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Fritz, Manuela Katharina; Fromell, Hanna

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How to dampen the surge of non-communicable diseases in Southeast Asia: insights from a systematic review and meta-analysis

Manuela Fritz ^{1,2,*} and Hanna Fromell ^{2,3}

¹Faculty of Economics, Business and Information Systems, Chair of Development Economics, University of Passau, Innstraße 29, Passau 94032, Germany

²Department of Economics, Econometrics and Finance, University of Groningen, Nettelbosje 2, Groningen 9747 AE, The Netherlands

³Department of Economics and Business Economics, Aarhus University, Fuglesangs Allé 4, Aarhus V 8210, Denmark

*Corresponding author. Chair of Development Economics, University of Passau, Innstraße 29, Passau 94032, Germany. E-mail: manuela.fritz@uni-passau.de

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Abstract

Non-communicable diseases (NCDs), such as diabetes, cancer, cardiovascular diseases and chronic respiratory diseases, have overtaken infectious diseases as the number one cause of death worldwide. The rise of these diseases is especially grave in Southeast Asia, where existing research however falls short on offering guidance on how policy can best prevent and control NCDs in the region. Additionally, low- and middle-income countries in Southeast Asia cannot directly incorporate lessons drawn from interventions in richer countries, since health system capacities and human and financial resources are thoroughly different. Preventive interventions, thus, need to correspond to local capacities and require contextual solutions. In this article, we provide a systematic review of a wide scope of NCD interventions conducted in Southeast Asia to inform about existing intervention designs and to derive sound evidence of their effectiveness. Our literature search results in 51 studies from five Southeast Asian countries from which we can extract 204 estimates. We sort the studies into six intervention categories and analyse them with respect to 23 different health and behavioural outcomes. While we find positive and significant average effects across all six types of interventions, we also document evidence of substantial publication bias. Using a meta-regression approach in which we correct for the publication bias, we instead fail to confirm positive average effects for some interventions. Especially dietary and physical activity interventions fail to achieve improvements in analysed health outcomes, while programs focusing on smoking cessation, on the take-up of preventive screening activities or educating patients on how to cope with NCDs achieve sizeable effects. We also present evidence that the size of the effect differs with the participants' characteristics as well as with design features of the intervention. For local policymakers, the results provide important knowledge on how to address the increasing NCD burden in the coming years.

Keywords: Non-communicable diseases, Southeast Asia, effectiveness, systematic review, meta-analysis, meta-regression, public health, health policy, prevention

Introduction

Non-communicable diseases (NCDs), such as diabetes, cancer, cardiovascular diseases (CVDs) and chronic respiratory diseases, have overtaken infectious diseases as the number one cause of death worldwide (Bollyky *et al.*, 2017; Niessen *et al.*, 2018). The spread of NCDs is especially grave in the Southeast Asian region, which, compared to other regions, saw the steepest increase in NCD deaths between 2000 and 2012 (WHO, 2014)¹ and which suffers a loss of more than 8.5 million deaths yearly due to NCDs (WHO, 2020). Especially vulnerable are the region's poor, who face the risk of carrying the greatest burden of NCDs and, as a result, also of facing the consequences of further widening health and economic inequalities (Mirelman *et al.*, 2016; Niessen *et al.*, 2018; Nugent *et al.*, 2018). This escalation is to a large extent driven by urbanization, economic development and

globalization, which rapidly have pushed the region's populations towards adopting more unhealthy lifestyles, such as consuming unhealthy diets, foregoing physical activity and smoking tobacco, and ultimately to a larger risk of contracting NCDs.

The double burden of both communicable diseases and NCDs poses a substantial challenge for Southeast Asia's commonly fragile healthcare systems and limited health budgets (Dans *et al.*, 2011; Bollyky *et al.*, 2017). Moreover, healthcare systems in the region have been designed to focus on infectious diseases and acute care and are, thus, not well prepared to respond to the increasing need for chronic care (Dans *et al.*, 2011; Meiqari *et al.*, 2020). As a response, the World Health Organization (WHO) has started the development of multi-sectoral national action plans for the prevention and control of NCDs in Southeast Asia (WHO, 2013; 2015).

Key messages

- We conduct a systematic review and meta-analysis of the literature that evaluates NCD interventions in Southeast Asia.
- Interventions to prevent and treat NCDs in Southeast Asia are on average effective, but the evidence is limited to few countries and the literature suffers from publication bias.
- Positive results are found for screening uptake and patient education interventions, while dietary and physical activity interventions fail to achieve improvements in analysed health outcomes.
- Design features of the interventions and participants' characteristics are relevant effect size moderators.

Yet, the prioritization of NCDs on the global and local health agenda remains limited (Heller *et al.*, 2019). The success of these action plans will crucially depend on the identification of regionally effective approaches. Therefore, systematic evaluations of local NCD interventions and programs to inform effective disease management strategies are urgently needed (Allen *et al.*, 2018; Hernandez *et al.*, 2020).

A vast body of literature covers NCD-related policies in western and high-income countries.² Economic health research is lagging behind, however, when it comes to NCDs in the developing world (Behrman *et al.*, 2009). The insights from western and high-income countries cannot alone constitute the decision base for designing effective implementation measures for Southeast Asian countries since these face distinctly different cultural backgrounds, lifestyles, health literacy, income levels and health system capacities. For example, using letters to invite women for breast cancer screening is a currently recommended policy in richer countries (Ritchie *et al.*, 2020). Yet, such a policy may have lower impact in poorer contexts where the ability to reach individuals in remote areas is limited, health literacy and thus take-up rates might be lower and the (opportunity-)cost to attend such screenings might be higher. Additionally, results from high-income countries might not be applicable to low- or middle-income countries if the ability to provide and finance health services is substantially lower (Revill and Sculpher, 2012). Similarly, as health insurance coverage is low in Southeast Asia and health expenses are largely financed out-of-pocket, individuals will be less willing to seek health care as long as they do not face acute health problems. This may, in comparison to western countries, reduce the effectiveness of NCD interventions, which largely rely on preventive measures.

Granted, the diversity of Southeast Asian countries might also limit the possibility for transferring evidence and lessons within this region as well. Yet, the geographic and cultural proximity and similarities, especially in the economic development and health system capacities, and the limited amount of evidence from single countries make a strong case for these countries to draw on the knowledge about effective NCD policies from this region as a whole. The objective of our review is, therefore, to provide a complete picture on the available evidence of NCD interventions in Southeast Asia and, thereby, establish a knowledge base that can inform local policymakers as well as future research in this region.

To this end, we conduct a systematic review and meta-analysis of interventions that address NCDs in low- and middle-income countries in Southeast Asia and thereby contribute to the literature in three ways. First, we review articles covering the entire region of Southeast Asia, aiming to derive policy conclusions that could be valid at the regional level and to identify countries for which evidence is vast or scarce, respectively. Second, we consider different types of NCD interventions jointly and thereby address the intertwined nature of the four major NCD risk factors (tobacco consumption, alcohol consumption, unhealthy diet and physical inactivity). Third, we address several shortcomings that are commonly neglected in conventional meta-analysis with econometrically more sophisticated methods.

We consider all evaluations implemented within the past 20 years and that are based on a method that allows for deriving causal evidence, leading to a sample of 51 studies, which we classify into six distinct intervention categories. We analyse the extracted estimates in a standard meta-analysis and in a more conservative meta-regression model in which we address problems of publication bias, cluster standard errors at the study level and account for different number of estimates per study. We also estimate effect sizes for different health outcomes, intervention categories and countries.

The remainder of this article is organized as follows. The 'Methods' section presents the search strategy and inclusion criteria that we applied to select the studies. In the 'Statistical considerations and analysis' section, we outline statistical considerations on how to calculate harmonized effect sizes and the analytical approach of the meta-analysis and meta-regression. We present the results in the 'Results' section, including the presentation of the included studies and extracted outcome estimates, statistical and meta-analytical results, and the results of a moderator analysis. The 'Discussion and implications' section provides a discussion of the results and implications for future interventions and research. The 'Conclusion' section concludes.

Methods

Literature search

The literature search was conducted using the databases 'Cochrane Library, EconLit, PubMed, Sociological Abstracts and Web of Science' and complemented by a search with 'Google Scholar'. We categorized our search terms under the following sections: (1) major NCDs and related risk factors; (2) Southeast Asian region and countries; (3) intervention setting; (4) evaluation study and (5) effectiveness or cost-effectiveness study. A detailed description of the search terms and procedure is provided in Supplementary Appendix A.³ Titles and abstracts were screened independently by two researchers and studies were excluded if they missed quantitative assessments, were duplicates or irrelevant. Information from the included studies was extracted by the researchers according to a coding tool. The information extracted consisted of the general information of the publication, i.e. author(s), title, year and type of publication. Furthermore, the country or countries and target population(s) were characterized for each study, as well as the outcome(s) measured, the type of intervention(s) and intervention impacts. Included studies were also characterized according to their research methodology, sampling strategy and sample size and time

period covered. Discrepancies and unclear citations were resolved through discussions. For included studies, we further made use of citation tracking (forward searching) and screened their list of references for further relevant studies (backward searching). The forward- and backward-search procedures were ended whenever a further search did not lead to new results.

Inclusion criteria

We defined our inclusion criteria following a basic PICO(S) (population, intervention, comparison, outcome, study design) framework (Haynes, 2006).

We included studies that focus on any population within the Southeast Asian region with the exception of Singapore.⁴ Studies had to evaluate the (cost-)effectiveness of health interventions that focused on the prevention or control of NCDs and/or any of their related main risk factors. Studies evaluating solely the impact of a specific drug or medical treatment alone were excluded.⁵ Given the broad scope of health interventions covered, our inclusion criteria for the outcome measure were also relatively comprehensive. We included studies that evaluated at least one relevant health outcome (such as metabolic or anthropometric measurements) or behavioural outcome (such as smoking, conducting physical activity or taking-up screening) directly related to NCDs or NCD risk factors. We did not consider outcomes that were mere measures of individuals' knowledge, beliefs, attitudes or intentions as outcomes. The study design had to be such that one could infer a causal relationship between intervention and outcome from the results. Studies were therefore included if they performed an impact evaluation that was based on either an experimental design, such as a randomized controlled trial (RCT), or a quasi-experimental design (i.e. with non-random assignment) that used a control group or alternative intervention for comparison. Finally, we only included studies that were written in English and published in an academic peer-reviewed journal after the year 2000.

Statistical considerations and analysis

Computation of effect sizes

Conducting a meta-analysis and meta-regression requires that extracted effect sizes are harmonized. A standard measure for continuous effect sizes is the standardized mean difference (SMD) (Higgins *et al.*, 2019). The measure expresses the single difference in a given indicator between a treatment and control group after some intervention, standardized by the pooled standard deviation of the same indicator before the intervention (i.e. at baseline). Yet, this measure relies on the assumption of statistically identical groups at baseline, because only then the entire effect can be attributed to the intervention. This requirement is often not met in studies that use non-random selection strategies or small samples, which makes the risk of falsely declaring equal samples at baseline worryingly high.

To minimize the risk of estimating effects incorrectly, we calculate the effect sizes for all studies while also accounting for existing differences between control and treatment populations at baseline. We do this by calculating the effect size θ for continuous outcomes as the standardized mean difference-in-difference (SMDD):

$$\theta_{SMDD} = \frac{((\mu_{T2} - \mu_{T1}) - (\mu_{C2} - \mu_{C1}))}{SD_{pooled}}, \quad (1)$$

where μ is the mean value of the respective outcome, with T1 and T2 representing the treatment group at the baseline and follow-up respectively and C1 and C2 the control group at baseline and follow-up respectively, and SD_{pooled} is the standard deviation of the outcome at the baseline pooled over both groups. Note that the numerator corresponds to the single difference in means if the means at the baseline are identical ($\mu_{T1} = \mu_{C1}$). Additionally, since many included studies work with very small sample sizes, we adjust for possible upward biases due to small samples, using Hedges' correction factor (Hedges, 1981; Hedges and Olkin, 1985):

$$\theta_{SMDD_{hedges}} = \left(1 - \frac{3}{4 * (n_T + n_C - 2) - 1}\right) * \theta_{SMDD} \quad (2)$$

where n_T and n_C represent the number of individuals in the treatment and control group, respectively.

For binary outcome variables, one standard measure for reviews and meta-analyses is the odds ratio (OR), which is the ratio of odds of an outcome in the treatment group over the odds of the same outcome in the control group. Just as the regular SMD for continuous outcomes, ORs at follow-up do not correct for differences at the baseline. We calculate ORs while correcting for such baseline differences by computing the difference in odds between the follow-up and baseline:⁶

$$OR_{corr} = \exp(\ln(OR_2) - \ln(OR_1)), \quad (3)$$

where OR_{corr} is the OR corrected for between-group differences at the baseline, and OR_1 and OR_2 correspond to the OR at baseline and follow-up, respectively. For studies that do not present outcome measures at the baseline, we compute OR_{corr} by assuming an OR_1 equal to one (equivalent to there being no difference in the outcome variable between treatment and control at the baseline). To be able to pool estimates across outcomes and studies, we transform the corrected ORs to standardized effect sizes, θ_{OR} , using the standard procedure of multiplying the log OR with a factor of $\sqrt{3}/\pi$ (Borenstein *et al.*, 2011; Ringquist, 2013).

In a last step, we code all measures such that desirable changes in health outcomes (e.g. a decrease in weight or an increase in physical activity) produce positive effect sizes and undesirable changes (e.g. an increase in weight or a decrease in physical activity) result in negative effect sizes.

In the remaining part of the paper, we will use the term 'effect size' (simply denoted as θ), irrespective of whether it has been retrieved from continuous outcomes or ORs.

Meta-analysis

The broad specification of the inclusion criteria is likely to result in studies that vary substantially with respect to specific design features, approaches and outcomes. Therefore, a random-effects meta-analysis, which assumes that the true effect size is a normally distributed random variable that varies across studies, is preferred over a fixed-effect meta-analysis (Borenstein *et al.*, 2011; Ringquist, 2013). Individual study- and outcome-specific effect sizes can therefore differ from the average effect size due to two components: the individual within-study variance, ν , and the random-effects variance component, τ^2 , with the latter being an indicator

of the between-study heterogeneity (Ringquist, 2013; Gallet and Doucouliagos, 2017). The estimated effect size $\hat{\theta}_{it}$ of an outcome estimate i in study t can therefore be described as

$$\hat{\theta}_{it} = \theta_i + \varepsilon_{it}, \text{ with } \varepsilon_{it} \sim N(0, v_{it} + \tau_i^2), \quad (4)$$

where θ_i is the true effect size for outcome i and ε_{it} is an error with zero mean and a variance of $v_{it} + \tau_i^2$. The weights used in the random-effects meta-analysis are the inverse of the total variance (DerSimonian and Laird, 1986).

Meta-regression and moderator analysis

The meta-analytical approach described in the previous subsection comes with three distinct drawbacks. First, estimates from the same study are likely to be strongly correlated, violating the assumption of independent errors when we pool the estimates. Because it is not possible to cluster the standard errors on a study level in the meta-analysis, the estimated average effect is likely to be biased. Second, the number of estimates can vary greatly across studies. If studies that contribute with more estimates find systematically larger or smaller effects, the estimated average effects will be biased towards this direction.⁷ Third, the average effect might be influenced through publication bias, commonly driven by underpowered studies.

To be able to analyse the overall effect sizes while accounting for such potential sources of bias, we use generalized estimation equations and conduct weighted least squares random-effects meta-regressions. This type of regression allows us not only to cluster the standard errors at the study level, but also for adjusting the emphasis on estimates from studies with a higher (lower) number of estimates downwards (upwards) by using a population average model (see Ringquist, 2013, for a technical summary of this approach). We furthermore control for publication bias and small-study effects by including the squared standard error SE^2 as an independent variable, known as PEESE⁸ (Stanley and Doucouliagos, 2012; 2014), which indicates the extent of publication bias and accordingly corrects the effect size. It has been shown that including the squared standard error, instead of the linear term, reduces the likelihood of underestimation when a true effect is present (Moreno *et al.*, 2011; Stanley and Doucouliagos, 2012; 2014). Meta-regressions also allow for analysing the influence of moderators, which we include in a subset of regressions. The model for the meta-regression hence reads

$$\hat{\theta}_{it} = \theta_i + \beta SE_{it}^2 + \gamma X'_{it} + \varepsilon_{it}, \text{ with } \varepsilon_{it} \sim N(0, v_{it} + \tau_i^2), \quad (5)$$

where SE_{it}^2 is the squared standard error of outcome i in study t , X'_{it} is a vector of moderators and γ is the corresponding vector of coefficients. The regression is again weighted by the inverse of the total variance.

Results

Study identification and characterization

Our literature search resulted in 3947 studies, of which 111 studies were fully reviewed by a team of researchers and assessed according to our inclusion criteria. One additional study was identified through further literature snowballing. The complete search procedure resulted

in a final sample of 51 studies⁹ and is depicted in Figure 1.

The 51 studies are described in detail in Table B1 in Supplementary Appendix B. They cover five Southeast Asian countries. The large majority evaluate interventions conducted in the region's two upper middle-income countries Thailand (25 studies) and Malaysia (17 studies). A smaller number of studies were conducted in Vietnam (4), the Philippines (4) and Indonesia (1). Other Southeast Asian low- and middle-income countries, such as Myanmar or Lao PDR, are not covered by any of these studies. This limitation in country coverage implies that the results and implications we draw from analyses where we aggregate data across countries are foremost applicable for Thailand and Malaysia, while lessons for other countries in this region should be drawn while carefully considering relevant cultural, economic and geographical differences. To further address potential heterogeneity issues across countries and present country-specific lessons where possible, we present our meta-analytical results for Thailand and Malaysia separately whenever the data allows. Despite our inclusion criteria being also designed to extract studies that focus on cost-effectiveness, none of the studies included an economic analysis of its costs.

We sort the 51 studies into six intervention categories¹⁰ (see Table 1). The first three categories, which aim at preventing NCDs by directly addressing the most common NCD risk factors, focus on smoking cessation ('smoking', 8 studies), reducing the consumption of alcohol ('alcohol', 4 studies), and improving diets and physical activity ('diet and physical activity', 20 studies). We assign studies concerning diet and physical activity to the same category as both risk factors are almost exclusively addressed jointly in the respective studies. The remaining studies are categorized as 'screening' (4 studies), 'patient education' (11 studies, e.g. studies that teach patients how to cope with their disease), or 'system approach' (5 studies, e.g. studies that change NCD-related processes within health facilities).

Within the categories of screening, patient education and system approach, the interventions can also be differentiated with respect to the targeted NCD. The four screening studies focus exclusively on screening uptake for breast or cervical cancer among female patients; the last two intervention categories—'patient education and system approach'—focus on patients with either diabetes (13 studies) or CVDs, such as stroke (3 studies).

For each study, we also collected information on the intervention format, i.e. whether the intervention took place in a group setting (including community settings or schools) or whether it was individually conducted (e.g. individual counselling sessions or home-based interventions). Twenty-four studies included some form of group intervention, while 22 studies were solely individually targeted. The five system approach studies focused on processes within facilities instead of directly at participants and were consequently not sorted into any of the two intervention format categories.

The study populations in our sample are consequently quite diverse and encompass elderly, adults and students as well as urban and rural populations. Individuals are of high and low risk of NCDs or are patients who already suffer from a disease, where the respective interventions aim to prevent further adverse health consequences through education or more efficient health facility processes. In what follows, we briefly

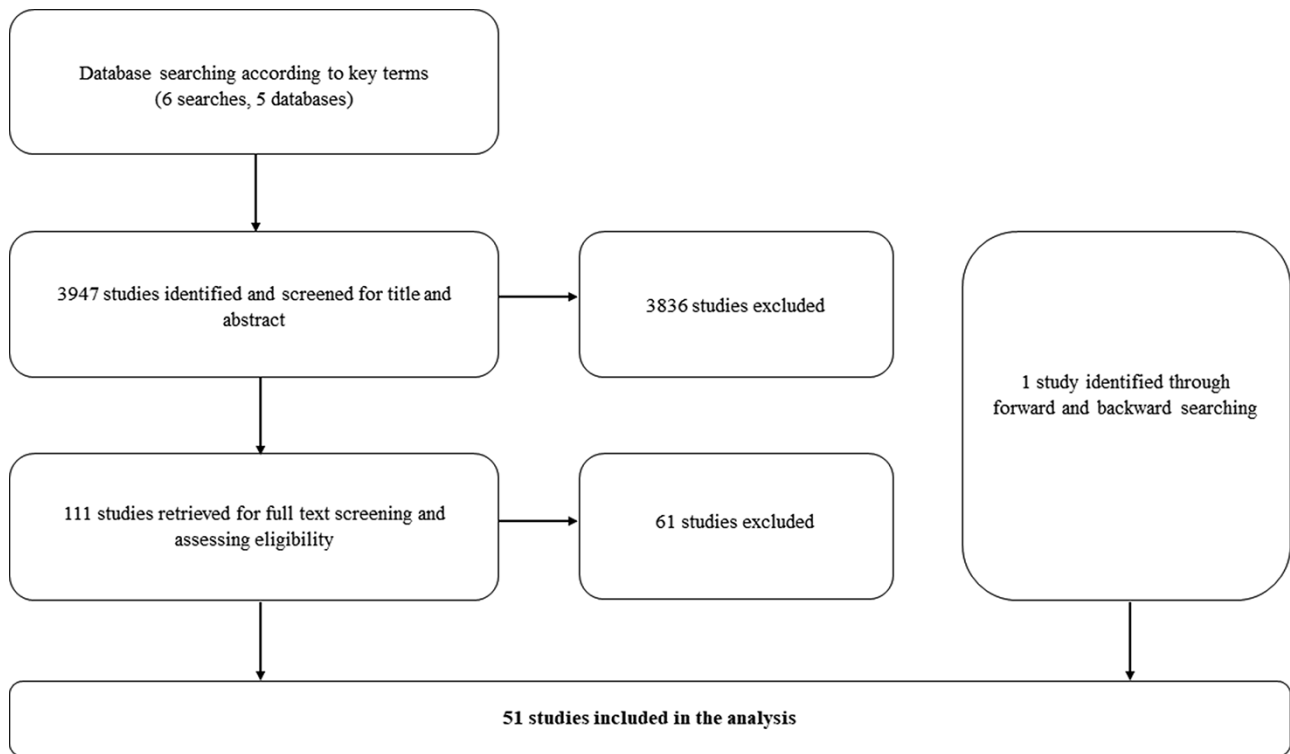


Figure 1. Search procedure and results

present the type of interventions that constitute each of the six intervention categories.

Smoking

Studies within this category evaluate interventions aiming to motivate and incentivize individuals to quit smoking or reduce their tobacco consumption. They encompass different strategies, such as individual counselling sessions, financial incentives or motivational interviews. Two studies focus particularly on adolescent smoking.

Alcohol

The four studies in this category examine interventions seeking to direct study participants towards a reduction in their alcohol consumption. Studies exclusively evaluate counselling interventions and focus on risky or harmful drinking, but differ with respect to the counselling design, i.e. length, frequency and setting of the implementation.

Diet and physical activity

The large majority of included studies falls under this category and focuses on participants' behavioural changes with respect to their diet and physical activity. Interventions often consist of not only education sessions, joint physical activities and general health promotion but also media-based assistance or self-monitoring tools. Also studies that evaluate school and workplace interventions and focus on obesity prevention through changing food policies are included in this category.

Screening

The four screening studies focus solely on uptake for cervical and breast cancer screening. They provide education to the

target groups about self-examination and/or how to seek professional examination. They further analyse invitations and reminders for screening events.

Patient education

The studies included in this category investigate how education for NCD patients can improve their disease management. The interventions aim to improve health outcomes by increasing patients' awareness about disease complications and consequently their self-care behaviour. Some studies include patients' family members or peers in part of the training to further increase the patients' understanding and adoption of the taught material.

System approach

The last intervention category includes studies that investigate how changes in the general practices of health facilities can affect patients' health outcomes. These practices include improved coordination between staff members and an increased usage of clinical practice guidelines. Also studies that investigate how involvements of pharmacists or nurses within the facilities' processes can improve a patient's disease management are sorted into this category.

Description of outcome estimates

In total, we extract 204 outcome estimates from the total of 51 studies, receiving 4 estimates per study on average, with a minimum of 1 and maximum of 14 estimates per study. Overall, the studies examine 23 different NCD-related outcomes. As the list of different outcome types in [Table 1](#) shows, the spectrum of study outcomes is broad, especially within the intervention categories diet and physical activity,

Table 1. Distribution of estimates by outcomes, countries and intervention category

	Intervention category						Total no. of estimates	Total no. of studies
	Smoking	Alcohol	Diet and physical activity	Screening	Patient Education	System Approach		
Outcome								
Smoking abstinence	9	0	0	0	1	0	10	
Alcohol abstinence	0	1	0	0	1	0	2	
Alcohol quantity ^a	0	2	0	0	0	0	2	
Alcohol drinking frequency ^a	0	3	0	0	0	0	3	
Alcohol score ^a	0	2	0	0	0	0	2	
Fasting blood glucose	0	0	7	0	5	2	14	
HbA1c	0	0	2	0	7	3	12	
Systolic blood pressure	0	0	12	0	2	2	16	
Diastolic blood pressure	0	0	12	0	2	2	16	
Body mass index	0	0	16	0	3	2	21	
Weight	0	0	9	0	3	0	12	
Waist circumference	0	0	11	0	2	1	14	
HDL-cholesterol	0	0	8	0	2	2	12	
LDL-cholesterol	0	0	8	0	2	2	12	
Total cholesterol	0	0	9	0	1	2	12	
Triglycerides	0	0	9	0	2	1	12	
Salt consumption	0	0	3	0	0	0	3	
Physical activity	0	0	12	0	2	0	14	
Quality of life	0	0	0	0	3	0	3	
Screening uptake—cervical cancer	0	0	0	4	0	1	5	
Screening uptake—breast cancer	0	0	0	3	0	1	4	
Activities of daily living ^a	0	0	0	0	2	0	2	
Illness severity ^a	0	0	0	0	0	1	1	
Country								
Thailand	5	8	35	2	19	5	74	17
Malaysia	1	0	48	5	6	17	77	25
Vietnam	0	0	30	0	4	0	34	4
The Philippines	1	0	5	0	11	0	17	4
Indonesia	2	0	0	0	0	0	2	1
Total no. of estimates	9	8	118	7	40	22	204	
Total no. of studies	8	4	20	4	11	5	(52)	51

Notes: The total number of studies adds up to 52 instead of 51 if counted by intervention category because one study (Pengpid *et al.*, 2015) is included in two categories: smoking and alcohol. ^aThe explanation of the outcomes are as follows: alcohol quantity: number of alcoholic drinks per day or grams of consumed alcohol per week. Alcohol drinking frequency: times per week alcohol was consumed. Alcohol score: a numerical score that indicates whether a person is at risk of alcohol dependence. Activities of daily living (ADL): score of ability to perform different self-care activities such as feeding oneself, bathing and dressing. Illness severity: medical classification of how severe a disease or illness is.

patient education and system approach. This is unsurprising since, among these types of studies, it is common that a single intervention is expected to influence a series of NCD-related outcomes and/or their associated risk factors such as metabolic indicators (blood sugar, blood pressure and blood lipids), anthropometric measurements and physical activity. The other three intervention categories provide only specific outcome estimates since, for smoking and alcohol, the evaluated interventions are not focused on any specific NCD, but on a specific high-risk behaviour. As for screening, the interventions regard not the impact of screening on a specific NCD, but on the rate at which individuals are de facto screened.

Including several outcomes for one intervention category provides the opportunity to give a more nuanced understanding of the relative impact of a given intervention and is a common approach for meta-analysis of health outcomes (e.g. Hamad *et al.*, 2018, assess the impact of education on 25 different health outcomes). Yet, at the same time the multitude of outcomes impedes a single analysis. We consequently provide detailed subgroup heterogeneity and moderator analyses

that allow for investigating differences in impact across intervention categories and countries, as well as across outcomes within intervention categories.

Table 1 shows that the majority of outcome estimates are metabolic indicators and anthropometric measurements. Blood sugar outcomes together with blood pressure and blood lipid outcomes account for more than half of all outcome estimates. BMI, weight and waist circumference make up for almost another quarter. The intervention category diet and physical activity does not only account for the majority of studies but also contributes with the highest number of estimates per study.

Publication bias and statistical power

Before presenting the meta-analysis and meta-regression results, we examine two common meta-analytical issues that, if ignored, risk to lead to large errors in the inference of the results; publication bias and, closely related, low statistical power of the underlying studies.

Publication bias regards the phenomenon that researchers or editors favour articles that show desirable and significant results and that these consequently are more likely to be published than articles with less desirable or interesting results (Stanley, 2008). This can cause the published literature to be systematically unrepresentative of the respective population (Rothstein *et al.*, 2005).

Publication bias will, in expected terms, produce a positive correlation between positive effects and their standard error. This is because studies with larger standard errors, which are also typically smaller in sample size, are, a priori, more likely to both underestimate and overestimate the effect compared to the underlying true effect. Plotting several studies that are estimating the same underlying effect on a graph with the standardized effect size on the horizontal axis and precision (the inverse of the standard error) on the vertical axis should thus, in expected terms, result in a symmetric and inverted funnel with its centre at the true underlying effect. Publication bias would, however, cut out some of the less favourable studies appearing on the left side, resulting in an asymmetric funnel with the scatter points for small studies at the bottom in a long right tail (Egger *et al.*, 1997).

Figure 2 displays the funnel plot for all 204 effect sizes. The red vertical line presents the estimated average effect from the meta-analysis. The funnel is clearly asymmetric and with a long right tail for small studies. This suggests that a publication bias is present, in which results that show positive impacts of health interventions are favoured. The distance between the vertical green line—which is the estimated overall effect from the meta-regression, which controls for publication bias—and the red line—which is the overall effect absent any controls—supports this suggestion.

To assess the presence of publication bias more formally we follow the recommendation of Higgins *et al.* (2019) and use Egger's regression test to test for funnel asymmetry. The test regresses the standardized effect size on its standard error weighted by the inverse of the standard error. A statistically significant value of the slope coefficient in this weighted regression indicates the presence of publication bias. The result of the test confirms the visual findings from the

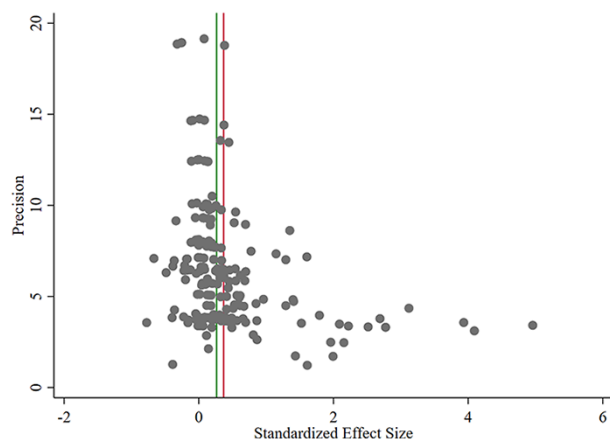


Figure 2. Funnel Plot ($n=204$)

Notes: Precision is the inverse of the standard error of the effect size. The red vertical line represents the average effect from the meta-analysis. The green vertical line represents the average effect from the meta-regression corrected for publication bias.

funnel plot. The coefficient is positive and statistically significant. Moreover, also the intercept is statistically significant, indicating that a genuine effect is present. This supports our decision to opt for the PEESE method and routinely include the squared standard error as an independent variable in all meta-regressions.

Closely related to publication bias is the issue of statistical power. Underpowered studies typically have lower levels of precision and will, in expected terms, together form the greatest variance around the true underlying effect. While they have a higher probability of committing a Type II error, they also have a higher probability of producing false positives, i.e. they detect falsely a significant effect and reject the true null effect (Wacholder *et al.*, 2004; Ioannidis, 2005; Christley, 2010; Gelman and Carlin, 2014). A process of publication bias whereby studies with undesirable results (such as negative and null effects) are systematically removed (or reduced in number) may overestimate the average effect at any level of standard error. Yet, in expected terms, this overestimation will be larger the higher the standard error, since the average effect is larger among low-power compared to high-power studies for the subset of studies that produce desirable results. Consequently, publication bias paired with the inclusion of several low-power studies is particularly prone to generate overestimated effects, also known as the small-study effect. Since the majority of included studies in our analysis work with comparatively small sample sizes, we next assess their statistical power.

We follow the approach proposed by Ioannidis *et al.* (2017). Assuming a statistical significance level of 5% and a power level of 80%, we divide the estimated average effect per intervention category from the weighted random-effects meta-analysis by 2.8 (being the sum of 1.96, representing a 5% significance level, and 0.84, representing the 20/80% split in the cumulative standard normal distribution). This gives a threshold to compare the standard errors of the individual underlying estimates. If the standard error is smaller than this threshold, the estimate is said to have sufficient power to reveal the true average effect. We find that only 46 (or 22.5%) of the 204 estimates in our sample, stemming from 13 of the included studies, have sufficient power.¹¹ This finding once more supports our choice to complement our simple meta-analyses with a more elaborated meta-regression using the PEESE method to reduce the biases stemming from publication bias and underpowered studies.

Meta-analysis

Figure 3a and b shows the results of the random-effects meta-analysis with the subgroup analysis by intervention category and by country. When pooling all 204 estimates of all intervention categories, we find a positive and significant overall effect of 0.37 (P -value: 0.000). However, the between-subgroup I-squared statistic indicates large heterogeneity across estimates ($I^2=96.42$), which is unsurprising, given that these stem from different intervention categories and health outcomes. The subgroup analysis also yields significant positive effects for each intervention category: 0.38 (P -value: 0.015) for interventions aimed at smoking reduction, 0.74 (P -value: 0.004) for interventions aimed at reducing alcohol consumption, 0.28 (P -value: 0.000) for those aimed at improving diets and physical activity, 0.27 (P -value: 0.025) for those promoting uptake of cancer

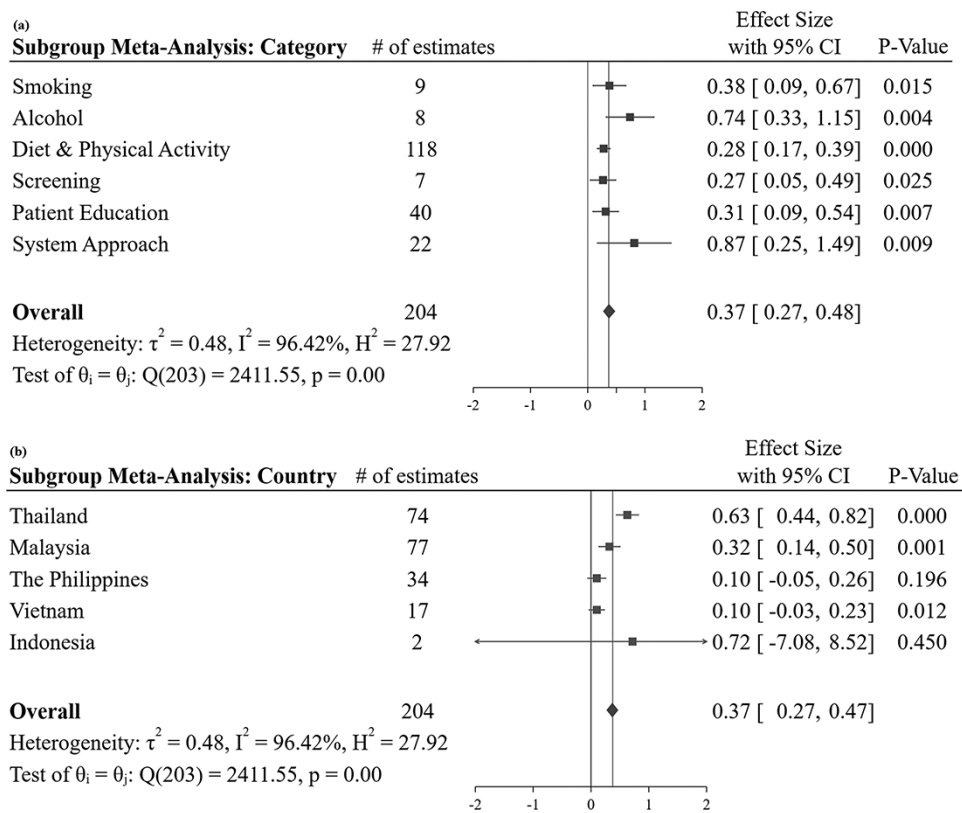


Figure 3. Results of the random-effects meta-analysis by (a) intervention category and (b) country

Notes: The meta-analysis pools all 204 estimates. Estimates are grouped by intervention category and country. Tau-squared is estimated using the restricted maximum likelihood method and Knapp–Hartung adjustment for standard errors.

screening, 0.31 (*P*-value: 0.007) for interventions providing education to NCD patients and 0.87 (*P*-value: 0.009) for interventions making general adjustments in the healthcare system.

The analysis by country reveals large effects for studies conducted in Thailand (0.63, *P*-value: 0.000) and Malaysia (0.32, *P*-value: 0.001), whereas studies conducted in The Philippines and Vietnam result in an equally small effect (0.10, *P*-value: 0.196 and 0.10, *P*-value: 0.120). The overall effect for Indonesia is large, yet insignificant (0.72, *P*-value: 0.450). Yet, since this coefficient is based on only two estimates from a single study, we cannot draw much conclusions from this result.

Figure 4 presents the subgroup analysis by outcome type. The effect size is only significant for 4 of the 23 health outcomes: smoking abstinence (0.37, *P*-value: 0.011), HbA1c (0.83, *P*-value: 0.019), diastolic blood pressure (0.56, *P*-value: 0.006) and illness severity (0.53, *P*-value: 0.016). Two additional metabolic indicators also result in sizable effects: fasting blood glucose (0.68, *P*-value: 0.060) and systolic blood pressure (0.53, *P*-value 0.065), although neither of them is significant at conventional levels. All of the anthropometric outcomes as well as all measures of alcohol reduction are insignificant. The reason why these effects are insignificant may be because these outcomes were truly not affected by the interventions but could also be explained by the fact that several of them stem from only a small number of studies, resulting in wide confidence intervals. Meta-analyses by outcome type for each intervention category separately are presented in Figures C2–C7 in Supplementary Appendix C.

Meta-regression

In this section, we present the meta-regression results in which we routinely control for publication bias and small-study effects (proxied by the squared standard error) and cluster standard errors at study levels and use a population average model to account for different numbers of estimates per study. The model in Column (1) of Table 2 estimates the average effect size for the pooled sample of 204 estimates. Compared to the overall effect size of the simple meta-analysis (0.37), the average effect in our more conservative model is noticeably reduced (0.27, *P*-value: 0.002). The statistical significance of the coefficient for the squared standard error formally confirms the existence of publication bias and hence underlines the importance of controlling for it. Columns (2)–(7) show the effect for each intervention category separately, which are, in comparison to the meta-analytical results, smaller in size. The effects for screening and patient education show only a small reduction but remain strongly significant (0.180, *P*-value 0.000 and 0.228, *P*-value: 0.025). The effects for smoking and alcohol are also somewhat reduced in size and significance (0.226, *P*-value: 0.079 and 0.617, *P*-value: 0.061), while the effect sizes for diet and physical activity and system approach are markedly reduced and insignificant, with the former being close to zero (0.039, *P*-value: 0.225).

In Columns (8) and (9), we present the average effect separately for the two countries that contribute with the major share of included studies, Thailand and Malaysia. While the average effect for Thailand is—as in the simple meta-analysis—larger than the overall effect and significant, the

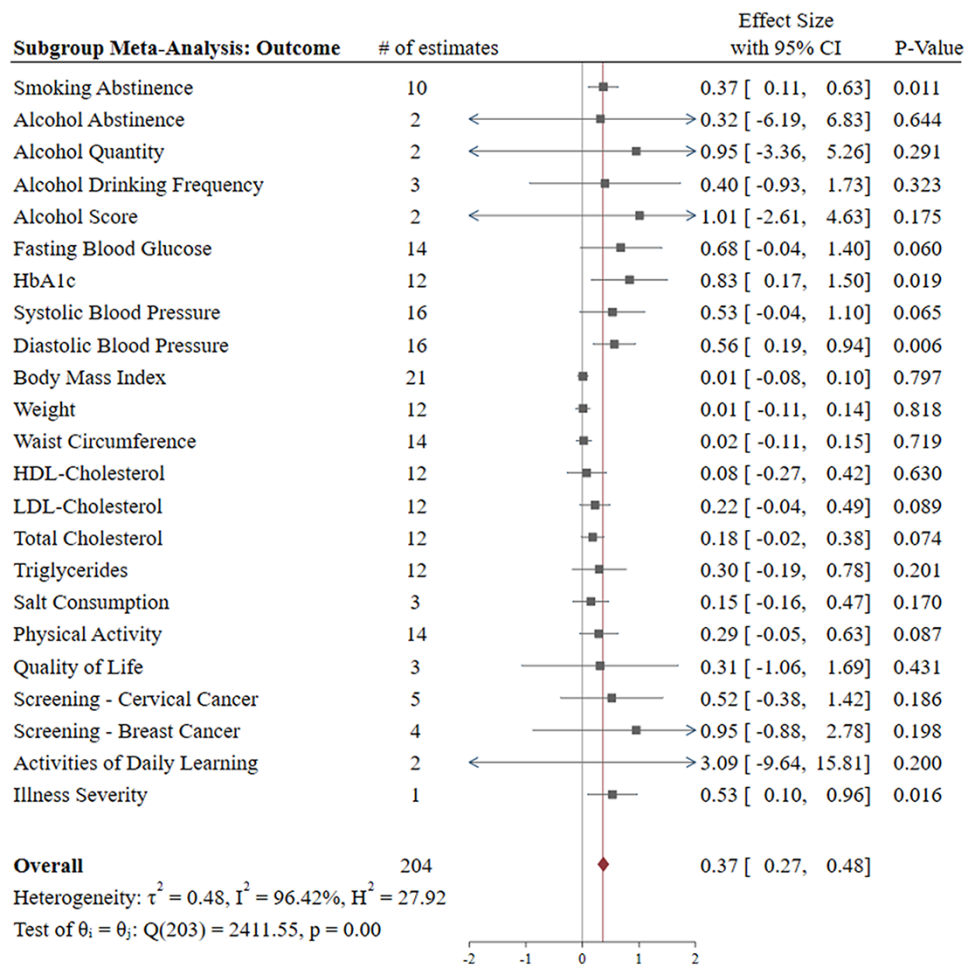


Figure 4. Results of the random-effects meta-analysis by outcome type

Notes: The meta-analysis pools all 204 estimates. Estimates are grouped by outcome type. Tau-squared is estimated using the restricted maximum likelihood method and Knapp–Hartung adjustment for standard errors.

Table 2. Meta-regression results

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
	Full sample	Smoking	Alcohol	Diet and physical activity	Patient education	Screening	System approach	Thailand	Malaysia
Effect size (constant)	0.273 ^{***} (0.089)	0.226 [*] (0.129)	0.617 [*] (0.329)	0.039 (0.067)	0.228 ^{**} (0.102)	0.180 ^{***} (0.001)	0.225 (0.272)	0.483 ^{***} (0.127)	-0.082 (0.140)
SE ²	3.779 ^{**} (1.888)	3.006 ^{***} (0.634)	2.884 (3.472)	6.625 ^{***} (2.012)	5.454 (5.104)	0.652 ^{***} (0.017)	16.837 ^{**} (7.889)	2.585 (2.005)	12.474 ^{***} (3.513)
Number of estimates	204	9	8	118	40	7	22	74	77
Number of studies	51	8	4	20	11	4	5	25	17

Notes: All models are random-effects meta-regressions, which apply weighted least squares, use a population average model and cluster standard errors at the study level, displayed in parentheses. Column (1) includes the full sample of 204 estimates. In Columns (2)–(7) we show the results separately for each intervention category, in Column (8) and (9) we show the results separately for Thailand and Malaysia.

*** $P < 0.01$, ** $P < 0.05$, * $P < 0.1$.

Malaysian effect is now close to zero, suggesting that the results from Malaysia suffer from the biases outlined above. A disaggregated analysis by intervention category shows that this overall insignificant effect for Malaysia results from a lack of positive effects in three intervention categories, namely diet and physical activity, screening and system approach, while a

large positive effect is detected among the patient education studies (see Table C1 in Supplementary Appendix C).

We next present meta-regressions by outcome type in Table 3; for the full sample in Column (1), for each intervention category separately in Columns (2)–(7), and again separately for Thailand and Malaysia in Columns (8) and (9).

Table 3. Meta-regression results—heterogeneity by outcome

	(1) Full sample	(2) Smoking	(3) Alcohol	(4) Diet and physical activity	(5) Patient education	(6) Screening	(7) System approach	(8) Thailand	(9) Malaysia
Smoking abstinence	0.138 (0.165)	0.226* (0.129)			0.060 (0.435)			0.291 (0.198)	0.244 (0.732)
Alcohol abstinence	-0.050 (0.203)		-5.369*** (0.469)		-0.147 (0.171)			0.578* (0.327)	
Alcohol quantity	0.693*** (0.221)		-0.970*** (0.192)					0.862*** (0.257)	
Alcohol drinking frequency	0.302 (0.192)		-1.158*** (0.110)					0.340 (0.257)	
Alcohol score	1.032*** (0.149)		0.0742 (0.269)					0.972*** (0.212)	
Fasting blood Glucose	0.463* (0.237)			0.169 (0.199)	0.320*** (0.090)		0.707 (0.600)	0.306* (0.124)	0.525 (0.334)
HbA1c	0.618*** (0.239)			1.980*** (0.477)	0.262** (0.121)		0.049 (0.076)	0.745* (0.401)	0.610* (0.345)
Systolic blood pressure	0.317* (0.175)			0.123 (0.093)	-0.048 (0.340)		0.396 (0.397)	0.770* (0.394)	0.240 (0.324)
Diastolic blood pressure	0.375*** (0.122)			0.306*** (0.099)	0.187* (0.107)		-0.315 (0.233)	1.043** (0.436)	0.051 (0.321)
Body mass index	-0.124 (0.078)			-0.180* (0.096)	-0.115 (0.100)		-0.865 (0.560)	0.010 (0.133)	-0.323 (0.278)
Weight	-0.045 (0.077)			-0.161** (0.075)	0.039 (0.103)			0.058 (0.116)	-0.348 (0.383)
Waist circumference	-0.021 (0.073)			-0.126 (0.080)	-0.055 (0.096)		-0.171 (0.217)	-0.032 (0.136)	-0.322 (0.324)
HDL-cholesterol	0.052 (0.160)			-0.056 (0.256)	-0.084 (0.093)		-0.306*** (0.094)	-0.102 (0.096)	-0.349 (0.311)
LDL-cholesterol	0.219** (0.111)			0.102 (0.142)	0.258*** (0.053)		-0.398* (0.161)	0.495* (0.278)	-0.215 (0.309)
Total cholesterol	0.135 (0.100)			0.027 (0.121)	0.157** (0.069)		-0.377*** (0.145)	0.313* (0.167)	-0.144 (0.310)
Triglycerides	0.228 (0.188)			0.091 (0.184)	0.158 (0.142)		0.026 (0.217)	0.380 (0.467)	-0.153 (0.339)
Salt consumption	0.155 (0.147)			-0.001 (0.153)					
Physical activity	0.082 (0.167)			-0.084 (0.220)	0.254*** (0.078)			0.574* (0.331)	-0.407 (0.370)
Quality of life	0.288 (0.312)				0.327 (0.228)			0.580*** (0.058)	-1.061 (0.776)
Screening— cervical cancer	0.366 (0.260)					0.186*** (0.001)	-4.507*** (0.249)	1.639*** (0.371)	-0.137 (0.382)
Screening— breast cancer	0.073 (0.539)					0.305*** (0.007)	-4.423*** (0.254)	0.521 (1.350)	-0.186 (0.754)
Activities of daily living	2.696*** (0.705)				2.950*** (0.748)			2.892*** (0.739)	
Illness severity	0.337*** (0.085)						-1.388*** (0.093)	0.437*** (0.110)	
SE ²	4.010** (1.773)	3.006*** (0.634)	43.255*** (3.206)	6.811*** (2.033)	0.914 (1.833)	0.450*** (0.025)	39.573*** (1.918)	1.944 (2.268)	12.696*** (3.628)
Number of estimates	204	9	8	118	40	7	22	74	77
Number of studies	51	8	4	20	11	4	5	25	17

Notes: All models are random-effects meta-regressions, which apply weighted least squares, use a population average model and cluster standard errors at the study level, displayed in parentheses. Column (1) includes the full sample of 204 estimates. In Columns (2)–(7), we show the results separately for each intervention category, in Columns (8) and (9) we show the results separately for Thailand and Malaysia. There is no constant included in the different models, hence, the coefficients represent the mean effect per outcome.

*** $P < 0.01$, ** $P < 0.05$, * $P < 0.1$.

We are able to confirm the positive and significant effects on HbA1c, diastolic blood pressure and illness severity for the full sample, which were also identified in the standard

meta-analysis above. Furthermore, the coefficients for alcohol quantity, alcohol score, LDL-cholesterol and activities of daily living become positive and significant. Instead, the effect

on smoking abstinence, which was positive and significant in the meta-analysis, turns insignificant in our more conservative estimation.

As we instead investigate whether the effect on any single outcome is different compared to the other outcomes, we find this only to be the case for seven outcomes (see Table D1 in Supplementary Appendix D). Alcohol quantity, alcohol score and activities of daily living stand out as significantly larger than the average effect, while three anthropometric measures, (BMI, weight and waist circumference) and alcohol abstinence are significantly smaller than the average effect. When we re-do the regressions by intervention category, we find that generally the metabolic indicators, such as blood pressure, blood sugar and cholesterol levels, show changes that are significantly larger than the average effect, while the effects for weight, BMI and waist circumference are significantly smaller in all intervention categories (Tables D2-D6, Supplementary Appendix D).

When we observe the results for specific outcome types for each intervention category separately in Columns (2)–(7) in Table 3, we can confirm that studies that only focus on smoking do increase the rate of smoking abstinence (0.26, P -value 0.079). When we only include the studies related to alcohol, we find that they have negative significant effects for three of the four alcohol-related outcomes. This change in sign occurs since the correlation between the effect size and the SE^2 term within the intervention category is dramatically larger than for the pooled sample (43.255 vs 4.010). This causes large reductions in the estimated outcome coefficients since, when SE^2 is controlled for, these represent the effect if standard errors are assumed to be zero. For the studies that focus on diet and physical activity, there is a marginally larger SE^2 coefficient of 6.811, which also contributes to further reduction in the estimated coefficients. Still, these interventions show significant improvements on participants' level of HbA1c and diastolic blood pressure. Yet, the coefficients for weight and BMI turn negative. Studies that focus on patient education instead display lower levels of publication bias and we can confirm significant improvements in patients' level of fasting blood glucose, HbA1c, cholesterol, physical activity and activities of daily living. The effects on the two screening uptake measures are positive and statistically significant for the screening studies. Instead, in the model for the system approach studies, the correction for the very large correlation between the SE^2 term and the effect size (39.573) results in insignificant or even negative effects for all outcomes.

These negative effect sizes occur not because the underlying estimates (i.e. the extracted raw estimates) are negative, but because the estimated publication bias in some models, specifically for alcohol studies and system approach studies, is large enough for the effect size coefficient (representing the estimated effect for when the SE^2 term is set to zero) to turn negative. While for the given specification, the results are consistent with that the true effect is negative, we deem this implausible in our case. The regression including the full sample (Column (1), Table 3) estimates that an increase in the SE^2 of 1 inflates the estimated effect size by 4. Granted, the coefficient of the squared standard error is merely an approximation of what remains an unknown relationship between the standard error and the effect size, which, in probabilistic terms, arises in the presence of a potential publication bias. Yet, the same specifications for the alcohol and system

approach studies alone estimate that a one-unit increase in the SE^2 increases the effect size by a staggering 43 and 39 units, respectively. It seems unlikely that the problem of small studies or publication bias should be 10 times as large as that of other studies included in this review and more likely that the relationship between SE^2 and the degree of inflated effect sizes is simply overestimated in these two specifications. Comparing SE^2 estimates presented in other meta-regression studies further confirms that the specifications in Columns (3) and (7) likely overestimate the extent of small-study effects (e.g. Neves and Sequeira, 2018; de Linde Leonard and Stanley, 2020, present SE^2 estimates of 5.25 and 4.18, respectively). To further illustrate that the strongly negative estimates in Columns (3) and (7) are due to the high SE^2 coefficients in these specifications, we run the same regression as in Column (1) of Table 3 while including interaction terms between each outcome and a dummy that equals 1 if the estimate is from an intervention in the alcohol category and interaction terms between each outcome and a dummy for system approach studies. None of the estimates of the two categories remains significantly negative; instead all but one estimate (BMI estimated for system approach studies) switch to a positive sign (results available upon request). For these reasons, we deem the results insufficient to interpret the sign of single outcomes in the one or other direction whenever the coefficient of the SE^2 term is extremely high (i.e. in the categories alcohol and system approach).

Column (8) confirms the overall large and positive effect for studies conducted in Thailand, with large and positive effects for alcohol outcomes, several metabolic indicators, quality of life, cervical cancer screening and illness severity. The results for the Malaysian studies, shown in Column (9), reveal that also the disaggregation by outcomes does not alter the overall insignificant effect, yet again, it is the metabolic indicators that outperform other health outcomes.

Moderator analysis

In a final step, we perform a moderator analysis to gauge the potential influence of a series of different factors: 'contact moments' measures the number of contacts between study participants and study officials (excluding measurement take-up); 'share of males' measures the share of study participants that were male; 'mean age' measures the average age of all study participants; the dummy 'group' indicates whether participants were treated as a group as opposed to individually; and 'length' measures the time period from the start of the intervention until the follow-up in months.¹² Table 4 presents this analysis for the pooled sample and by intervention category and country. In the full sample, the number of contact moments has a small positive influence (0.027, P -value: 0.056) on the average effect size. The number of contacts also turns out to play a major role in three of the intervention categories. In diet and physical activity, screening and system approach studies, one more contact moment between the study officials and participants increases the effect by 0.04 (P -value: 0.000), 0.15 (P -value: 0.004) and 1.3 (P -value: 0.000), respectively. The number of contacts also moderates the effect size when assessing it separately for Thai and Malaysian studies. This suggests that increased interaction with patients or individuals at risk and repeated stimulation can help to maximize an intervention effect.

Table 4. Meta-regression results—moderator analysis

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
	Full sample	Smoking	Alcohol	Diet and physical activity	Patient education	Screening	System approach	Thailand	Malaysia
Moderator									
<i>Study design</i>									
Contact moments	0.027* (0.014)	0.012 (0.018)	-0.179 (0.184)	0.040*** (0.011)	-0.002 (0.048)	0.153*** (0.053)	1.310*** (0.004)	0.036** (0.026)	0.055** (0.018)
Length	0.001 (0.008)	0.003 (0.885)	-0.295*** (0.000)	-0.008** (0.011)	0.100* (0.058)	0.018** (0.022)	-0.008 (0.580)	0.016* (0.063)	0.035** (0.036)
Group	-0.171 (0.113)	0.023 (0.189)		0.013 (0.150)	-0.622* (0.336)	0.171** (0.078)		-0.125 (0.546)	0.007 (0.959)
<i>Participants' characteristics</i>									
Share of males	0.121 (0.164)	0.163 (0.605)	-2.650 (3.945)	-0.040 (0.132)	-0.483 (0.815)		-1.197 (2.034)	0.159 (0.558)	0.080 (0.785)
Mean age	0.005 (0.004)	0.011* (0.006)	-0.027 (0.041)	0.003 (0.003)	0.000 (0.045)	-0.009*** (0.003)	-0.007 (0.048)	0.006 (0.297)	0.023*** (0.000)

Notes: All models are random-effects meta-regressions, which apply weighted least squares and use a population average model and cluster standard errors at the study level, displayed in parentheses. Each coefficient is derived from a single regression in which only the respective moderator is included. Missing coefficients occur when the moderator could not be defined for a given intervention category.

*** $P < 0.01$, ** $P < 0.05$, * $P < 0.1$.

This seems plausible, assuming that with each contact moment, the participants are again encouraged or reminded to take actions to improve their health. The finding is also in line with the results from earlier meta-analyses and studies assessing the impact of interventions intended to address nutrition and physical activity (Anderson *et al.*, 2009; Greaves *et al.*, 2011).

Neither for the pooled sample nor for any intervention category, we find an effect associated with the share of males among the participants, which also aligns well with the broader literature (see, e.g. Murray *et al.*, 2017, on interventions focusing on physical activity or Gallet and Doucouliagos, 2017, on healthcare spending).

The coefficients for the mean age moderator reveal that smoking studies with on average older participants achieve larger effect sizes (0.011, P -value: 0.054) all else equal, while screening studies with on average older participants find smaller effect sizes (-0.009, P -value: 0.007). The Malaysian studies support the results from the smoking studies. These age differences highlight the need for interventions to clearly specify the targeted age group and adjust the intervention design accordingly.

We also find evidence for an increase in the effect size for screening interventions targeted at groups (0.17, P -value: 0.028). This suggests that community- or group-based approaches can effectively increase screening rates, which is favourable, given that several Southeast Asian countries focus on community-based approaches for NCD prevention.

Finally, the evidence for whether the effect size depends on the time length between start and follow-up is mixed. The moderator seems to negatively affect the outcomes in alcohol and diet and physical activity studies, while it increases the effect size in patient education and system approach studies as well as when the effect is assessed by country. The former is well in line with the observation that behavioural changes that come with a trade-off between short-term cost (e.g. cutting back in alcohol and unhealthy food consumption) but only long-term health benefits are often not long sustained (Murray *et al.*, 2017; Hunter *et al.*, 2018). On the other hand, interventions focusing on patients that are already diagnosed with

an NCD seem to be more sustainable over time, and screening interventions with a longer time horizon might allow for more individuals taking the opportunity to get screened.

Discussion and implications

Discussion

The objective of this review and the meta-analysis is to give an all-encompassing picture of the effectiveness of NCD prevention and control interventions in the Southeast Asian context. We identify an overall effect and also give a nuanced picture of differences in the effectiveness across various intervention categories and across many different health outcomes that these interventions target. We found 51 studies that assess credibly the effect of NCD-related interventions, ranging from studies that focus on the four common risk factors (smoking, alcohol, physical inactivity and unhealthy diet) to studies evaluating the impact of interventions on health and behavioural outcomes for patients with diabetes, CVDs or cancer. The 51 included studies cover only five Southeast Asian countries, with the major share of studies being conducted in Thailand and Malaysia. This geographical restriction is a critical limitation in our aim to derive policy recommendations for the entire region and we therefore consider the results presented in this review as a base on which future research on this region can build.

With a meta-analysis using the entire sample of 204 estimates stemming from 51 studies, we find that the overall effect size is positive and significant, i.e. the interventions do on average improve the prevention and treatment of NCDs. Yet, as expected the effectiveness varies substantially across different intervention categories, but the effect remains positive and significant for each of them.

As discussed, the results from the meta-analysis are subject to several potential biases, which we address with statistically more sophisticated meta-regressions. These regressions account for problems related to publication bias and small-sample effects, correlations among estimates pertaining to the same study and differences in the number of estimates included from each single study. For the pooled regression,

the overall effect size drops markedly (from 0.37 to 0.27). Additionally, the results differ substantially as we compare the meta-regression results performed for each intervention category separately. Only interventions pertaining to the screening and patient education categories remain positive and significant. The effect sizes in the smoking and alcohol studies are somewhat reduced in size and significance, and the effect sizes for the studies in the diet and physical activity and system approach categories are close to zero.

Our relatively large sample of estimates also allows investigating the impact on single outcomes. We find significant positive effect sizes among a few outcomes in the full sample as well as within categories. Outstanding in this aspect are metabolic indicators, including fasting blood glucose, HbA1c and blood pressure, which result in consistently positive effects across interventions. For the majority of the outcomes, however, the estimates are insignificant. Yet, it does not allow us to conclude that all other outcomes have been left unaffected by the interventions since many of the coefficients are based on only a handful of estimates (10 of the 23 outcome coefficients are represented by 5 or fewer estimates), which substantially limits the power to detect even moderate effect sizes.

Yet, we identify three outcomes that appear especially hard to improve: BMI, weight and waist circumference. The effects on these three outcomes are close to zero or negative in several cases. While we mentioned above that we are careful to interpret negative effects from the meta-regressions as clear evidence that these interventions have adverse effects if the SE^2 coefficient is extraordinarily large, we want to highlight here a different, actual adverse interpretation, as the SE^2 coefficient for this intervention type remains small in Column (4) of Table 3. Moreover, several of the underlying estimates in the diet and physical activity studies (i.e. the raw estimates extracted from the studies) are in fact negative, indicating that study participants rather gained than lost weight. Also, the investigation of the relative effects (i.e. the effect of one outcome in comparison to the mean of all other outcomes shown in Appendix D) consistently shows that these three outcomes are significantly smaller and result in an absolute effect that is close to zero. This is quite alarming given the increasing rates of people suffering from overweight and obesity in the Southeast Asian region (Angkurawaranon *et al.*, 2014; Chan *et al.*, 2017; Rachmi *et al.*, 2017).

In the moderator analysis, we identified specific design features of interventions that play a significant role in explaining why some of the interventions seem to be more effective than others. Especially the number of contact moments the study participants have with the implementing authorities strongly relates to the intervention effectiveness. Also, the age of the targeted participants, whether the intervention is implemented in a group design, and the length of the follow-up moderate the effect size. These findings should be considered by policymakers aiming to design a highly effective NCD intervention.

Implications for interventions and future research

While our results show that some of the considered interventions are effective and may successively be integrated into the region's national action plans against NCDs, other interventions lead to no effects or ambiguous effects, leaving substantial gaps that require further research.

The results for smoking interventions are mainly positive and suggest that counselling and financial interventions are a promising measure to decrease the extraordinarily high smoking rates in Southeast Asia. Yet, controlling for potential biases reduces the size and significance of the effect which questions its robustness and calls for further in-depth studies. It is also of concern that only one single study on smoking was conducted in Indonesia, given that the country has the highest smoking prevalence rate among men in the entire Southeast Asian region and that the country has not yet ratified the WHO Framework Convention on Tobacco Control (WHO, 2019). More studies on how to reduce tobacco consumption in Indonesia are needed.

The average effect size for interventions that address alcohol consumption is the largest among our six retained intervention categories. Also, in our more conservative meta-regression the effect remains sizeable. Yet, the total number of studies focusing on alcohol is marginal and this restriction in data availability limits an in-depth analysis for specific outcomes and prevents us from declaring this evidence as sound. Furthermore, all included studies in this category have been implemented in a single country (Thailand) which, similar to the evidence on tobacco consumption, also speaks for a need for further research in other countries in the Southeast Asian region.

Moreover, we identify only a modest average effect size for diet and physical activity interventions, which even turns insignificant in our more conservative analysis. Investigating separate outcomes shows positive effects only for HbA1c and diastolic blood pressure, while no positive effect can be confirmed for any of the remaining 11 outcomes, including measures of dietary intake and physical activity. Especially hard to improve are weight-related outcomes, such as weight, BMI and waist circumference. The gloomy results from these studies do not look much brighter as we consider the findings outside the Southeast Asian region: in a literature survey of studies promoting physical activity, Murray *et al.* (2017) conclude that such interventions often result in no more than short-term changes in behavioural outcomes that quickly abate over time.

We can confirm a significant impact on the aggregated level for patient education interventions that typically provide education to NCD patients. Also, the outcome-specific analysis shows the results of patients making lifestyle changes towards more physical activity and also shows progression in patients' activities of daily living score as well as improvements in a range of metabolic indicators such as blood lipids and blood cholesterol levels. Hence, it is safe to conclude that the patient education interventions do have a meaningful positive impact on the health of NCD patients and that this type of interventions should be considered by policymakers in Southeast Asia.

For the studies aimed at increasing the rates of cancer screening uptake among women, we detect a significant positive effect size of around 0.18 in all models. The effect size is somewhat larger for breast cancer screening compared to cervical cancer screening, which could be an indication of women being generally unwilling to undergo the intimate process of performing a pap smear test (Knops-Dullens *et al.*, 2007) and feel more confident to individually perform breast cancer screening via self-examination at home.

System approach studies, focusing on internal processes in health facilities, report a large set of outcomes, which, in the standard meta-analysis if taken all together, give rise to a sizeable effect size of 0.87. Yet, when we address the potential publication bias, this effect fully vanishes. While we can only speculate about the concrete explanations, one possible obstacle in achieving results with a structural approach could be the insufficiency of financial and human resources in health facilities and in sectors concerned with NCDs more specifically that must accompany such reforms. The urgent need for a mobilization of NCD-specific health services is also stressed by [Dans et al. \(2011\)](#) who review the rise of NCDs in Southeast Asia.

Our meta-analysis highlights not only the need for more rigorous evaluation designs and larger samples to determine the effectiveness of the various types of interventions considered in our review but also a general lack of studies that adequately represent all countries, dimensions and contexts relevant to the prevention and control of NCDs in Southeast Asia. First, Thailand and Malaysia serve as the implementing countries for 42 of the in total 51 studies while relatively few studies have been conducted in the remaining low- and middle-income countries in the region. While we aimed to provide a comprehensive analysis and to derive reliable policy recommendations for the entire Southeast Asian region, this geographical restriction is a great limitation. Second, we identified no study targeting patients with chronic respiratory diseases. This is reason for concern, given that the number of life years lost due to chronic respiratory disease is the highest worldwide in the Southeast Asian region, driven by extraordinarily high smoking rates ([Soriano et al., 2020](#)). Third, and related to the former, the number of studies concerned with smoking cessation and alcohol consumption was surprisingly low and such studies should be conducted more frequently in the near future.

Conclusion

NCDs are rapidly gaining importance throughout Southeast Asia, calling for an effective policy response to adequately address and manage the problem. To provide policymakers with the relevant evidence, we reviewed the literature on NCD-related health interventions considering in total more than 20 different health outcomes. To conclude, our findings show that these interventions are on average effective but result generally only in small improvements. Additionally, we highlight a large heterogeneity with respect to effects for different outcomes and intervention categories. We also show that this literature suffers from substantial publication bias and is based to a large extent on underpowered studies. To address the challenge of NCDs in the Southeast Asia in the decades to come much more large-scale and rigorous evidence on what works is needed in this context.

Supplementary data

[Supplementary data](#) are available at *Health Policy and Planning* online.

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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Ethical approval. This is a systematic review of the peer-reviewed published literature; therefore ethical approval for the data used in this article was not required.

Conflict of interest statement. The authors declare no conflicts of interest.

Notes

1. An equally steep increase was seen in the WHO Western Pacific region. The numbers are based on the WHO classification of the Southeast Asian and Western Pacific Region.
2. See, e.g. [Cobiac et al., 2010](#); [Li et al., 2010](#); [Pennant et al., 2010](#); [Adler et al., 2014](#); [Dunkley et al., 2014](#); [Graudal et al., 2014](#); [Baker et al., 2015](#); [Long et al., 2015](#); [Hartley et al., 2016](#); [Gaziano et al., 2017](#).
3. We follow the 'Preferred Reporting Items for Systematic review and Meta-Analysis Protocols' (PRISMA). The study protocol was not pre-registered, yet the authors declare that the study protocol has not been adjusted since the initiation of the study implementation and no further analyses have been conducted in addition to the ones mentioned in this paper.
4. Singapore stands out as the single high-income country in the region, while remaining countries are classified as lower and upper middle-income countries with a GNI per capita between USD 1026 and USD 12 375 ([World Bank, 2020](#)). We use the geographical classification of Southeast Asia, which includes the 10 ASEAN countries and Timor-Leste, which are all located in either of the two WHO regions of Southeast Asia and Western Pacific.
5. We excluded studies that simply test the effectiveness of a drug on medical outcomes, e.g. the effect of anti-hypertensives, as we focus our analysis on interventions that are primarily dependent on behavioural responses and thus likely sensitive to geographic-specific factors such as customs and culture.
6. The difference in odd ratios (e.g. used in [Parekh et al., 2012](#)) corresponds to the double difference for continuous outcomes. Note that by computing the 'exponent of the difference in log ORs', the resulting OR, OR_{corr} , takes the same value as the follow-up OR whenever there is precisely no difference between treatment and control at the baseline.
7. This bias is only present in the subgroup analyses by intervention category, as we here include more than one outcome per study per subgroup. In the analyses by outcome type, we include never more than one outcome estimate per study within one subgroup.

8. PEESE stands for precision-effect estimate with standard error. Including the squared term instead of the linear term has been shown to be appropriate whenever the funnel asymmetry and precision estimate test suggests that a genuine effect is present, indicated as a significant intercept in Egger's regression test. As this is true for our data (see the 'Publication bias and statistical power' section), we estimate effect sizes with the inclusion of the squared term. However, we re-run all of the regressions with the linear term for comparison. As expected, the effect sizes are on average smaller and occasionally lose significance. The results are available on request.
9. The reference list of included studies is provided jointly with the detailed study description in Supplementary Appendix B.
10. One study, Pengpid *et al.* (2015), is sorted into two intervention categories, because it focusses on both smoking cessation and alcohol consumption. Therefore, the sum of studies within categories adds up to 52.
11. A separate meta-analysis with only the sufficiently powered estimates can be found in Figure C1 in the Supplementary Appendix C. The results of this sub-meta-analysis are close to the results from the meta-regression, indicating that the PEESE method used in the meta-regression performed well in correcting the effect sizes. We thank an anonymous reviewer for proposing to include this additional subanalysis.
12. Additional summary statistics and details on the definition of the moderators can be found in Supplementary Appendix E. It would have been interesting to investigate the 'length of the intervention' as another possible moderator but this information was not available in enough studies to allow for a meaningful analysis.

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