1.17-2.62) or pre-schoolers (OR1.63; 1.10-2.42) vs controls. No association in males. PreN: Higher LDL-c in women fetal-exposed to severe famine (OR1.80; 1.26–2.57) (BW: n/r)
Wang, Z 2019[49] Retrospective cohort	Study population: men and women born 1956-64 from CHARLS baseline survey (2011-12) (n=1415, ~52% across exposed groups) Controls: conceived post-famine (n=733, 60%)	Fetal: n=429 Infant: 0-1y, n=269 Pre-schoolers: 2-6y, n=717	~50y	MetS	-Higher MetS risk in infant-exposed group (OR1.83; 1.24-2.70) vs controls -Higher risk of FPG in infant-exposed group (OR2.00; 1.32-3.04). Associations between other components of MetS and famine exposure not significant but showed positive trends. (BW: n/r)
Woo 2010[30] Cross-sectional	Study population: adults ≥ 65 years who attended a health check at Chinese University of Hong Kong (n=2222, 49%) Controls: reported no famine exposure in childhood (n=1510)	Childhood: age n/s, n=2222	~60y	NCDs, grip strength, walking speed, stride length, blood pressure, anthropometry	-Participants exposed to famine in childhood were shorter (OR0.92; 0.86-0.99), had higher BMI (OR1.11; 1.03-1.19) and appendicular lean mass/height^2 (OR1.17; 1.06-1.29) (ie. lower height but similar appendicular mass as controls) -Higher risk of recurrent falls (OR1.67; 1.17-2.37), myocardial infarction (OR1.43; 1.09-1.86), arthritis (OR1.26; 1.05-1.51) and back pain (OR1.31; 1.12-1.54) in exposed vs controls -No difference in grip strength between groups (OR1.06; 0.98-1.14)

					(BW: n/r)
Xin 2019[50] Retrospective cohort	Study population: adults born 1941-66 from CHNN (2009) (n=3705, ~53% across groups) Controls: conceived post-famine (n=1138)	Fetal/infant: fetal-2y, n=433 Childhood: 3-12y, n=2132 Adolescent: 13-20y, n=1140	~50y	Dyslipidemia	Higher risk of dyslipidemia in childhood (OR1.44; 1.23–1.69) and adolescence exposed (OR1.41; 1.17–1.71) vs controls PreN: Higher risk of dyslipidemia after fetal exposure (OR1.34; 1.05–1.70) vs controls (BW: n/r)
Yao 2019[51] Retrospective cohort	Study population: adults born 1955-65 who completed health checkup at hospital in Hefei, China (2013) (n=333, 51%) Controls: conceived post-famine (n= 271)	Fetal: n=127 Early-childhood: 2-4y, n=206	~50y	Dyslipidemia	-No association between childhood famine exposure and dyslipidemia (OR0.97; 0.67-1.41, p=0.89) PreN: Fetal exposure to famine increased dyslipidemia risk in adult women vs controls (OR2.00; 1.03–3.86). No association in men. (BW: n/r)
Yu 2017[52] Retrospective cohort	Study population: retirees born 1952-64 from Dongfeng Motor Corporation cohort in Shiyan, China (2013 follow-up) (n=7698, 94% fetal, 84% early, 80% mid, 73% late childhood) Controls: conceived post-famine (n=1044, 91%)	Fetal: n=1394 Early-childhood: 0-3y, n=2115 Mid-childhood: 3-5y, n=1941 Late-childhood: 5-7y, n= 2248	~50y	Hypertension	-Higher HT risk after famine exposure in early (OR1.44; 1.20–1.73), mid-(OR1.67; 1.38–2.02), and late childhood (OR2.11; 1.75–2.55) (P for trend<0.0001) vs controls PreN: Higher HT risk after fetal famine exposure (OR1.24; 1.01–1.51) vs controls (BW: n/r)
Yu 2018[53] Retrospective cohort	Study population: retirees born 1952-64 from Dongfeng Motor Corporation cohort in Shiyan, China (2013 follow-up) (n=6959,	Fetal: n=1268 Early-childhood: 0-3y, n=1940	~50y	MetS	-Higher MetS risk in women exposed to famine in early (OR1.26; 1.02‑1.56), mid- (OR1.43; 1.14‑1.78) and late childhood (OR1.47; 1.18-

	95% fetal, 84% early, 80% mid, 73% late childhood) Controls: conceived post-famine (n=956, 92%)	Mid-childhood: 3-5y, n=1741 Late-childhood: 5-7y, n=2010			1.84) vs controls. No association in men (P for famine-gender interaction = 0.0001). (BW: n/r)
Zhang 2018[61] Cross-sectional	Study population: adults born 1956-65 from chronic disease survey in northeastern China (2012) (n=3704, ~54% across groups) Controls: conceived post-famine (n=1986)	Fetal: n=1442 Early-childhood: 0-3y, n=1582	~50y	Hyperglycemia, T2D	-Higher HG risk in women exposed in early childhood (OR1.55; 1.10–2.19) vs controls. No association in men. PreN: Increased T2D risk in women in fetal-exposed group (OR1.67; 1.12–2.49) vs controls. No association in men. (BW: n/r)
Zheng 2011[54] Retrospective cohort	Study population: urban adults who underwent routine physical exams at Chongqing Medical University in China (2008) (n=2366, ~38% across groups) Controls: conceived post-famine (n=2674)	Fetal: n=1022 Post-natal: 0-2y, n=1344	~45y	MetS	Higher MetS risk in postnatally exposed women (OR1.50;1.20-1.87, p=0.0003) vs controls. No association in men. PreN: Higher MetS risk in prenatally exposed women (OR1.87; 1.15–3.04, p=0.012) (BW: n/r)
Zheng 2017[55] Retrospective cohort	Study population: urban women who underwent routine physical exams at Chongqing Medical University in China (2011-14) (n=4276, 100%) Controls: conceived post-famine (n=4476)	Fetal: n=1873 Post-natal: 0-2y, n=2403	~50y	NAFLD	Higher risk of NAFLD in postnatally exposed women (OR1.26; 1.03-1.55) vs controls PreN: Higher risk of NAFLD in prenatally exposed women (OR1.33; 1.04-1.70) and abnormal alanine aminotransferase (OR1.30; 1.05-1.61) vs controls (BW: n/r)

Zheng 2019[56] Retrospective cohort	Study population: urban adults who underwent routine physical exams at Chongqing Medical University in China (2017) (n=220, 61% fetal, 48% post-natal) Controls: conceived post-famine (n=396, 57%)	Fetal: n=125 Post-natal: 0-2y, n=95	~60y	Thyroid function and nodules	-Lower FT4 and higher uTSH (p<0.05) in post-natal group vs controls -No difference in numbers of thyroid nodules, TI-RADS score or maximal diameters of thyroid nodules -No difference in heart rate or BMR between groups (p>0.05) -No differences in BMI, waist circumference, BP, blood lipids, BG between groups (all p>0.05) (BW: n/r)
Zhou 2019[62] Cross-sectional	Study population: adults 45-60y recruited to medical centre for physical exams in Anhui, China (2011-12) (n=558, ~43% across groups) Controls: conceived post-famine (n=381)	Fetal: n=84 Early-childhood: 0-2y, n=160 Mid-childhood: 3-5y, n=173 Late-childhood: 6-8y, n=141	~50y	Chronic diseases, dietary patterns	-Higher diabetes risk in early (PR3.13; 1.43-6.84) and mid-childhood (PR2.37; 1.05-5.36) groups vs controls -Higher risk of hypercholesterolaemia in early childhood group (PR2.07; 1.01-4.25) vs controls -Combination of early-life famine exposure and high-dichotomous high-fat/high-salt dietary pattern in adulthood increased risk for diabetes (PR4.95; 1.66-9.05) and hyper-cholesterolaemia (PR3.71; 1.73-7.60) compared to controls w/ low-dichotomous dietary pattern (BW: n/r)

Abbreviations: **BG**: blood glucose; **BL**: blood lipids; **BP**: blood pressure; **BW**: birthweight; **CHD**: coronary heart disease; **CHARLS**: China Health and Retirement Longitudinal Study; **CKD**: chronic kidney disease; **CNNHS**: China National Nutrition and Health Survey; **dBP**: diastolic blood pressure; **eGFR**: glomerular filtration rate; **HDL**: high-density lipoprotein; **HG**: hyperglycemia; **IFG**: impaired fasting glucose; **IGT**: impaired glucose tolerance; **LDL**: low-density lipoprotein cholesterol; **MetS**: metabolic syndrome; **NAFLD**: non-alcoholic fatty liver disease; **n/r**: not reported; **n/s:** not specified; **OGTT**: oral glucose tolerance test; **PAD**: peripheral artery diseases; **sBP**: systolic blood pressure; **SPECT-China**: Survey on Prevalence in East China for Metabolic Diseases and Risk Factors in East China; **T2D**: type 2 diabetes

Table 3. Detailed summary of studies examining effects of documented severe childhood malnutrition on NCD outcomes

Lead author, year, study design	Population, setting, sample size (%female)	Type and timing of exposure to severe malnutrition	Age at follow-up	Outcome(s)	Key findings
Benefice 1999[63] Prospective cohort	Study population: Children admitted to NRU for severe malnutrition (SM) 1988-1992 in Central Senegal (n=52, 48%) Comparison: Chronically undernourished children from same area (n=54, 41%) Controls: Age-matched, well-nourished (WN) (n=33, 52%)	Marasmus Median age at admission:14m	5.5±0.5y	Motor fitness, anthropometry	-WN children taller, heavier for age than other groups ($p<0.0001$) -WN group score better than chronic and SM groups in all outcomes except for endurance run (distance throw $p<0.03$, jump $p<0.0001$, agility/shuttle $p<0.005$, handgrip $p<0.001$) -Reduced handgrip in SM vs chronic group, no other differences -Stature is strongest predictor of motor performance, most differences between groups disappear after controlling for age and body size (BW: n/r)
Boulé 2003[64] Prospective cohort	Study population: young men admitted for SM treatment, Mexico City (n=26, 0%) Controls: young men, no hx of SM (n=27, 0%)	Marasmus, kwashiorkor Age at admission: ≤1y	SM: 22.0±3.6 Controls: 26.5±2.1	Insulin sensitivity (IS), abdominal obesity	-Negative association btw abdominal adipose tissue area and IS in both groups in post-SM and controls ($r2=0.65$ and 0.35, $p<0.01$) -Similar insulin sensitivity when groups matched for low abdominal fat -However, when matched for high amounts of abdominal fat, post-SM groups had lower insulin sensitivity (4.74 vs 6.85mgkg_1 min_1, $P<0.05$) than controls (BW: not associated w/ IS or abdominal obesity)

Bourdon 2019[65] Prospective cohort	Study population: Children treated for SM in 2006-2007 at central hospital in Malawi (n=69, 43%) Sibling controls: closest in age, no hx of SM (n=44, 50%) Community controls: age/sex matched (n=37, 41%)	Marasmus, kwashiorkor Median age at admission: 21.5m	9.6±1.6y	Cardiometabolic disease markers (194 metabolites)	-No difference in metabolite profiles of survivors, siblings, and controls -Current stunting associated w/ low IGF-1 and relationship modulated by SM (B=17.4, partial R^2=2.8%,p=0.025) -Metabolites not associated w/ changes in WAZ or BMI-for-age since hospitalisation, severity, or type of SM (BW: n/r)
Chege 2010[15] Case-control	Study population: diabetic patients resident in rural Kenyan hospital's catchment area (n=45, 71%) Controls: age/sex matched non-diabetics from same area attending outpatient clinics (n=45, 71%)	Self-reported childhood SM Exposure age: n/s	61.8±10.9y	T2D risk factors	Childhood SM identified as T2D risk factor (RR2.08;1.20-3.61, p<0.009) (BW: n/r)
Cook 1968[23] Prospective cohort	Study population: inpatients cases of kwashiorkor at urban NRU in Uganda (n=31, 42%) Controls: no hx of SM, raised in similar environment (n=21, 38%)	Kwashiorkor Mean age at admission:1.9y	10.4y (6.7-14.9y)	Carbohydrate tolerance	-Rate of glucose clearance (%/min) for post-SM group (2.15±0.17) lower than controls (3.79±0.27), p<0.001 -Rise in BG 2hr post-OGTT (mg/100ml) higher in post-SM group (20.2±2.4) vs controls (10.5±3.7), p<0.05 (BW: n/r)

Fekadu 2010[16] Case-control	Study population: insulin-requiring diabetics attending two urban health centres in Ethiopia (n=107, 27%) Controls: age/sex-matched patients attending other hospital clinics (n=110, 32%)	Self-reported childhood SM Exposure age: n/s	18-40y	Risk factors for insulin-requiring diabetes, anthropometry	-Diabetes associated w/ hx of childhood SM (OR=5.5; 1.0-29.0, p=0.047) -Male diabetics shorter, lighter (p<0.001), with reduced sitting height (p<0.015), biacromial (p<0.003), and bitrochanteric (p< 0.008) diameters (BW: n/r)
Francis-Emmanuel 2014[66] Prospective cohort	Study population: adult Jamaican marasmus survivors (MS) (n=42, 42%) and kwashiorkor survivors (KS) (n=38, 47%) treated at urban NRU 1963-1992 Community controls (CC): age/sex/BMI-matched (n=70, 47%) BW-matched controls (BWC): age-matched (n=40, 53%)	Marasmus, kwashiorkor Age at admission:6-18m	17-50y	Glucose metabolism	-No difference in fasting glucose between groups (p>0.06) -Glucose intolerance more common in MS (19%) than KS (3%), CC (11%), and BWC (10%) (OR10.9; 2.1–55, p=0.004, compared to KS) -ISI lower in MS than KS (p<0.06) but similar between MS and controls. Insulinogenic index and oral disposition index lower in MS compared with all groups (p<0.01). (BW: matched controls)
Gonzalez-Barranco 2003[67] Prospective cohort	Study population: young men w/ hx of SM <1y recruited from four pediatric hospitals in Mexico City (n=52, 0%) Controls: young men w/ no hx of SM (n=50, 0%)	Marasmus, kwashiorkor Mean age at admission:4.5m	20.2±3.6y	Glucose metabolism, blood lipids, BP	-AUCG (p<0.012) and AUCI (p<0.002) higher in cases vs controls, ISI lower in cases (p<0.003) independent of BW, BMI, age -No difference in FPL or FBG between groups (all p>0.1) -Increasing BMI associated w/ higher FPI (p<0.006), AUCI (p<0.005), TGs (p<0.003), and lower HDL-C (p<0.006) and ISI (p<0.02) in cases but not controls

					-sBP (p<0.0001) and dBP (p=0.001) lower in cases than controls (BW: not a predictor of any metabolic outcome)
Idohou-Dossou 2003[20] Prospective cohort	Study population: children hospitalised for SM in poor suburb of Dakar, Senegal (n=24, n/a) Sibling controls (SC): closest in age, no hx of malnutrition (n=24, n/a) WN controls: age-matched healthy children from wealthier urban area (n=19, n/a)	Marasmus Age at admission:1-3y	6-8y	Biochemical indicators of nutritional status, growth factors, anthropometry	-Apo A1 concentrations reduced in post-SM (p<0.05) and sibling controls (p<0.001) compared w/ WN children but no difference between post-SM and siblings. No difference in Apo B between groups. -Mean anthropometrics of WN controls higher than post-SM and SC (p<0.001) but no difference between post-SM and SC -FFM deficits in post-SM (p=0.014) and SC (p=0.019) associated w/ low IGF-1. HFA associated w/ IGF-1 in post-SM group only (p=0·026) (BW: n/r)
Kajubi 1972[24] Prospective cohort	Study population: adolescents admitted for SM as children to urban NRU in Kampala, Uganda (n=15, 33%) Controls: adolescents w/ no hx of SM (n=11, 27%)	Kwashiorkor Age at admission: 1.5-3y	11-19y	Pancreatic function	-Mean BG concentrations at all time points post-OGTT similar between cases and controls (all p>0.05) -Fasting insulin higher in controls (p=0.05) -Fasting concentrations of growth hormone lower in controls (p=0.05) (BW: n/r)
Lelijveld 2016[9] Prospective cohort	Study population: children admitted for SM to urban NRU in Blantyre, Malawi 2006-07 (n=320, 46%)	Marasmus, kwashiorkor Median age at admission: 24m	9.6±1.6y	Blood markers of NCD risk, anthropometry, physical capacity, lung function	-No differences between survivors and controls for lung function, lipid profile, glucose tolerance, HbA1c, salivary cortisol, sitting height, head circumference (all p>0.05) -dBP higher in survivors than SC (d=1.91mmHg, p=0·03) -Weaker handgrip in post-SM group (adjusted diff vs CC –1.7kg;2.4 to –0.9,p<0.0001; adjusted diff vs SC

	Sibling controls: closest in age, no hx of SM (n=217, 51%) Community controls: age, sex matched, no hx of SM (n=184, 48%)				1.01kg;0.3-1.7,p=0.005) and fewer minutes completed of exercise test (SC OR1.59;1.0-2.5,p=0·04; CC OR1.59;1.0-2.5,p=0·05) -Post-SM had less lean mass than CC (adjusted diff vs CC –24.5, –43 to –5.5, p=0·01) but similar levels to SC after adjustment for age, (adjusted diff vs SC –11.5, –29 to –6, p=0.19) (BW: n/r)
Moore 2001[25] Prospective cohort	Study population: adults with known month of birth, born 1949-74 residing in three rural villages in The Gambia with detailed growth records available (n=145, 100%, WAZ analysis in females only)	Low WAZ WAZ measured:18m	35.8y	CVD risk factors	-FPI marginally different between WAZ quartile groups (p=0.05) but no associations with any other risk factors for adult disease (fasting BG, p=0.85; 30min and 120min BG and insulin levels post-OGTT,all p>0.18; cortisol, p=0.2311; sBP, p=0.7579; dBP, p=0.81) -Change in WAZ between early childhood and adulthood did not predict any measured risk factors PreN data: no associations between season of birth (harvest vs hungry, proxy for fetal undernutrition) and any CVD risk factors (BW: fetal undernutrition approximated by season of birth)
Sheppard 2017[68] Prospective cohort	Study population: adult survivors of kwashiorkor (KS) (n=21, 56%) or marasmus (MS) (n=23 ,53%) in childhood treated at urban NRU in Kingston, Jamaica 1963-94	Marasmus, kwashiorkor Mean age at admission:11m	KS:29.82±9.03y MS:25.02±5.69y	Epigenetic profile in muscle	-Differences between KS and MS in methylation of CpG sites from 63 genes in skeletal muscle DNA related to immunity, body size and composition, glucose metabolism, musculoskeletal growth, neuronal function, and cardiovascular pathways -Gene body is most likely region of variable methylation (OR:1.45, p=0.0036)

					-dmCpGs predominantly located on chromosome 6 (16% of total; OR2.4; p=0.0004); 10.5% each was found on chromosomes 7 and 17 (OR1.8; p=0·036 and OR1.9; p 0·021) (BW: n/r)
Tennant 2014[69] Prospective cohort	Study population: adult survivors of kwashiorkor (n=62, 34%) and marasmus (n=54, 46%) in childhood treated at urban NRU in Kingston, Jamaica 1963-99 Community controls: age/sex matched, no hx of SAM (n=45, 60%)	Marasmus, kwashiorkor Mean age at admission:12m	MS:29.2±8.4y KS:27.2±7.8y	Cardiovascular structure and function	-Reduced left ventricular outflow tract parameter of 0.67 (0.16; p<0.0001), stroke volume 0.44 (0.17; p=0.009), cardiac output 0.5 (0.16; p=0.001) and pulse wave velocity 0.32 (0.15; p=0.03) in post-SM vs controls -Higher dBP (d=4.3;1.2-7.3mmHg; p=0.007) in cases, sBP similar across groups -No differences between KS and MS except heart rate (p=0.03) -Systemic vascular resistance higher in post-SM, overall (5.5;2.8-8.4mmHg min/L; p<0.0001) -No evidence of large vessel or cardiac remodeling or differences in other parameters (BW: n/r)

Abbreviations: **AUCG**: areas under curves of glucose; **AUCI**: area under curves of insulin; **BL**: blood lipids; **BMI**: body mass index; **BW**: birthweight; **BWC**: birthweight-matched controls; **CC**: community controls; **CVD**: cardiovascular disease; **dBP**: diastolic blood pressure; **FBG**: fasting blood glucose; **FPI**: fasting plasma insulin; **FPL**: fasting plasma lipids; **GH**: growth hormone; **HbA1c**: glycated haemoglobin A1c; **HDL**: high-density lipoprotein cholesterol; **Hx**: history; **IGF-1**: insulin-like growth factor 1; **IGFBP-3**: insulin-like growth factor binding protein; **ISI**: insulin sensitivity index; **KS**: kwashiorkor survivor; **MS**: marasmus survivor; **n/r**: not reported; **NRU**: nutritional rehabilitation unit; **sBP**: systolic blood pressure; **SC**: sibling controls; **SES**: socio-economic status; **SM**: severe malnutrition; **SP**: study population; **TGs**: triglycerides; **Tx**: treatment; **WN**: well-nourished

Table 1. Studies examining effects of early life famine exposure on NCD outcomes by study design

Study	Country and population	Exposure age group in years (sample size)	Outcome(s)	Key findings*	Risk of bias score (IV/EV)†
Retrospective cohort studies					
Chen *et al* 2019[31]	China, adults > 40y	0–9y (n=1799) 10–37y (n=1064)	Visceral adipose dysfunction (VAD)	↑ VAD (women 0–9y)	● / ●
Finer *et al* 2016[21]	Bangladesh, adults ~30y	1–2y (n=81)	Glucose tolerance, epigenetics	↔ Glucose tolerance ↕ Epigenetics	● / ●
Head *et al* 2008[22]	England, adults ~70y	8–22y (n=225)	Cardiovascular disease (CVD)	↑ CVD	– / –
Head *et al* 2009[32]	England, adults ~70y	8–22y (n=87)	Cholesterol levels	↔ Cholesterol levels	– / –
Huang *et al* 2010[33]	China, women ~50y	0–1.5y (n=1035) 1.5–2.5y (n=743)	Hypertension, body mass index (BMI)	↑ Hypertension (0–1.5y) ↑ BMI (1.5–2.5y)	● / ●
Idris *et al* 2013[29]	Netherlands, women ~70y	0–9y (n=93) 10–18y (n=54)	Coronary artery calcifications, valve calcification	↑ Coronary calcium score (10–18y) ↔ Valve calcification	● / –
Li, Y *et al* 2010[34]	China, adults ~45y	0–2y (n=1654) 3–5y (n=1588) 6–8y (n=1673)	Hyperglycemia, type 2 diabetes (T2D)	↑ Fasting plasma glucose ↑ Hyperglycemia (6–8y)	● / ●
Li, Y *et al* 2011[35]	China, adults ~45y	0–2y (n=1654) 3–5y (n=1588) 6–8y (n=1673)	Metabolic syndrome (MetS)	↑ MetS (0–2y)	● / ●
Liu, L *et al* 2017[19]	China, adults 35–74y	0–9y (n=n/r) 10–17y (n=n/r)	Obesity	↑ Obesity	– / ●
Liu, L *et al* 2017[36]	China, adults 45–53y	0–3y (n=455)	Hypertension	↔ Hypertension	– / –
Portrait *et al* 2011[37]	Netherlands, adults 60–76y	0–1y (n=81) 1–5y (n=293) 6–10y (n=244) 11–14y (n=181)	Heart diseases, peripheral arterial diseases (PAD), T2D	↑ T2D, PAD (women, 11–14y)	● / ●
Rotar *et al* 2017[38]	Russia, adults 64–81y	0–1y (n=50) 1–10y (n=210)	Cardiovascular health, telomere length	↔ CVD, organ damage ↓ Telomere length	● / –
Shi *et al* 2018[39]	China, adults ~55y	0–2y (n=1149) 3–5y (n=1217) 6–8y (n=1250)	CVD	↑CVD (with hypertension and famine exposure)	● / ●
Wang, J *et al* 2016[40]	China, adults ~60y	1–3y (n=1932) 3–5y (n=1712) 5–7y (n=1953)	T2D, hyperglycemia	↑ T2D, hyperglycemia (women 3–5y, 5–7y)	● / –
Wang, N *et al* 2015[41]	China, adults 52–93y	0–9y (n=1911) 10–37y (n=1188)	T2D	↑ T2D (women, 0–9y)	● / ●●
Wang, N *et al* 2016[42]	China, adults 52–93y	0–9y (n=1778) 10–37y (n=1076)	Non-alcoholic fatty liver disease (NAFLD)	↑ NAFLD (women, 0–9y)	● / ●●
Wang, N *et al* 2017[43]	China, adults 52–77y	0–9y (n=1140) 10–33y (n=706)	T2D	↑ T2D (0–9y)	● / ●●
Wang, N *et al* 2017[44]	China, adults 52–93y	0–9y (n=1776) 10–37y (n=1053)	MetS	↑ MetS (women, 0–9y)	● / ●●
Wang, N *et al* 2018[45]	China, women 52–93y	0–9y (n=1679) 10–37y (n=1003)	Chronic kidney disease (CKD)	↔ CKD	● / ●●
Wang, P *et al* 2012[46]	China, adults ~50y	0–2y (n=3126)	Hypertension, obesity	↑ Hypertension ↔ Obesity	● / ●●
Wang, Y *et al* 2010[46]	China, adults ~50y	1–3y (n=4,563)	Overweight, obesity	↑ Weight/BMI (women) ↑ Obesity (women)	– / –
Wang, Z *et al* 2016[47]	China, adults ~50y	0–1y (n=338) 2–6y (n=457)	Hypertension	↑ Hypertension (0–1y)	● / ●
Wang, Z *et al* 2017[48]	China, adults ~50y	0–1y (n=536) 2–6y (n=597)	Dyslipidemia	↑ Low-density lipoprotein cholesterol (women)	– / ●

Wang, Z *et al* 2019[49]	China, adults ~50y	0–1y (n=269) 2–6y (n=717)	MetS	↑ MetS (0–1y)	– / ●
Xin 2019[50] *et al*	China, adults, ~60y	3–12y (n=2132) 13–20y (n=1140)	Dyslipidemia	↑ Dyslipidemia	– / –
Yao *et al* 2019[51]	China, adults, ~60y	2–4y (n=206)	Dyslipidemia	↔ Dyslipidemia	– / –
Yu, C *et al* 2017[52]	China, adults ~60y	0–3y (n=2115) 3–5y (n=1941) 5–7y (n= 2248)	Hypertension	↑ Hypertension	● / –
Yu, C *et al* 2018[53]	China, adults ~60y	0–3y (n=1940) 3–5y (n=1741) 5–7y (n=2010)	MetS	↑ MetS (women)	● / –
Zheng, X *et al* 2011[54]	China, adults ~55y	0–2y (n=1344)	MetS	↑ MetS (women)	● / –
Zheng, X *et al* 2017[55]	China, women ~55y	0–2y (n=2403)	NAFLD	↑ NAFLD	● / –
Zheng, X *et al* 2019[56]	China, adults ~55y	0–2y (n=95)	Thyroid function	↓ Free thyroxine ↑ Thyroid stimulating hormone	– / –
Prospective cohort studies					
Hult *et al* 2010[17]	Nigeria, adults ~40y	0–3y (n=246)	Hypertension, glucose tolerance, BMI	↑ Blood pressure ↔ Glucose tolerance, BMI	● / –
Meng *et al* 2018[57]	China, adults ~45y	1–3y (n=31,363)	T2D, obesity	↔ T2D, obesity ↓ Abdominal obesity	● / ●
Sparen *et al* 2014[58]	Russia, men 64 – 83y	6–8y, 9–15y, 16–26y (total n=1406)	CVD risk factors and mortality	↑ Blood pressure (9–15y) ↑ Ischaemic heart disease mortality, stroke (9–15y)	●● / ●
Sun *et al* 2018[59]	China, adults ~55y	1–3y (n=1297) 4–6y (n=1476) 7–10y (n=1499)	Hyperglycemia, T2D	↑ Hyperglycemia (women) ↓ T2D (men 1–3y, 7–10y)	– / –
Vaiserman *et al* 2013[18]	Ukraine, adults ~70y	0–3y (n=n/r)	T2D	↔ T2D	● / ●
van Abeelen *et al* 2012[27]	Netherlands, women 49–70y	0–9y (n=n/r) 10–17y (n=n/r)	T2D	↑ T2D (0–9y)	● / ●
van Abeelen *et al* 2012[28]	Netherlands, women 49–70y	0–9y (n=2196) 10–17y (n=1773)	Coronary heart disease (CHD), stroke	↑ CHD (10–17y) ↓ Stroke	● / ●
Cross-sectional studies					
Khalangot *et al* 2017[26]	Ukraine, adults > 44y	Age in childhood n/s (n=62)	Glucose tolerance	↓ T2D	● / ●
Koupil *et al* 2007[60]	Russia, adults 40–70y	1–5y (n=81) 6–8y (n=287) 9–15y (n=739) 16–25y (n=813)	CVD risk factors and mortality	↑ Hypertension (men 6–25y) ↑ Ischaemic heart disease mortality (men 6–8y) ↑ Cerebrovascular disease mortality (men 9–15y)	● / ●
Woo *et al* 2010[30]	China, adults > 65y	Age in childhood n/s (n=2222)	NCDs, blood pressure, BMI	↑ BMI, myocardial infarction ↔ T2D, hypertension	● / –
Zhang *et al* 2018[61]	China, adults ~55y	0–3y (n=1582)	Hyperglycemia, T2D	↑ Hyperglycemia (women)	● / ●
Zhou *et al* 2019[62]	China, adults 45–60y	0–2y (n=160) 3–5y (n=173) 6–8y (n=141)	NCDs	↑ T2D (0–2y, 3–5y) ↑ Hypercholesterolaemia (0–2y)	– / –

* Symbols for effect direction: ↑ increased; ↓ decreased; ↕ mixed (indicate statistically significant results were reported, defined as $p < 0.05$); ↔ none (indicates no statistically significant result was reported). If no age group is indicated beside the finding, then all age groups were affected.

† The scoring system used in the risk of bias assessment is described in the methods section.

Abbreviations: Body mass index (BMI), cardiovascular disease (CVD), chronic kidney disease (CKD), coronary heart disease (CHD), metabolic syndrome (MetS), non-alcoholic fatty liver disease (NAFLD), n/r (not reported), n/s (not specified), peripheral arterial diseases (PAD), type 2 diabetes (T2D), visceral adipose dysfunction (VAD)

Online supplementary file 3
Severe malnutrition or famine exposure in childhood on cardiometabolic non-communicable disease risk later in life: a systematic review (Grey K et al., 2020)

Results for outcomes with ≤3 studies examining outcomes

Non-alcoholic fatty liver disease (NAFLD) outcomes

Two Chinese studies examined NAFLD outcomes in famine survivors and both found an increased risk among those exposed in childhood between 1–10y (OR 1.82; 95%CI: 1.35–2.46) and 0–2y (OR 1.26; 95%CI: 1.03–1.55), respectively.[42,55] Wang et al. (2016) found this effect in women only, while all participants in Zheng at al.'s (2017) study were female.[42,55]

Both studies also found similarly increased risk for NAFLD in prenatally exposed women (OR 1.77; 95%CI: 1.22–2.57[42]; OR 1.33; 95%CI: 1.04–1.70[55]).

Physical capacity outcomes

Famine studies
Woo et al. (2010) found no difference in hand-grip strength, average stride length, or walking speed between those who reported a period of famine in childhood compared with those who reported no exposure.[30]

Documented severe malnutrition studies
Two studies examined physical capacity in older children who survived an episode of severe malnutrition. Compared with a well-nourished control group, Bénéfice et al. (1999) found that children who had been both chronically and severely malnourished generally had poorer motor fitness scores with the exception of endurance run scores; however, reduced hand-grip strength in severe malnutrition survivors was the only significant difference between the malnourished groups ($p<0.0001$).[63] Lelijveld et al. (2016) also found reduced hand-grip strength among severe malnutrition survivors compared with sibling ($p=0.005$) and community controls ($p<0.0001$) as well as fewer minutes completed of an exercise test.[9]

Epigenetic & genetic outcomes

Famine studies
Finer et al. (2016) found DNA methylation differences at six of 16 metastable epialleles previously found to be sensitive to maternal nutrition.[21,88] While there were significant methylation differences between post-natal, fetal, and unexposed groups, the predominant differences were among the gestationally-exposed compared to those exposed postnatally or unexposed.[21]

In terms of genetic differences, Rotar et al. (2015) found a shortening of telomere length in Leningrad siege survivors ($p<0.0001$), with a clear association with the timing of famine in early life. The newborn/infant-exposed group (0–1y) had longer telomeres compared with those exposed between 1–10y and in utero.[38]

Documented severe malnutrition studies
Sheppard et al. (2017) found differences between marasmus and kwashiorkor survivors in DNA methylation near 63 genes in skeletal muscle related to cardiovascular pathways, glucose metabolism, musculoskeletal growth, and body size and composition. However, this study did not include a control group to allow for comparisons with those not exposed to severe malnutrition.[68]

Chronic kidney disease outcomes

Wang et al. (2018) found no association between famine exposure in childhood (1–10y) (OR 1.23; 95%CI: 0.52–2.90) or adolescence/young adulthood (OR 1.18; 95%CI: 0.39–3.59) and chronic kidney disease compared with unexposed controls among a female sample.[45]

Thyroid function outcomes

Zheng et al. (2019) found that compared with non-exposed controls, postnatally exposed participants had lower free thyroxine and higher thyroid stimulation hormone ($p<0.05$). There was no difference in thyroid autoimmune antibodies, heart rate or BMR between groups. Famine exposure did not affect either the number or maximal diameters of thyroid nodules or the TI-RADS score of thyroid nodules.[56]

Metabolomics outcomes

Bourdon et al. (2019) found no differences in metabolite profiles (194 metabolites) between severe malnutrition survivors and sibling and community controls. However, current stunting was associated with IGF-1 ($p<0.0001$) and the relationship was modulated by having experienced severe malnutrition ($B=17.4$, partial $R^2=2.8\%$, $p=0.025$). Metabolites were not associated with anthropometric recovery after severe malnutrition nor with severity or type of severe malnutrition.[65]