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Common risk factors for major noncommunicable disease, a systematic overview of reviews and commentary: the implied potential for targeted risk reduction

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Abstract: Noncommunicable disease now contributes to the World Health Organization top 10 causes of death in low-, middle- and high-income countries. Particular examples include stroke, coronary heart disease, dementia and certain cancers. Research linking clinical and lifestyle risk factors to increased risk of noncommunicable disease is now well established with examples of confirmed risk factors, including smoking, physical inactivity, obesity and hypertension. However, despite a need to target our resources to achieve risk reduction, relatively little work has examined the overlap between the risk factors for these main noncommunicable diseases. Our high-level review draws together the evidence in this area. Using a systematic overview of reviews, we demonstrate the likely commonality of established risk factors having an impact on multiple noncommunicable disease outcomes. For example, systematic reviews of the evidence on physical inactivity and poor diet found each to be associated with increased risk of cancers, coronary heart disease, stroke, diabetes mellitus and dementia. We highlight the potential for targeted risk reduction to simultaneously impact multiple noncommunicable disease areas. These relationships now need to be further quantified to allow the most effective development of public health interventions in this area.

Keywords: non-communicable disease, dementia, heart disease, cancer, diabetes, hypertension, obesity, physical activity, hyperten, air pollution

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Introduction

A world with inevitably limited resources requires prioritization of those resources and the arena of public health is no exception. As the world faces unprecedented numbers of older adults and levels of noncommunicable disease (NCD),[1] there has been an increased orientation towards strategies for risk reduction, NCD prevention[2] and effective ways to support healthy ageing.[3] The most recent NCD area to rise to prominence, partly due to our ageing population, is dementia.[4] The last 20–30 years has seen an exponential rise in research on the identification and understanding of dementia risk factors. This began with investigation of single risk factors, for example,[5–7] clinical trials[8–10] and evidence synthesis,[11–13] most recently moving towards a developing understanding of the impact of multiple co-occurring risk factors[14] and multifactorial risk reduction.[15–17]

In 2016, dementia also appeared for the first time as one of five NCDs ranked in the World Health Organization (WHO) top 10 causes of death globally alongside other NCD categories, coronary heart disease (CHD), stroke, diabetes mellitus (DM) and cancers.[18] When evaluated across lower-, middle- and high-income economies, CHD and stroke maintain their places consistently within the top five causes of death and top causes of NCD-related death. DM is present in all but the lowest income category and dementia is within the top five causes of death in

upper-middle- and high-income countries. Amongst the cancers, trachea, bronchus and lung, liver and stomach, colon and rectum and breast cancers also ranked within the top 10 causes of death in upper-middle- and high-income countries in 2016.[18] Importantly, dementia and other NCDs, such as CHD, share more than their ranking in the WHO top 10 causes of death. They are also characterized by multiple overlapping lifestyle and clinical risk factors (for example, obesity, physical inactivity, high blood pressure), acting singly or together to increase risk, and may all benefit from risk reduction efforts.[19–22] Depression, diabetes or impaired glucose tolerance, high cholesterol, high blood pressure, obesity, unhealthy diet, smoking, physical inactivity and excess alcohol consumption have been identified by the WHO Global Health Observatory data as common and preventable risk factors that underlie most NCDs.[23] Increasing evidence also points to air pollution as an emerging risk factor for dementia, heart and cardiovascular disease and lung cancer.[1,14]

To more accurately model the influence of risk factor prevalence and risk factor modification on incident disease and health outcomes, and to effectively target risk reduction strategies, we now need to understand the overlap between risk factors and the main NCDs. The aim of this systematic overview of reviews was to identify and evaluate the evidence for overlapping risk factors between dementia, DM, CHD, stroke and selected cancers.

Methods

We completed a detailed systematic overview of reviews.[24] That is, we reviewed published overviews and reviews reporting on one or more common risk factors and one or more of the NCD categories, dementia, DM, CHD, stroke and selected cancers. A written protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42019129265) and the review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[25]

The Cochrane Database of Systematic Reviews, and Ovid MEDLINE were searched from inception to 1 March 2019. The following NCD keywords were used: dementia, Alzheimer's (or Alzheimer or Alzheimers) disease, diabetes, ischaemic (or ischemic) heart disease, coronary artery disease, coronary heart disease, myocardial infarction, stroke, cancer, together with the following keywords for the nine common risk factors: depression, cholesterol, hypertension, obesity, diet, smoking, physical activity, alcohol or air pollution. Supplementary text file 1 provides full details of the search terms. Additional data sources included a review of guidelines published by the WHO, the UK National Institute for Health and Care Excellence, systematic reviews commissioned by the Agency for Healthcare Research and Quality and expert recommendation.

Given the volume of data in this area and the need to include the most up-to-date evidence synthesis, we used a pragmatic selection method, adapted from guideline development methodology, selecting the most comprehensive and recent evidence sources.[26] To achieve this we selected published overviews or reviews (sometimes referred to as umbrella reviews) or, where these were unavailable, single systematic reviews. We selected the most recently published review in each area first examining those published within the last 5 years and only looking at earlier literature where recent publications were not available. If two publications were available from the same year, the publication with the most recent search dates was used. Reviews were required to report meta-analyses of prospective studies reporting an association between one or more of the nine selected risk factors and one or more of the selected incident NCDs. Established and prevalent risk factors were selected (based on those recognized by the WHO www.who.int/healthinfo/global_burden_disease/global_health_risks/en) to include depression, high cholesterol, high blood pressure, obesity, diet (whole dietary pattern), smoking, physical inactivity, excess alcohol consumption or air pollution). The NCDs included: dementia [all-cause or Alzheimer's disease (AD) or vascular dementia (VaD)], DM, CHD (defined as coronary artery disease, ischaemic heart disease or myocardial infarction), stroke (ischaemic or haemorrhagic) or cancer (of all types or of the lung, liver, bowel or breast in accordance with the cancer types featured in the WHO top 10 causes of death).[18] Meta-analyses of prospective longitudinal cohort studies were selected to provide the most robust information on relationships between risk factor exposure and disease development. Cross-sectional and case-control studies were excluded because they do not provide sufficiently

robust data with regard to the evaluation of causality between risk factors and disease outcomes. Furthermore, clinical trials were not included, as the focus of this research was on the relationship between risk factors and disease rather than on risk reduction. We also excluded nonsystematic reviews, narrative reviews, reviews focusing solely on dietary constituents, as opposed to whole diet and reviews including studies conducted in secondary prevention populations (i.e. in populations that already have one of the five selected NCD outcomes). The varied source data also meant that it was not possible to statistically synthesize the data nor to fully take subgroups, such as the age of risk factor exposure, into account; however, where differing results were reported from broad subgroups such as mid/late-life, pre/postmenopausal women, these are reported.

All titles were screened for relevance. Those that were selected as relevant, progressed to abstract screening by two independent reviewers. Disagreement between reviewers was resolved by discussion and further full-text screening took place, with disagreement similarly resolved by discussion. Data extraction was completed by one reviewer and checked by a second independent reviewer. Data on key population and demographic information, risk factor classification, outcome identification and pooled values for the associations between risk factors and outcomes were extracted into an *a priori* designed extraction table. Reviews were assessed for bias using the revised instrument, AMSTAR-2 (A MeaSurement Tool to Assess systematic Reviews 2) criteria.[27]

Results

Searching and expert recommendation resulted in 1374 unique records. There were 1173 records rejected at the title screening stage for not reporting results for overview or single systematic reviews relevant to the selected risk factors and NCD categories. The remaining 201 articles were screened at abstract stage, 125 were rejected and 76 were examined at full-text screening (Figure 1). A further 49 articles[12,13,28–74] were rejected at the full-text stage, primarily due to their relative redundancy given the availability of a more recent review or more current search dates. Overall, nine of these articles[38,44–47,58,62,63,68] were excluded due to reasons such as nonstandard or inappropriate exposure or outcome measures, data derived from only one cohort study or unclear methodology (Supplementary Table 4 and supplementary reference list), leaving 27 reviews[11,14,75–99] to be included.

Of the 27 publications selected for inclusion, 5 were overview reviews and 22 were single systematic reviews. All but one review[78] were published within the last 5 years. From these 27 articles, 89 relevant unique meta-analyses and 1 systematic review, with a figurative rather than statistical forest plot summarizing the data, were examined and extracted (Supplementary Table 1). Overall data on risk factors and dementia, DM, CHD and stroke was reasonably comprehensive. No reviews reported on the relationship between diabetes and cholesterol, diabetes and alcohol, CHD and smoking, stroke and depression, and of the five NCD categories, the least data were available for cancer (Table 1). Table 1 shows the extent of the evidence and the direction of the reported relationships between the risk factors and NCD disease outcomes.

The most consistent and comprehensive evidence was available for diet and physical activity. High adherence to a Mediterranean diet was shown to reduce risk across all five NCDs by between 4% and 36%,[11,77,90,93,98] and higher levels of physical activity similarly resulted in risk reduction of between 13% and 45%.[11,75,77,94] The detrimental effects of smoking and obesity were also evident from available data. Smoking was associated with an increased risk of AD, any dementia, VaD, DM, stroke, and lung, bowel and breast cancer with increased risk estimates variously reported between 9% and 633%.[11,77,78,87,89,95] Obesity was associated with an increased risk of AD, DM, CHD, stroke and liver and bowel cancer by between 33% and 588%.[11,77,81,85] Obesity may also increase the risk of breast cancer in postmenopausal women.[85] No association was found between obesity and VaD[11] and an anomalous protective effect was found for lung cancer that was reported to be derived from a small sample of heterogeneous studies.[85] High blood pressure was associated with a 7–75% increased risk of VaD, DM, CHD, stroke and breast cancer,[11,77,83,84,96] but no association was found for AD.[11] The evidence for excess alcohol consumption was the least consistent across the NCDs, with three meta-analyses showing significant associations with

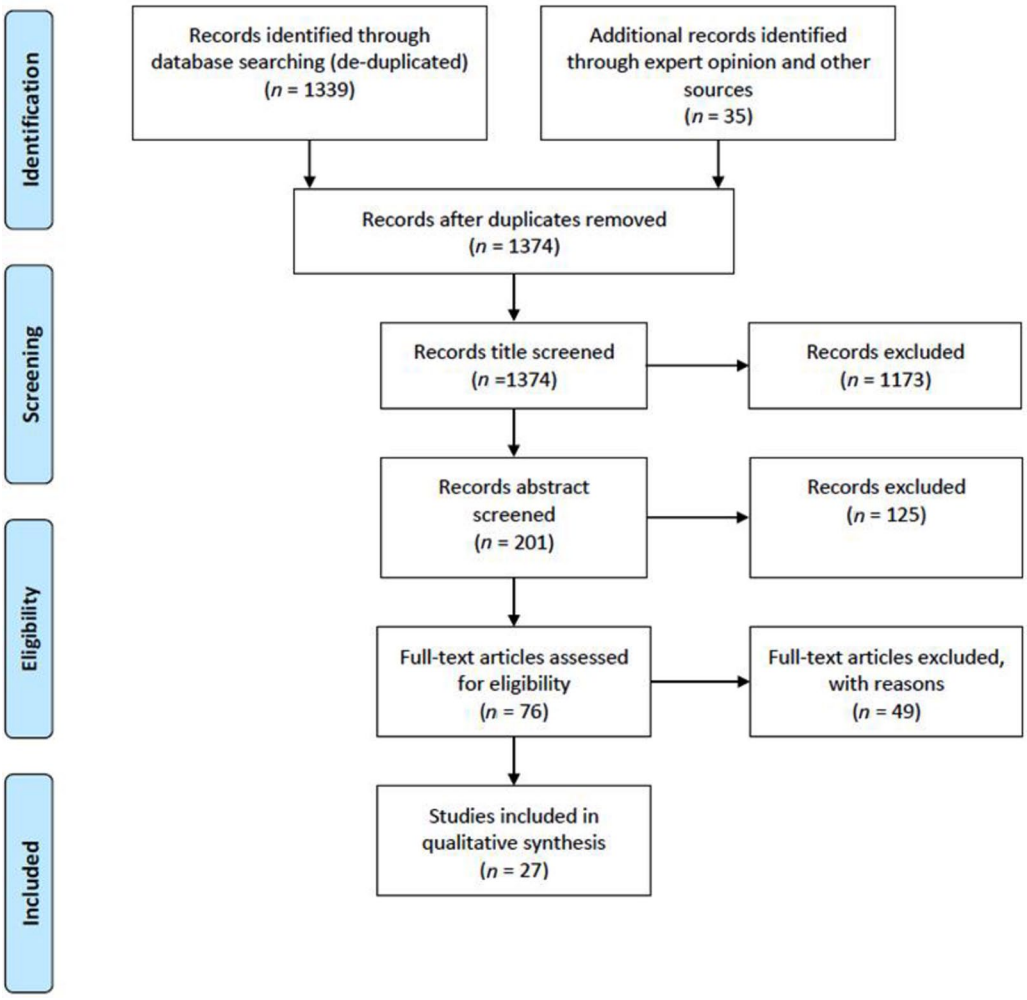

Figure 1. PRISMA flow chart.
PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

increased risk and six showing no association. Excess alcohol consumption was associated with an increased risk of stroke, bowel and breast cancer (between 20% and 50%).[11,76,97] However, no association was found between excess alcohol consumption and the dementias,[11] CHD,[91] lung[76] or liver cancer.[99]

Whilst less evidence was available for the remaining risk factors, broad associations were reported between air pollution and an increased risk of dementia,[14] DM,[77] stroke,[92] lung cancer[82] and CHD.[79] Depression was found to be associated with an increased risk of AD, any dementia, DM and CHD by between 30% and 104%,[11,77,80] but had no effect on VaD risk.[11] High cholesterol was associated with a 20–24% increased risk of CHD[11] and (when present in midlife) was associated with a doubling in the risk of AD[88] but had no effect on any dementia, VaD[11] or stroke.[86] Whilst the current data are insufficient to allow the building of a structural equation model, the complexity and overlaps within these relationships can be shown diagrammatically, see Figure 2. Figure 2 also provides additional contextual information, beyond the scope of this review, by highlighting the potential further relationships between the risk factors themselves and between NCD categories. For example, poor diet and lack of physical activity may increase risk of obesity with consequent increased risk of hypertension, and stroke and diabetes are known to raise the risk of later dementia.[100,101]

Table 1. Showing the direction of relationships and extent of the systematic review and meta-analysis evidence for the associations between the selected risk factors and noncommunicable diseases.

		Dietary pattern	Physical activity	Smoking	Air pollution	High blood pressure	Obesity	Depression	High cholesterol	Excess alcohol consumption
Dementia	Any dementia	↓↓ Anstey and colleagues[11]	↓↓ Anstey and colleagues[11]	↑↑ Anstey and colleagues[11]	↑↑ $PM_{2.5}$ Peters and colleagues[14]	.	↑ Anstey and colleagues[11]	↑↑ Anstey and colleagues[11]	≠ Anstey and colleagues[11]	≠ Anstey and colleagues[11]
				↑↑ NO_2, NOx Peters and colleagues[14]			≠ Late life Anstey and colleagues[11]			
	AD	↓↓ Anstey and colleagues[11]	↓↓ Anstey and colleagues[11]	↑↑ Anstey and colleagues[11]	.	≠ Anstey and colleagues[11]	↑↑ Anstey and colleagues[11]	↑↑ Anstey and colleagues[11]	↑↑ Mid life Anstey and colleagues[11]	≠ Anstey and colleagues[11]
									≠ Late life Anstey and colleagues[11]	
	VaD	.	↓↓ Anstey and colleagues[11]	↑↑ Anstey and colleagues[11]	.	↑↑ Anstey and colleagues[11]	≠ Anstey and colleagues[11]	≠ Anstey and colleagues[11]	≠ Late life Anstey and colleagues[11]	≠ Anstey and colleagues[11]
DM		↓↓ Bellou and colleagues[77]	↓↓ Bellou and colleagues[77]	↑↑ Bellou and colleagues[77]	↑↑ Bellou and colleagues[77]	↑↑ Bellou and colleagues[77]	↑↑ Bellou and colleagues[77]	↑↑ Bellou and colleagues[77]	.	.
Stroke		↓↓ Psaltopoulou and colleagues[90]	↓↓ Wahid and colleagues[94]	↑↑ Peters and colleagues[89]	↑↑ Scheers and colleagues[92]	↑↑ Huang and colleagues[84]	↑↑ Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration and colleagues[81]	.	≠ Lindbohm and colleagues[86]	↑↑ Zhang and colleagues[97]
CHD		↓↓ Galbete and colleagues[98]	↓↓ Wahid and colleagues[94]	.	↑↑ PM10 Cesaroni and colleagues[79]	↑↑ Wei and colleagues[96]	↑↑ Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration and colleagues[81]	↑↑ Gan and colleagues[80]	↑↑ Peters and colleagues[88]	≠ Roerecke and Rehm[91]

(Continued)

Table 1. (Continued)

		Dietary pattern	Physical activity	Smoking	Air pollution	High blood pressure	Obesity	Depression	High cholesterol	Excess alcohol consumption
					≠ $PM_{2.5}$ Cesaroni and colleagues[79]					
Cancer	All cancers	↓↓ Galbete and colleagues[98]	↓↓ de Rezende and colleagues[75]	.	.	.	.	.	.	.
	Breast	↓↓ Schwingshackl and colleagues[93]	↓↓ de Rezende and colleagues[75]	↑↑ Wang and colleagues[95]	.	↑↑ Han and colleagues[83]	↑↑ Postmenopausal Kygriou and colleagues[85]	.	.	↑↑ Bagnardi and colleagues[76]
							≠ pre-menopausal Kygriou and colleagues[85]			
	Bowel	↓↓ Schwingshackl and colleagues[93]	↓↓ de Rezende and colleagues[75]	↑↑ Botteri and colleagues[78]	.	.	↑↑ Kygriou and colleagues[85]	.	.	↑↑ Bagnardi and colleagues[76]
	Lung	.	↓↓ de Rezende and colleagues[75]	↑↑ O'keeffe and colleagues[87]	↑↑ $PM_{2.5}$ Hamra and colleagues[82]		↓↓ Kygriou and colleagues[85]	.	.	≠ Bagnardi and colleagues[76]
					≠ PM_{10} Hamra and colleagues[82]					
	Liver	.	.	.	.	.	↑↑ Kygriou and colleagues[83,85]	.	.	≠ Turati and colleagues[99]

↑↑, denotes probable positive association; ↓↓, denotes probable negative association; ↑, denotes possible positive association (meta-analyses show mixed but generally positive outcomes); ↓, denotes possible negative association (meta-analyses show mixed but generally negative outcomes); ≠, denotes no association found; ., denotes no review identified.
AD, Alzheimer's disease; CHD, coronary heart disease; DM, diabetes mellitus; PM, particulate matter.

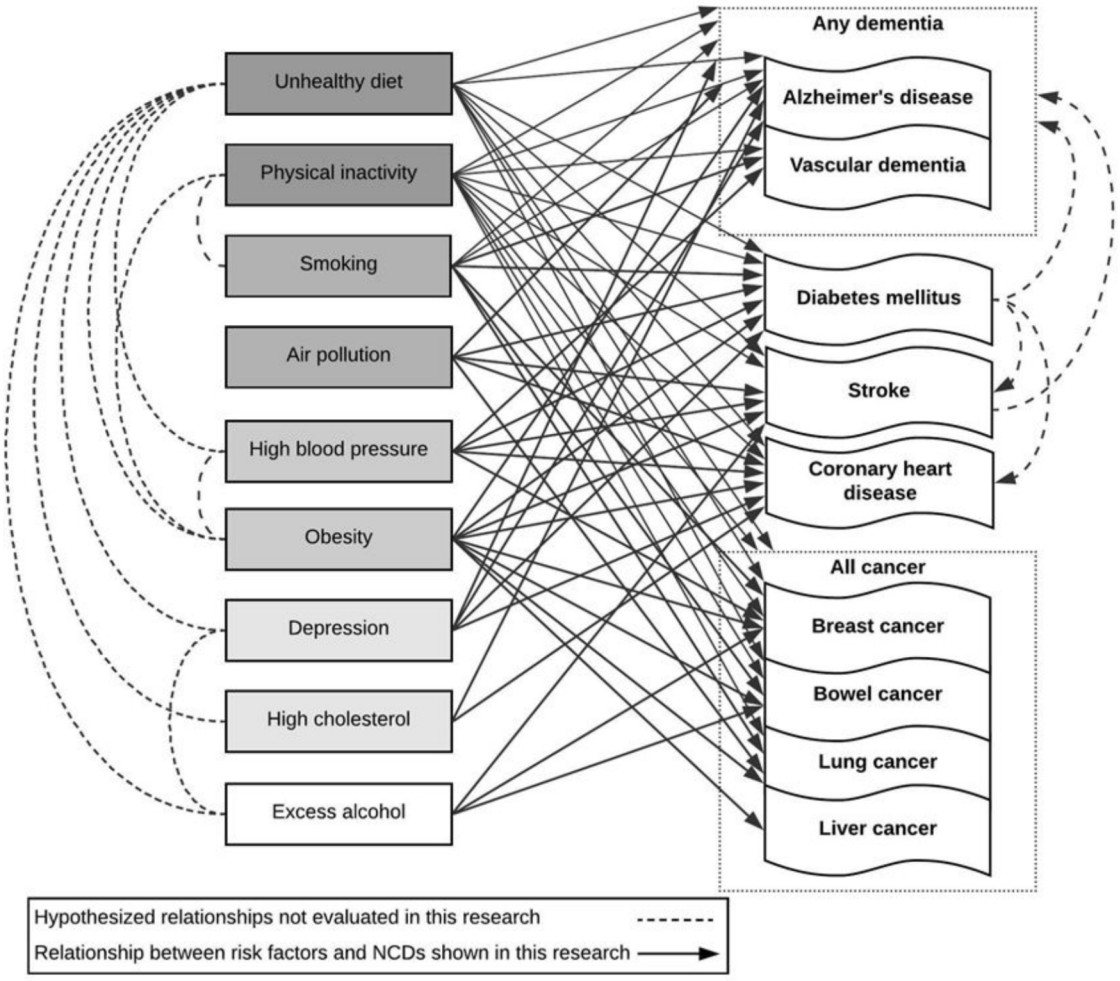

Figure 2. Diagram showing the reported relationships between established risk factors and NCDs.
NCD, noncommunicable disease.

Overall, probable or possible associations were observed between all risk factors and at least two of the five NCDs. The strongest protective factors were healthy diet and physical activity, which were shown to impact risk across all five NCDs. Air pollution was linked to all five NCDs with the strongest evidence for fine particle ($PM_{2.5}$) exposure. Depression, high blood pressure and obesity were linked to all the NCDs for which there was available data, with some variability amongst dementia and cancer subtype.

Quality rating

The AMSTAR-2 was employed to assess the quality of selected reviews. Of the 27 included publications, 11 (41%) were characterized as critically low quality, 12 (44%) of low quality and 4 (15%) of moderate quality (Supplementary Table 2).

Discussion

Summary of findings

Both healthy dietary pattern and physical activity were consistently associated with reduced risk across the NCD categories,[11,75,77,90,93,94,98] and a comprehensive body of evidence substantiated these findings. Smoking and air pollution were also associated with increased risk of incident NCDs,[11,14,77–79,82,87,89,92,95] and to a lesser extent, so were high blood pressure and obesity.[11,77,81,84,85,96] The evidence for depression and high cholesterol was suggestive of increased risk

for the cardiovascular rather than the cancer outcomes,[11,77,80,86,88] with the weakest evidence for alcohol as a common risk factor.[11,76,91,97,99]

Strengths and limitations

The strengths of our review include the use of a pragmatic high-level but systematic overview of reviews strategy. This has allowed us to deliver a broad evidence-based overview, drawing together information on the relationships between prevalent NCD and common risk factors. This has been further facilitated by the recent rise in published overview and single systematic reviews examining single disease or single risk factors. The global ageing population, rising prevalence of concomitant lifestyle and NCD risk factors and disease also make research across common NCDs both timely and important. Our review is an essential step towards a greater public health understanding of the interacting relationships driving NCDs. It has allowed us to document and highlight the overlapping risk factors and will help direct future work in this area.

Limitations inherent in drawing together existing reviews, and in particular overview reviews, inevitably include the risk of propagating existing bias. This may include selection bias driven by the inclusion of particular participants in cohort studies, inclusion of particular cohort studies or cohort study results in systematic reviews and meta-analyses and the inclusion of particular reviews in overview reviews. As in any review, further bias may come from drawing together varied reporting of results, analytical approaches, assessment of risk factor exposure, accounting for confounders and the possibility of reporting error. The AMSTAR-2 assessment tool, although the most appropriate, is not designed to assess overview reviews and, in part due to its rigour, is likely to assess anything other than very recent reviews as lower quality. Bias in overview reviews may also come from the age of the constituent studies with older studies potentially included in greater numbers of meta-analyses, and possibly also of lower quality. Our methods too, while systematized, may be a source of bias. Overall our review process was pragmatic and rigorous but inevitably open to bias. Taking a top-level focus and using existing reviews and meta-analyses meant that we were able to review a wide area but were unable to statistically synthesize the evidence or revisit the original cohort studies or participant level data where (1) evidence although present, might feature only to a lesser degree, for example for AD and hypertension, or (2) where risk relationships are long established and meta-analyses may never have been performed, for example smoking and CHD. Caution also needs to be applied where constituent studies were themselves rated poorly in terms of risk of bias. Furthermore, in taking a pragmatic approach to the classification of NCDs we may have missed some subtleties in the varied cancer diagnoses and inadvertently introduced a false level of certainty with regard to dementia type where overlapping pathology, rather than definitive diagnosis, is acknowledged as the most common occurrence.[102] Finally, for dementia at least, there is some evidence that age of exposure to the different risk factors may moderate their impact[103–105] and we were unable to take this into account. Nevertheless, our findings are consistent in showing the complexity and overlap of the relationships in this area.

Implications and research recommendations

Although our results suggest that exposure to individual risk factors may act to concurrently raise the risk of more than one NCD we did not find sufficient evidence to allow us to extract or infer the strength of these relationships. Furthermore, we know that risk factors often co-occur[106] and, at least for dementia, there is a dose response with greater numbers of risk factors conferring higher levels of risk.[14] In addition, neither the risk factors nor the outcomes are independent. For example, both stroke and diabetes increase risk of dementia and obesity raises risk of diabetes, high blood pressure and dementia.[101,107] In fact, it is more likely that the true relationships are best represented as a web of influence with relationships within and between both risk factors and outcomes. These putative relationships now need to be clarified using high quality longitudinal participant level data. Suitable datasets should represent relevant global populations and have sufficiently long follow up to evaluate confounded and competing relationships and to allow sufficient confidence about inferred causal relationships, thereby avoiding issues such as reverse causality.[100] Further risk factors and outcomes may exist beyond those examined here and these too need to be investigated.

Our review also noted age as a risk factor common to each of the NCDs. Although typically considered a nonmodifiable risk factor, the risk it contributes varies between individuals. Variability in

the risk of death for people of the same age was labelled as 'frailty' in 1979.[108] The concept was later generalized to describe variability in the risk of an adverse outcome for people with the same degree of exposure. It is commonly implemented as a term that accounts for unobserved random effect in proportional hazards models. As reviewed elsewhere, frailty is also operationalized as a clinical syndrome or as a state.[109] As noted there, in either guise, it is an important independent risk for common late-life illnesses, including heart disease, osteoporotic fracture and dementia. Recently, the degree of frailty was found to moderate the relationship between neuropathologically defined AD and its clinical expression as dementia. Inasmuch as some degree of frailty may be modifiable, then understanding its role in disease is important. Further, understanding what it is about ageing that makes it such a common risk factor may lead to interventions that can reduce the burden of age.[110]

Wider context and the next steps

In this overview, we have highlighted the likely overlap between risk factors for NCDs and called for further work to quantify the strength and direction of the relationships between risk factors and incident NCDs. In addition, given the likely complexity of the associations, we have also highlighted the need to evaluate the relationships between the risk factors themselves and between the disease states. This is timely. The changing prevalence of NCD around the world makes further understanding of these complex inter-relationships a priority. The WHO recorded the top two global causes of death in 2000 and 2016 as CHD and stroke, but by 2016, AD and other dementias and trachea bronchus and lung cancers were present. In wealthier countries in 2016, NCDs were even more strongly represented alongside CHD, stroke and DM in lower-middle- and low-income countries.[18] Furthermore, research looking at population-attributable risk for established dementia risk factors reported the possibility of reducing dementia risk by up to 28% (taking account of overlaps between risk factors), with some of the biggest drivers of increased risk identified as physical inactivity and smoking.[106] This analysis now needs to be extended to incorporate wider NCDs. Once we have clarified the strength of the relationships in the web of influence between the risk factors and disease states our next step must be to extend this to include population-attributable risk, design and evaluation of informed and targeted NCD risk reduction intervention and eventually, economic impact. The main NCDs and their risk factors are connected and prevalent; prevention is vital, but resources inevitably limited. An interactive economic model, where we can explore and evaluate the impact of risk reduction strategies on multiple interacting disease states, would be an invaluable public health tool. Such a tool is currently conceptual but represents a goal towards which all interested parties should be working.

In our high-level overview of the epidemiology we demonstrate the interconnected and overlapping relationships between common risk factors and common NCDs. Gaining a greater understanding and taking greater account of these relationships will facilitate more appropriate and targeted risk reduction, and this should now be our goal.

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Supplemental material

Supplemental material for this article is available online.

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