

**MEDIATION EFFECT OF NEUTROPHIL
LYMPHOCYTE RATIO ON CARDIOMETABOLIC
RISK FACTORS AND CARDIOVASCULAR EVENTS**

TEERANAN ANGKANANARD, MD, PhD.

***Division of cardiovascular medicine,
Faculty of Medicine, Srinakharinwirot University***



Mahidol University

Faculty of Medicine Ramathibodi Hospital

Section for Clinical Epidemiology and Biostatistics

MEDIATION EFFECT OF NEUTROPHIL LYMPHOCYTE RATIO ON CARDIOMETABOLIC RISK FACTORS AND CARDIOVASCULAR EVENTS

A PhD Dissertation Defense

Doctor of Philosophy Program in Clinical
Epidemiology

(International Program)

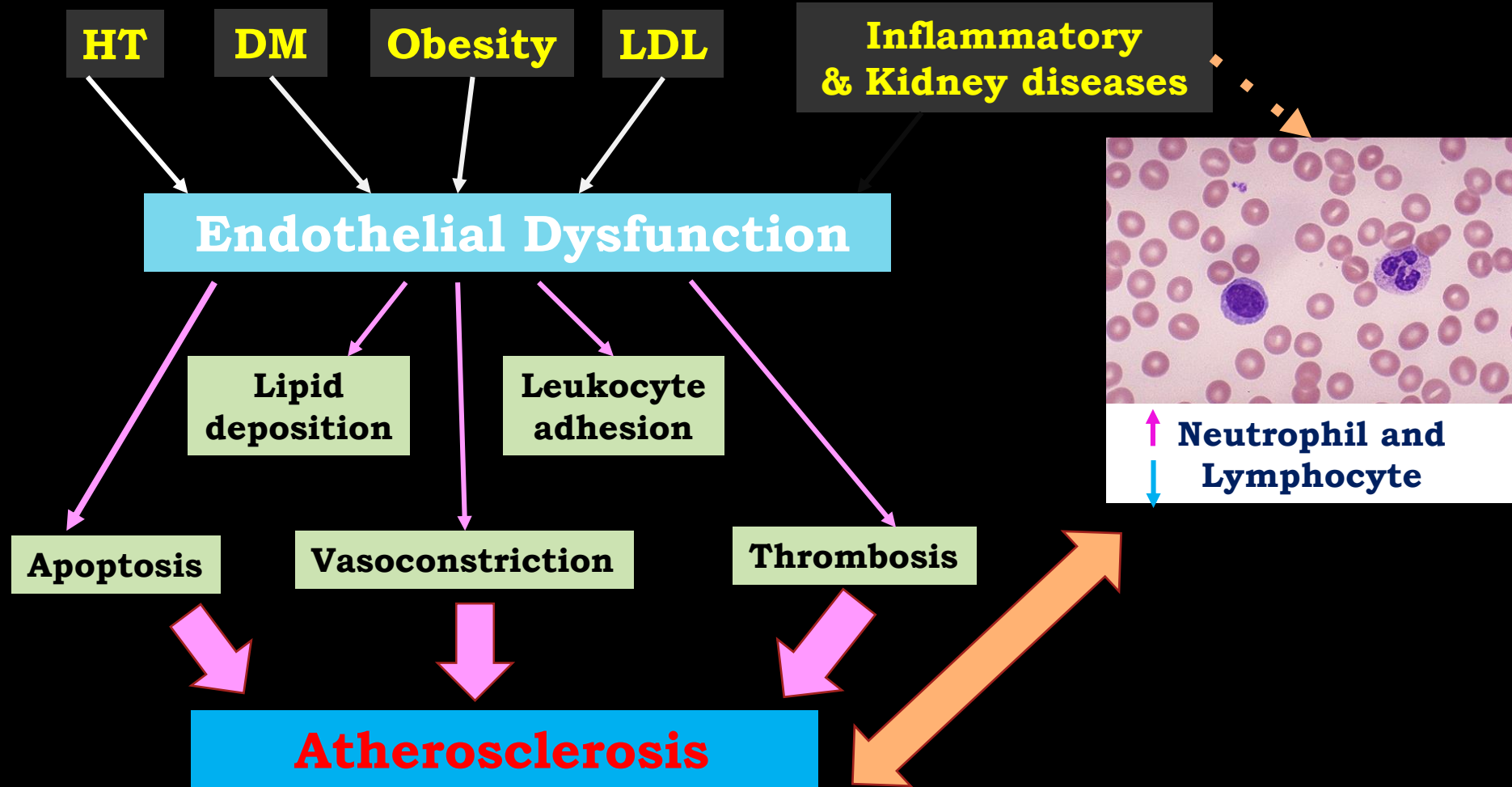
By

TEERANAN ANGKANANARD, MD

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19 December, 2017

BACKGROUND & RATIONALE



CAD, ACS, CVA, PAD, CVEs

Review Article

Neutrophil Lymphocyte Ratio and Cardiovascular Disease Risk: A Systematic Review and Meta-Analysis

**Teeranan Angkananard,^{1,2} Thunyarat Anothaisintawee ,³ Mark McEvoy,⁴
John Attia ,⁴ and Ammarin Thakkinstian ¹**

¹*Section for Clinical Epidemiology and Biostatistics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand*

²*Division of Cardiovascular Medicine, Department of Medicine, Faculty of Medicine, HRH Princess Maha Chakri Sirindhorn Medical Center, Srinakharinwirot University, Nakhon Nayok, Thailand*

³*Department of Family Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand*

⁴*Center for Clinical Epidemiology and Biostatistics, The School of Medicine and Public Health, The University of Newcastle, Newcastle, NSW, Australia*

Correspondence should be addressed to Thunyarat Anothaisintawee; thunyarat.ano@mahidol.ac.th

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“Neutrophil Lymphocyte Ratio and Cardiovascular Disease Risk: A Systematic Review and Meta-Analysis”

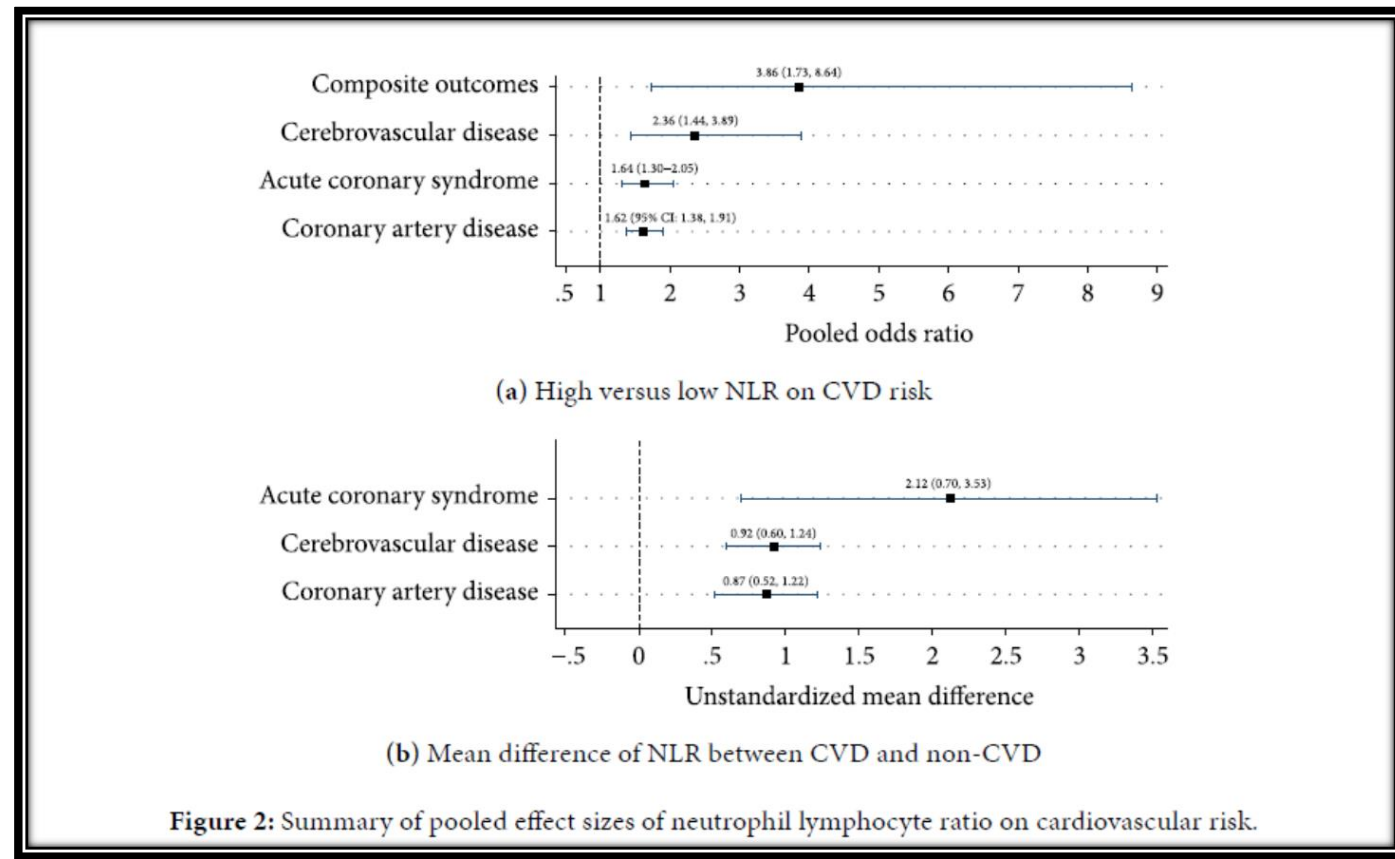
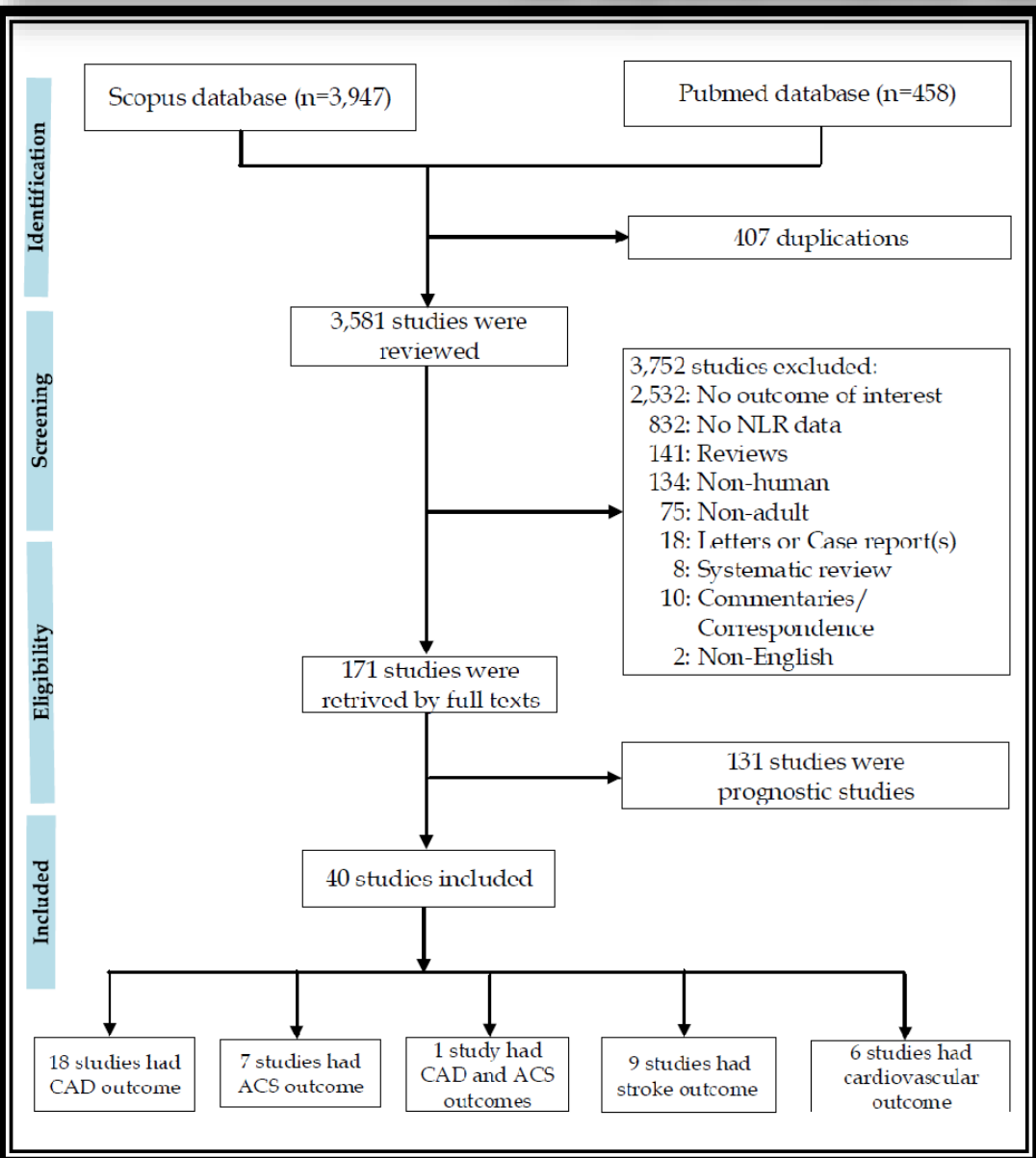
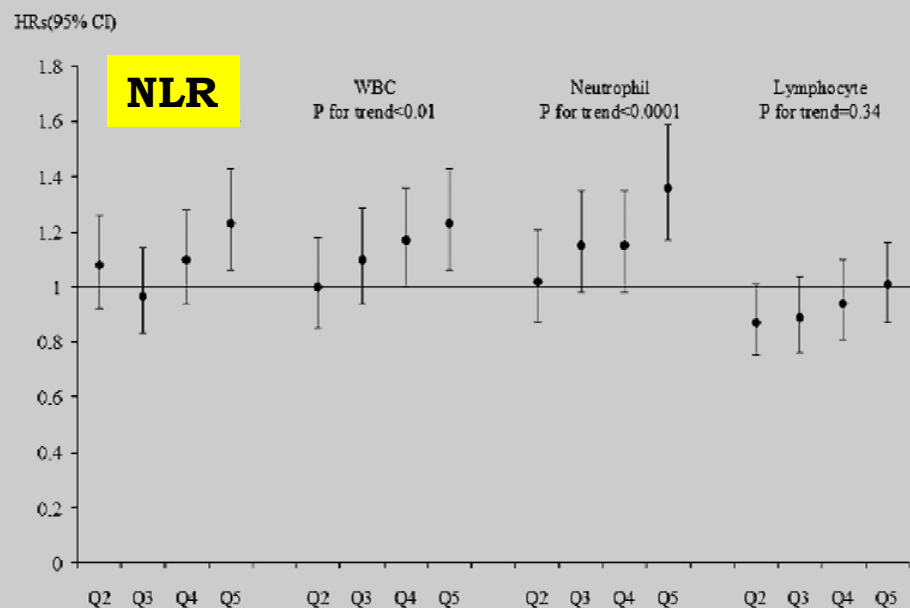


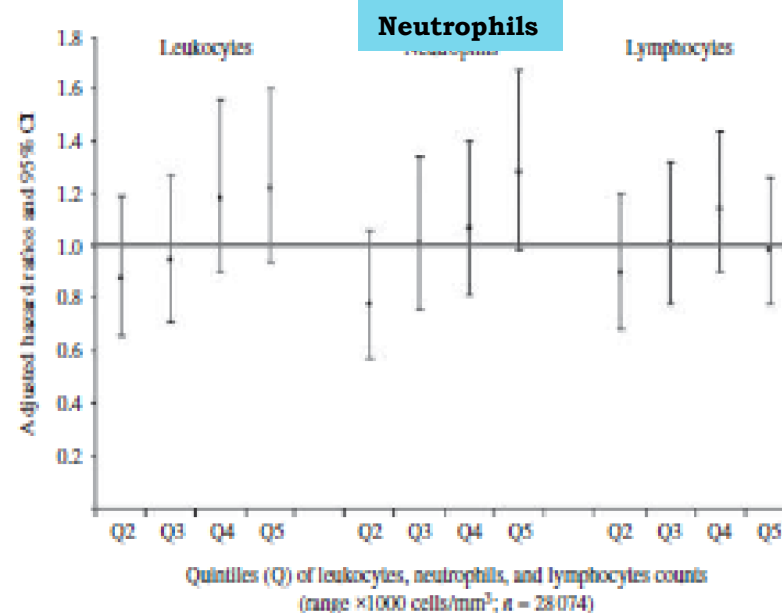
Figure 2: Summary of pooled effect sizes of neutrophil lymphocyte ratio on cardiovascular risk.

BACKGROUND & RATIONALE

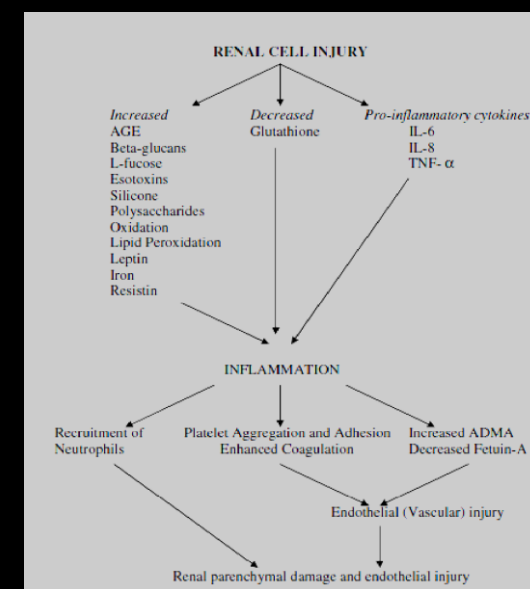
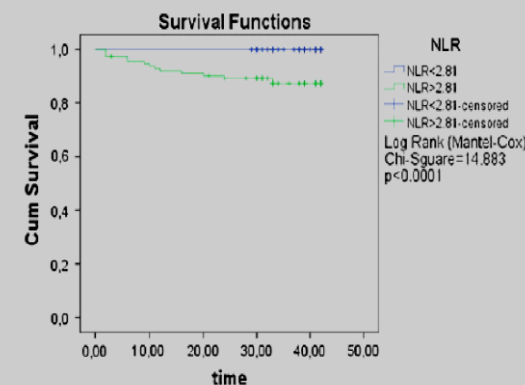
NLR vs. Hypertension



NLR vs. Diabetes



NLR VS. CKD



Blood Neutrophil to Lymphocyte Ratio as a Predictor of Hypertension. American journal of hypertension. 2015;28(11):1339-46.

Neutrophil:lymphocyte ratio is positively related to type 2 diabetes in a large-scale adult population: a Tianjin Chronic Low-Grade Systemic Inflammation and Health cohort study. European journal of endocrinology. 2015;173(2):217-25.

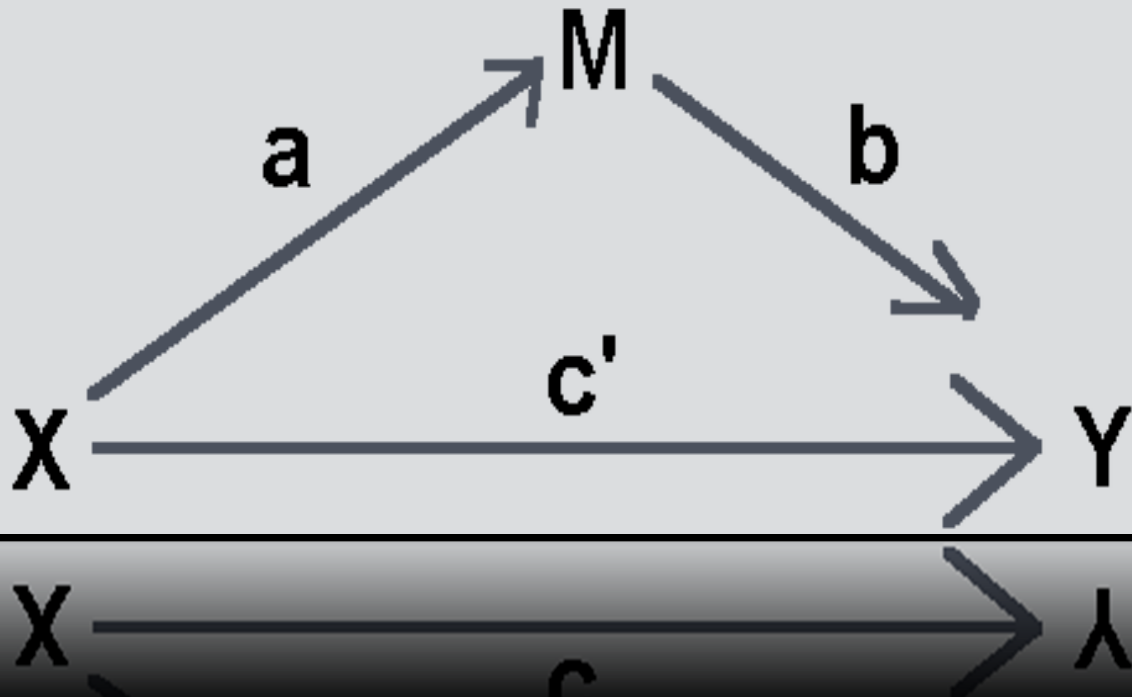
RESEARCH QUESTIONS

1. Is neutrophil lymphocyte ratio (NLR) level associated with incidence of future cardiovascular events (CVEs)?
2. Does NLR level directly associate with CVEs or it indirectly associate via diabetes?
3. Does NLR level directly associate with CVEs or it indirectly associate via HT?
4. Does NLR level directly associate with CVEs or it indirectly associate via creatinine?



*Causal Model:
Mediation Analysis*

Mediation Analysis



★ **Mediator (M)** is a variable that is in a causal sequence and explains the relationship between two variables (X and Y).

★ **Moderator or Interaction:** is one that influences or may also modify the strength of a relationship between two other variables

- Represents the consideration of how a third variable (M) affects the relation between two other variables (X and Y).
- Clarifying the assumptions needed for a causal interpretation of direct and indirect effect estimates.
- Become a very popular approach in psychology, social science and business research

Hypotheses for Mediation Analysis (Rungtusanatham et al., 2014)

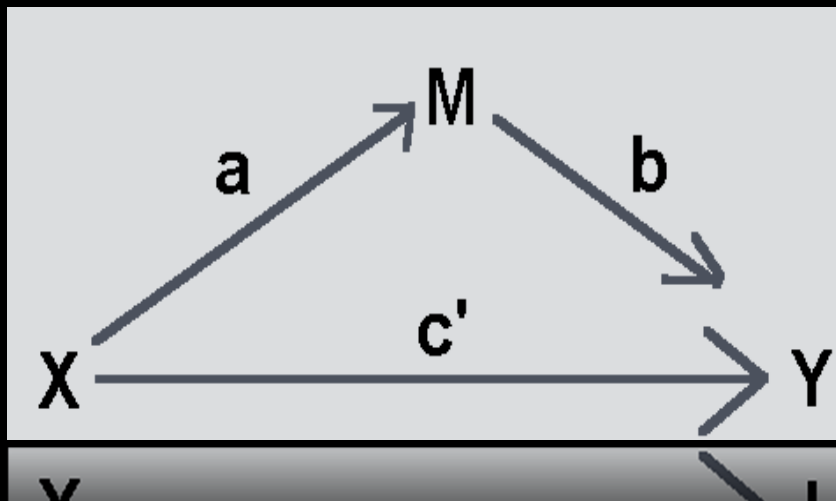
Segmentation Approach

- H1 : The effect of X on M*
- H2 : The effect of M on Y*
- H3 : Mediation effect*

Transmittal Approach

Mediation effect

- Example 1: M mediates the relationship between X and Y
- Example 2: X has an indirect effect on Y through M



MEDIATION ANALYSIS

- A causal model analysis
- Originally proposed by Baron and Kenny and MacKinnon and colleagues
- On the basis of the linear regression for continuous mediators and outcome with only single measurement.

$$Y = \theta_1 + cX + Z_1 \quad (1)$$

$$Y = \theta_2 + c'X + \beta M + Z_2 \quad (2) \text{ Outcome model}$$

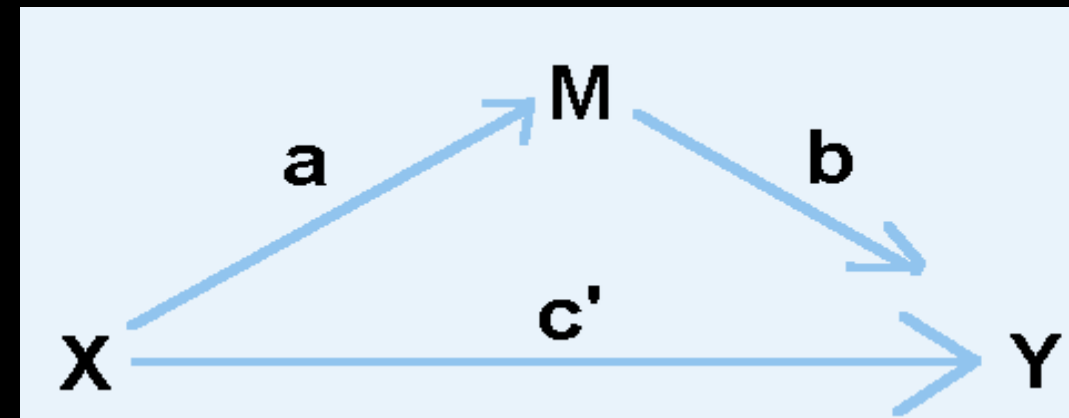
$$M = \theta_3 + \alpha X + Z_3 \quad (3) \text{ Mediator model}$$

- X : a predictor or independent variable (NLR),
- M : a potential mediator (DM, HT, Cr),
- Y : an outcome (CVEs), and
- Z : a set of baseline confounders

Effect of X and Y without considering mediation.



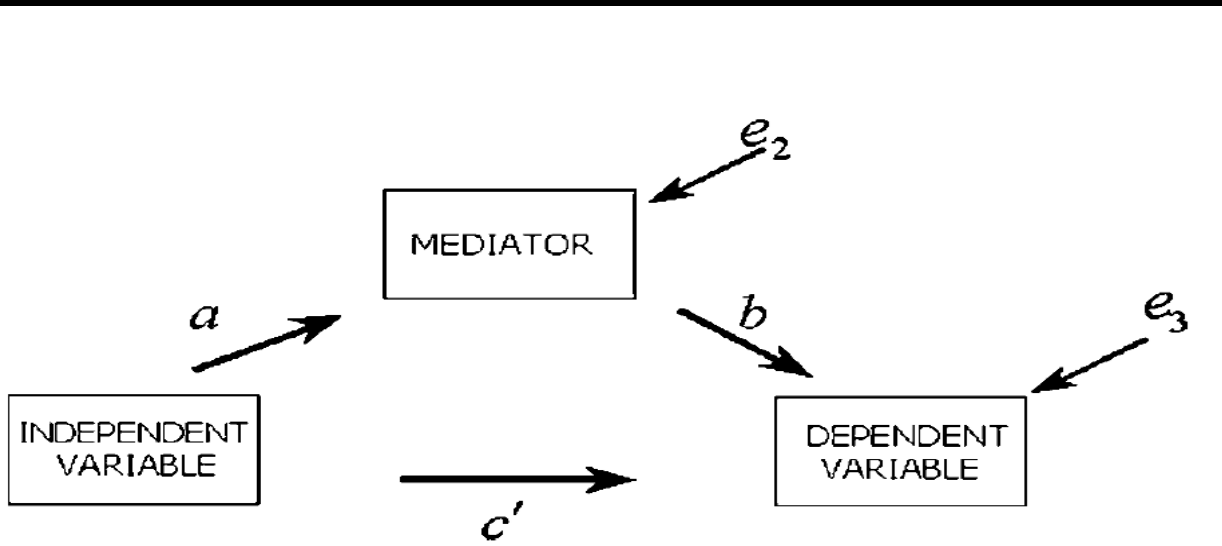
C = Total



- Path c' : **direct effect**.
- Path ab : **indirect effect**
- Total effect (C) = direct effect (c') + indirect effect (ab)
- Difference or the product-of-coefficients method

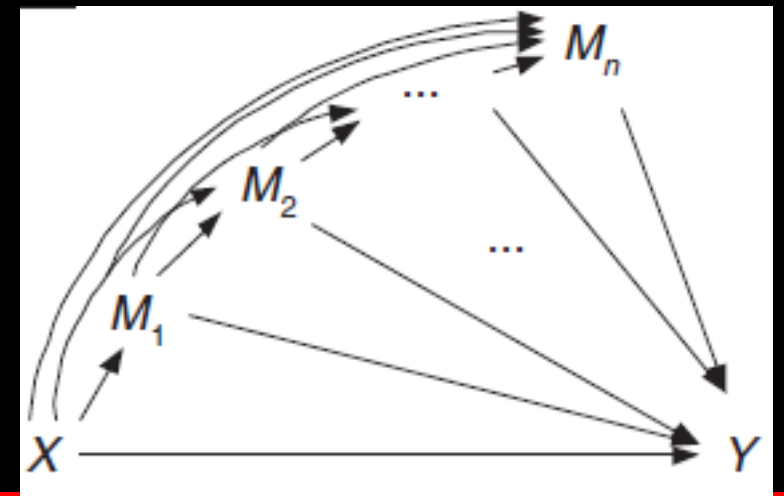
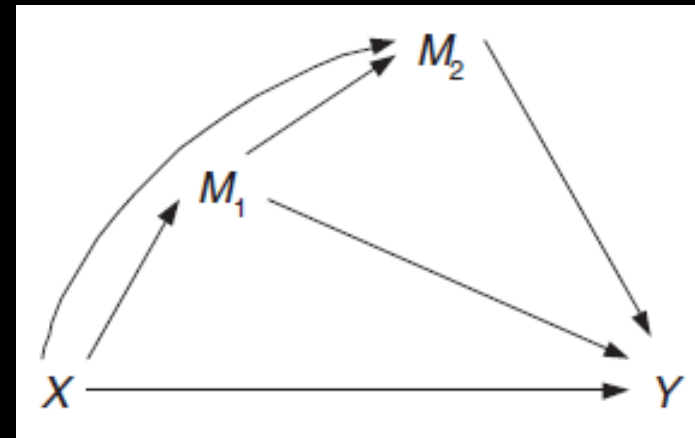
MEDIATION ANALYSIS

Single-mediator model

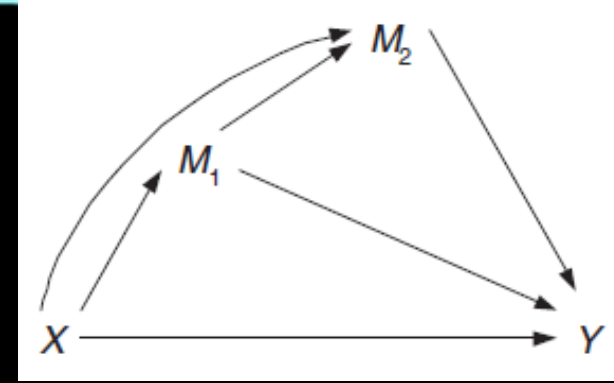


e_2 and e_3 : residuals in the M and Y variables

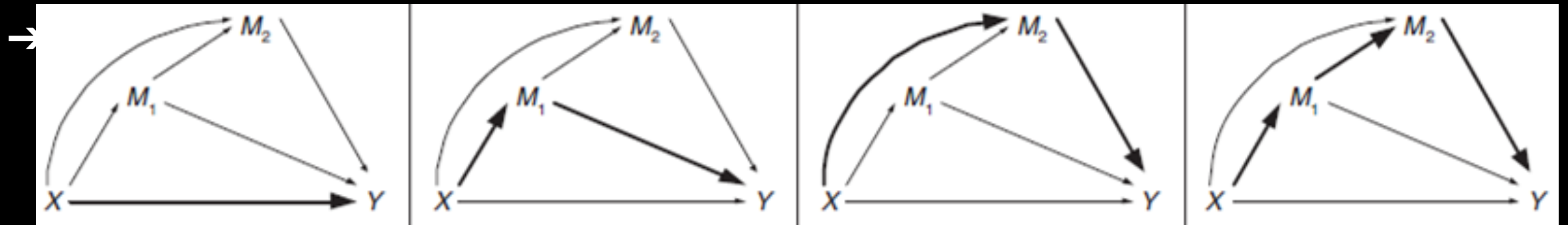
Multiple Mediators model



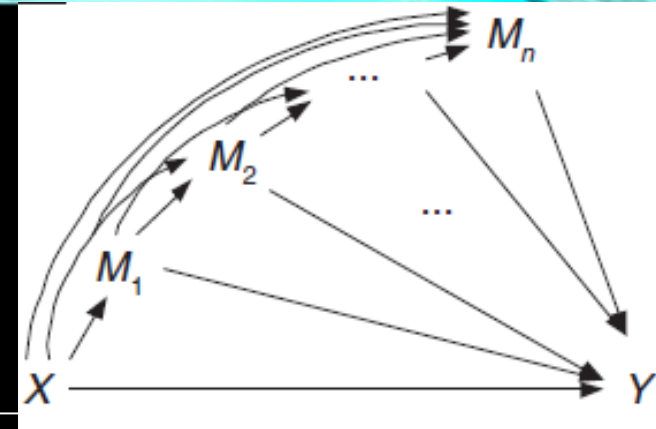
Multiple Mediation Analysis



- The concepts proposed by Vansteelandt and VanderWeele.
- Each potential mediator must be statistically significantly associated with both exposure in a mediation model and the outcome in the outcome model after controlling for the other confounders.
- Two Causally Ordered Mediators



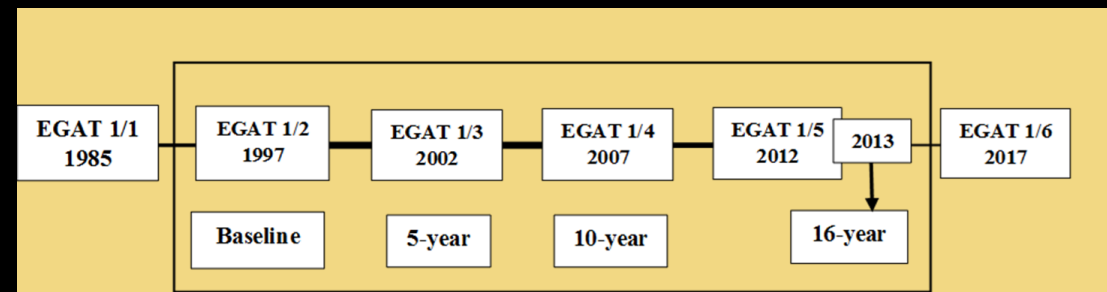
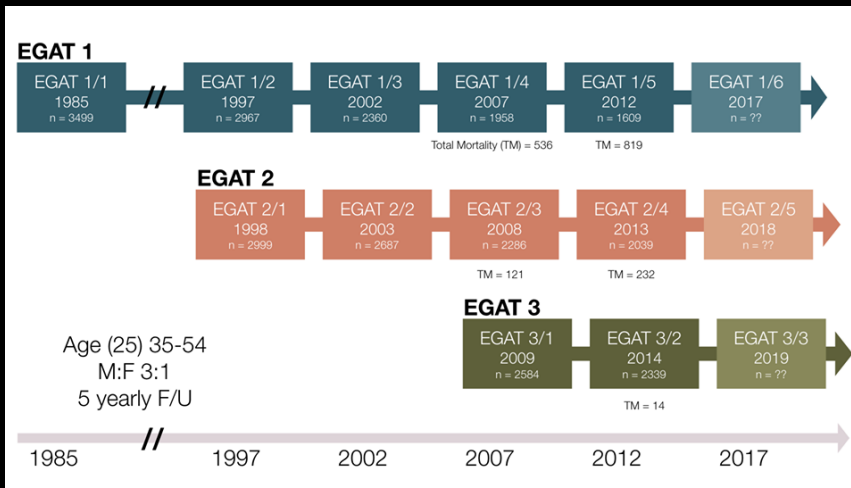
MEDIATION ANALYSIS WITH MULTIPLE MEDIATORS



- Mediators: Diabetes (M_1), well-controlled HT (M_2), poor-controlled HT (M_3) and creatinine (M_4)
- The relationship between HT and serum Cr can be bidirectional.
 - A) NLR \rightarrow $M_1 \rightarrow M_4 \rightarrow$ **M_2 or M_3** \rightarrow CVEs
 - B) NLR \rightarrow $M_1 \rightarrow M_2$ or $M_3 \rightarrow$ **M_4** \rightarrow CVEs
- Parallel and Serial multiple mediation models (SMMM)

METHODOLOGY

Electricity Generating Authority of Thailand (EGAT)



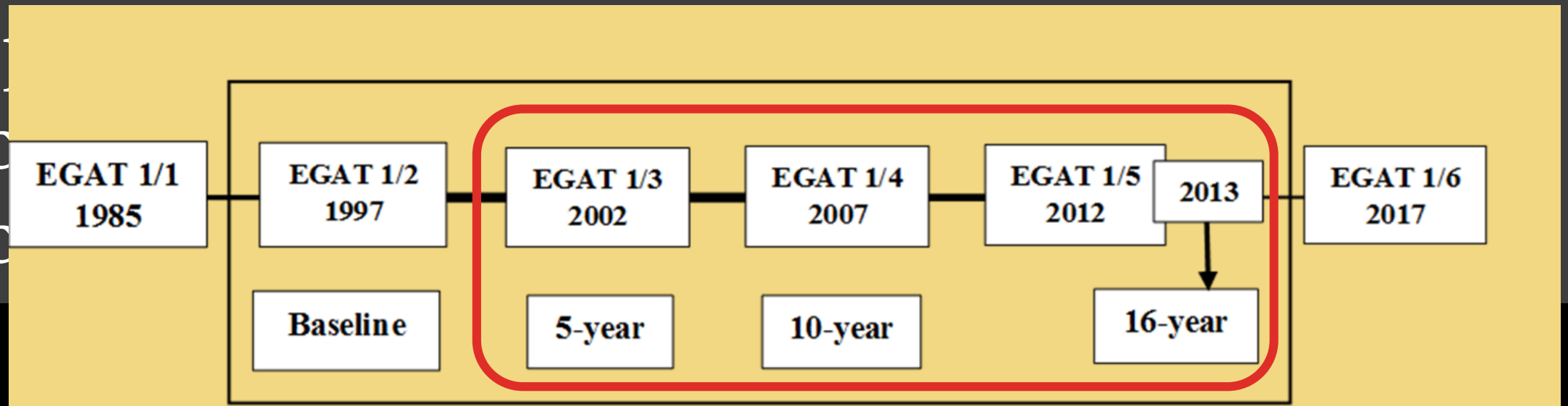
METHODOLOGY

Inclusion Criteria

- Had CBC data, including number of neutrophils and lymphocytes.

Exclusion Criteria

- CVD
- Partic
- Partic



IMPUTATION OF MISSING DATA

- Multiple imputation by chained equations (MICE)

“Missing at Random”

- **Regular variables:**

- Age, gender, family history of DM, HT and DLP, composite of CVEs and history of taking NSAIDs

- Further statistical analysis were performed on mi imputed dataset and ***“mi estimate”*** prefix Stata command was used for every statistical analysis

Post Imputation Management

Imputed variables

Weight & Height
Waist & Hip

SBP and DBP

TC, TG, HDL, LDL,
Lipid medication

Fasting Plasma Glucose

Neutrophils & Lymphocytes

Missing categorical variables

BMI and WHR

Hypertension

Dyslipidemia

Diabetes

NLR



METHODOLOGY

**Studied
factor
NLR**

**Neutrophil Lymphocyte Ratio(NLR)
= Neutrophils/Lymphocytes count or %**

Available CBC : EGAT 1/3 (2002)

Mediators: DM, HT, Cr

Co-variables:

Age, Gender, Education, Income, Physical activity, Smoking and Alcohol consumption, history of taking NSAIDs, BMI, WHR, Dyslipidemia, Anemia, Platelet count, serum uric level.

**Outcome: CVEs
MI, PTCA/CABG,
TIA/Ischemic
Stroke
CV Death**

DATA ANALYSIS

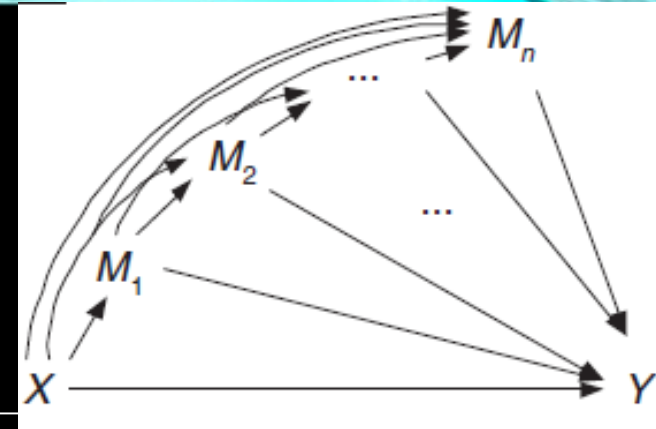
Continuous data: Mean(SD) or Median(IQR)

Categorical data: Frequency (%)

Incidence rate of CVEs

Multiple Mediation analysis

MEDIATION ANALYSIS WITH MULTIPLE MEDIATORS

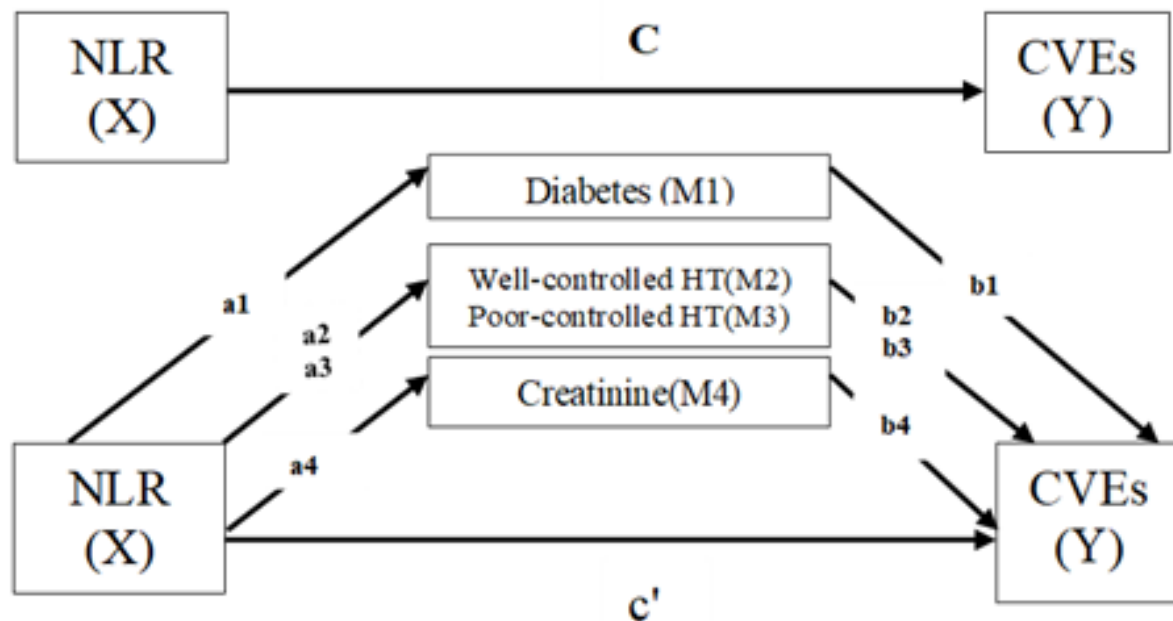


- Mediators: Diabetes (M_1), well-controlled HT (M_2), poor-controlled HT (M_3) and creatinine (M_4)
- The relationship between HT and serum Cr can be bidirectional.
 - A) NLR \rightarrow $M_1 \rightarrow M_4 \rightarrow$ **M_2 or M_3** \rightarrow CVEs
 - B) NLR \rightarrow $M_1 \rightarrow M_2$ or $M_3 \rightarrow$ **M_4** \rightarrow CVEs
- Parallel and Serial multiple mediation models (SMMM)

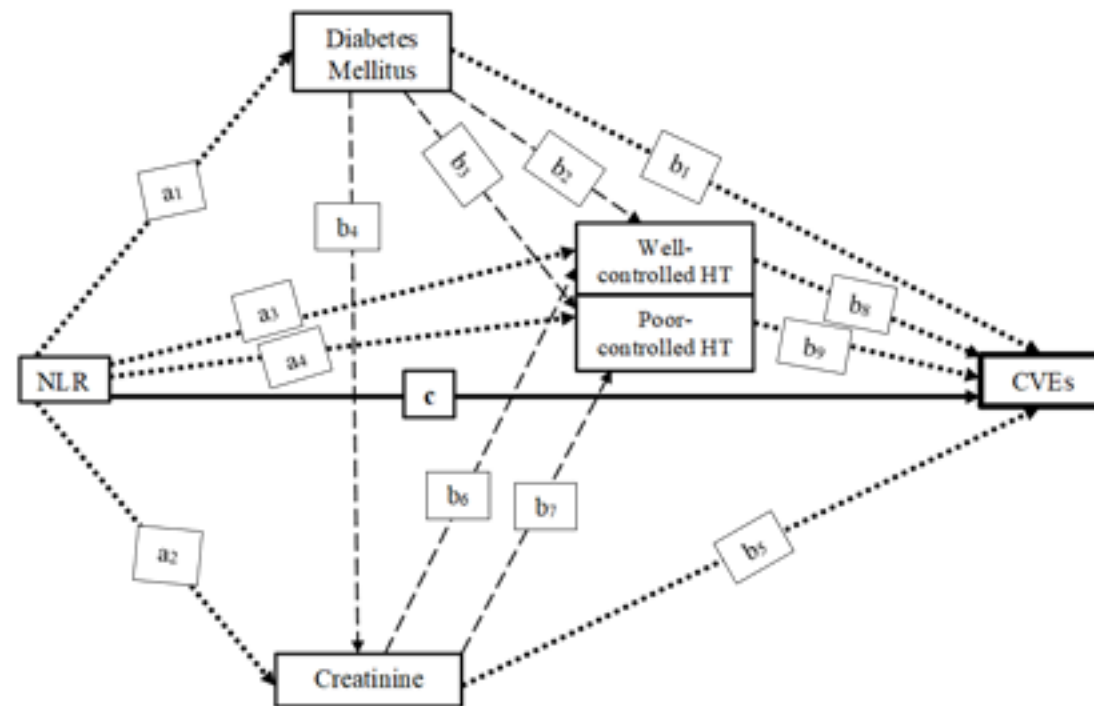
PATHWAY A

NLR ->DM-> Cr-> HT1 or HT2-> CVEs

Parallel multiple mediation model

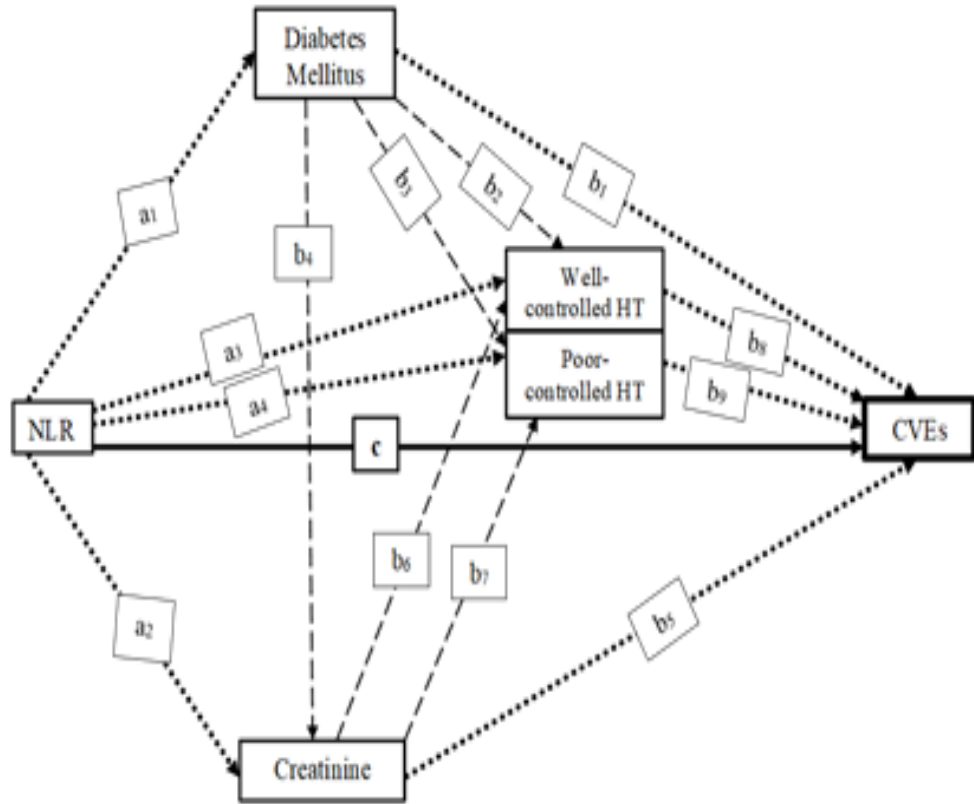


Serial multiple mediation model



PATHWAY A

pathway A (SMMM_A)



SMMM_{A1}

1) $a_1 b_1$	NLR	→	DM	→				CVEs	
2) $a_1 b_2 b_8$	NLR	→	DM	→	well-controlled HT	→		CVEs	
3) $a_1 b_3 b_9$	NLR	→	DM	→	poorly-controlled HT	→		CVEs	
4) $a_1 b_4 b_5$	NLR	→	DM	→	Creatinine	→		CVEs	
5) $a_1 b_4 b_6 b_8$	NLR	→	DM	→	Creatinine	→	well-controlled HT	→	CVEs
6) $a_1 b_4 b_7 b_9$	NLR	→	DM	→	Creatinine	→	poorly-controlled HT	→	CVEs

SMMM_{A2}

7) $a_2 b_5$	NLR	→	Creatinine	→				CVEs
8) $a_2 b_6 b_8$	NLR	→	Creatinine	→	well-controlled HT	→		CVEs
9) $a_2 b_7 b_9$	NLR	→	Creatinine	→	poorly-controlled HT	→		CVEs

SMMM_{A3}

10) $a_3 b_8$	NLR	→	well-controlled HT	→				CVEs
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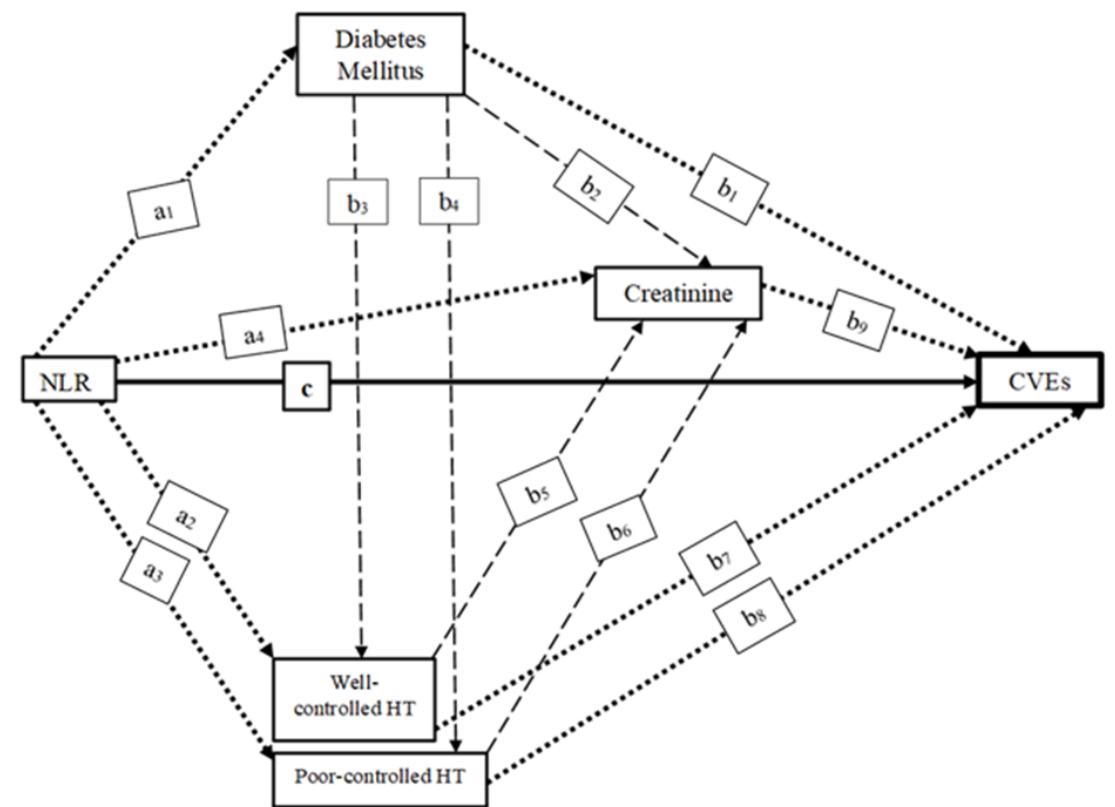
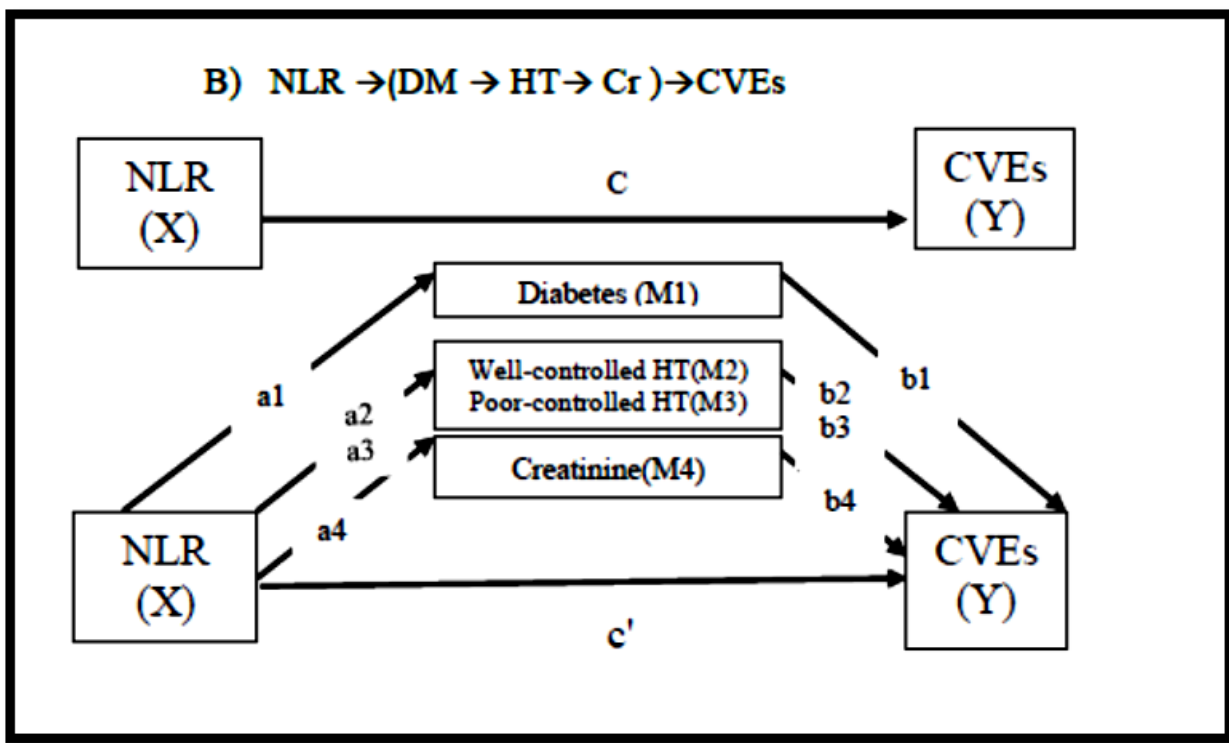
SMMM_{A4}

11) $a_4 b_9$	NLR	→	poorly-controlled HT	→				CVEs
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PATHWAY B **NLR** → (DM → HT1 or HT2 → Cr) → **CVEs**

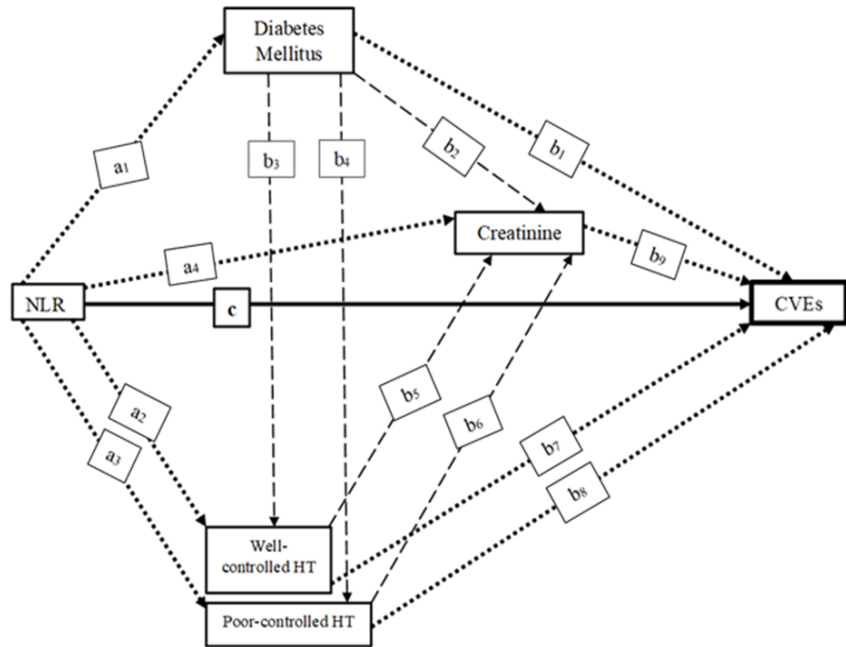
Parallel multiple mediation model

Serial multiple mediation model



PATHWAY B

pathway B (SMMM_B)



SMMMB1						
1) a_1b_1	NLR	→	DM		→	CVEs
2) $a_1b_2b_9$	NLR	→	DM	→	Creatinine	→ CVEs
3) $a_1b_3b_7$	NLR	→	DM	→	well-controlled HT	→ CVEs
4) $a_1b_4b_8$	NLR	→	DM	→	poorly-controlled HT	→ CVEs
5) $a_1b_3b_5b_9$	NLR	→	DM	→	well-controlled HT	Creatinine → CVEs
6) $a_1b_4b_6b_9$	NLR	→	DM	→	poorly-controlled HT	Creatinine → CVEs
SMMMB2						
7) a_4b_9	NLR	→	Creatinine		→	CVEs
SMMMB3						
8) a_2b_7	NLR	→	well-controlled HT		→	CVEs
9) $a_2b_5b_9$	NLR	→	well-controlled HT	→	Creatinine	→ CVEs
SMMMB4						
10) a_3b_8	NLR	→	poorly-controlled HT		→	CVEs
11) $a_3b_6b_9$	NLR	→	poorly-controlled HT	→	Creatinine	→ CVEs

BOOTSTRAP METHOD

- To test mediation effects, we need to obtain empirical standard errors of the parameter estimates.
- A limitation of the multivariate extension of the product-of-coefficients strategy: multivariate normality.
- Proposed by Preacher and Hayes (2008)
- This process was repeated k times, where k is preferably at least 1,000, yielding k estimates of the total and specific IDEs of X on Y .
- This method is active in increasing power and controlling over the type I error.
- All estimated effects in this study were done by bootstrapping with 1,000 re-estimation and resampling.

Bootstrapping command

```
nlrht
set seed 12345
bootstrap total_dm=r(total_dm) total_dm_1ht=r(total_dm_1ht)
total_dm_2ht=r(total_dm_2ht) /// total_cr=r(total_cr) total_ht=r(total_ht)
total_1ht=r(total_1ht) total_2ht=r(total_2ht) /// direct_nlr=r(direct_nlr)
total_effects=r(total_effects) direct_nlr2total=r(direct_nlr2total) ///
total_dm2total=r(total_dm2total) total_cr2total=r(total_cr2total) ///
total_1ht2total=r(total_1ht2total) total_2ht2total=r(total_2ht2total) ///
total_ht2total=r(total_ht2total) or_direct_nlr=r(or_direct_nlr)
or_total_dm=r(or_total_dm) /// or_total_dm_1ht=r(or_total_dm_1ht)
or_total_dm_2ht=r(or_total_dm_2ht) /// or_total_cr=r(or_total_cr)
or_total_ht=r(or_total_ht) or_total_1ht=r(or_total_1ht) ///
or_total_2ht=r(or_total_2ht), reps(1000) cluster(empnm): nlrht
estat bootstrap, bc p norm
```

The percent total MEs were estimated as follows:

- i) Percent total ME or IDE of NLR through DM = $\frac{ME(DM)}{TE} \times 100$
- ii) Percent total ME or IDE of NLR through HT₁ = $\frac{ME(HT1)}{TE} \times 100$
- iii) Percent total ME or IDE of NLR through HT₂ = $\frac{ME(HT2)}{TE} \times 100$
- iv) Percent total ME or IDE of NLR through Cr = $\frac{ME(Cr)}{TE} \times 100$

The percent of DE (% DE) = $c' / ME_{DM} + ME_{HT_1} + ME_{HT_2} + ME_{Cr} + c'$

The ORs of each mediation effect ($OR_{ME_{M_i}}$) = $\exp^{ME_{M_i}}$

95% CI of each mediation effect = 95%CI $OR_{ME_{M_i}} = \exp\left(ME_{M_i} \pm z_{\alpha/2} \sqrt{\text{var}(ME_{M_i})}\right)$

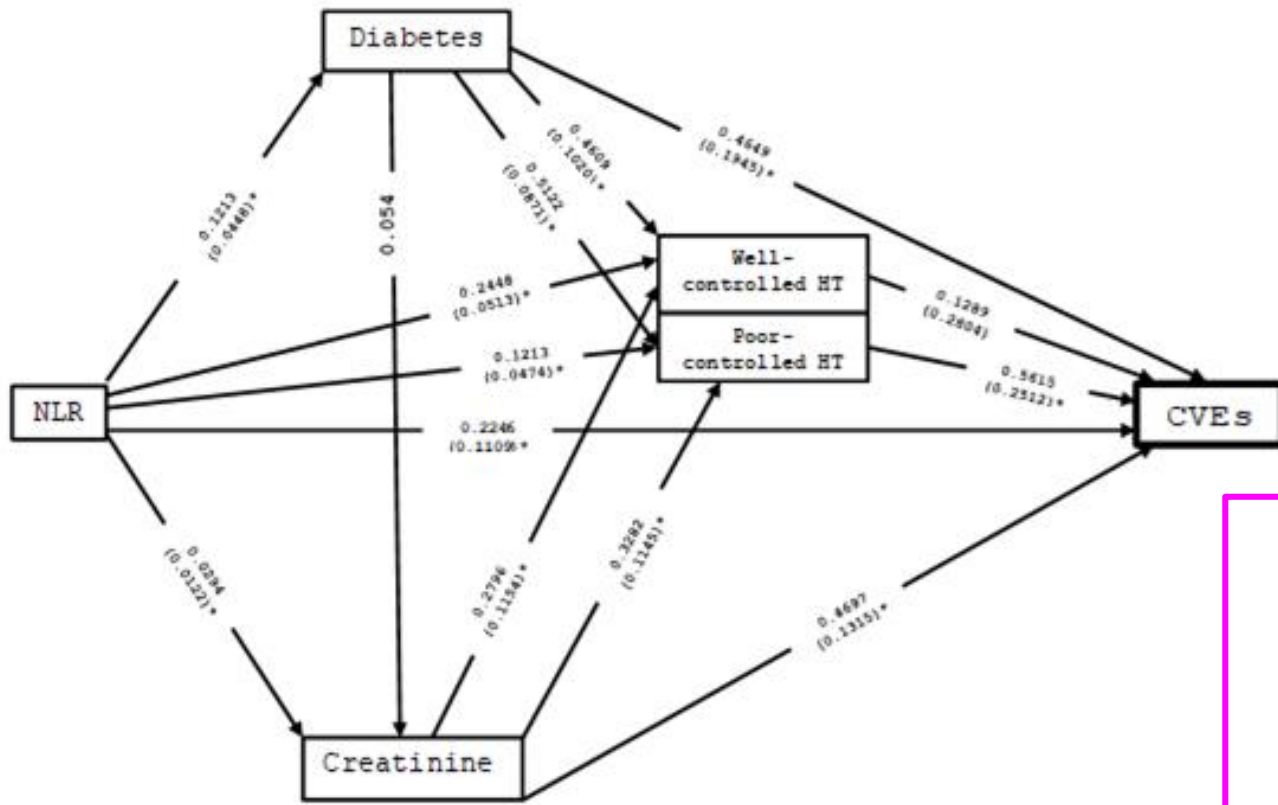
Pathway A

Path	Effect	SE	z	P-value	Bootstrapping		Odds Ratio	95% CI	Proportion mediated(%)
					Bias	Corrected 95%CI			
Direct effect	0.2246	0.0535	4.20	<0.001	0.1235, 0.3306		1.2518	1.1315,1.3918	44.73
Indirect effects									
Overall	0.2775	0.1344	2.06	0.039	0.0505, 0.5864		1.3198	1.0141,1.7176	55.27
Through DM	0.1030	0.0402	2.56	0.010	0.0423, 0.2127		1.1085	1.0199,1.1971	20.51
Through Cr	0.0248	0.0083	3.00	0.003	0.0111, 0.0443		1.0251	1.0084,1.0418	4.94
Through HT ₁	0.0400	0.0759	0.53	0.598	-0.1144, 0.1842		1.0409	0.8849,1.1968	7.97
Through HT ₂	0.1097	0.0427	2.56	0.010	0.0438, 0.2122		1.1159	1.0209,1.2108	21.85
One mediator model									
NLR→DM→CVEs	0.0564	0.0250	2.25	0.024	0.0203, 0.1209		1.0580	1.0058,1.1102	11.23
NLR→Cr→CVEs	0.0138	0.0041	3.37	0.001	0.0060, 0.0219		1.0139	1.0058,1.0220	2.75
NLR→HT ₁ →CVEs	0.0315	0.0605	0.52	0.602	-0.0886, 0.1478		1.0320	0.9089,1.1551	6.27
NLR→HT ₂ →CVEs	0.0681	0.0306	2.23	0.026	0.0227, 0.1477		1.0705	1.0054,1.1355	13.56
Two mediators model									
NLR→DM→Cr→CVEs	0.0031	0.0014	2.19	0.028	0.0012, 0.0069		1.0031	1.0003,1.0058	0.62
NLR→DM→HT ₁ →CVEs	0.0072	0.0142	0.51	0.612	-0.0180,0.0397		1.0072	0.9791,1.0354	1.43
NLR→DM→HT ₂ →CVEs	0.0349	0.0161	2.16	0.031	0.0129, 0.0791		1.0355	1.0025,1.0685	6.95
NLR→Cr→HT ₁ →CVEs	0.0011	0.0023	0.45	0.649	-0.0027, 0.0076		1.0011	0.9965,1.0056	0.22
NLR→Cr→HT ₂ →CVEs	0.0054	0.0033	1.66	0.097	0.0015, 0.0151		1.0054	0.9989,1.0119	1.08
Three mediators model									
NLR→DM→Cr→HT ₁ →CVEs	0.0002	0.0005	0.46	0.646	-0.0006, 0.0016		1.0002	0.9992,1.0012	0.04
NLR→DM→Cr→HT ₂ →CVEs	0.0012	0.0007	1.64	0.101	0.0004, 0.0035		1.0012	0.9998,1.0027	0.24
Total effect	0.5021	0.1388	3.62	<0.001	0.2480, 0.7941		1.6522	0.2301,0.7741	100

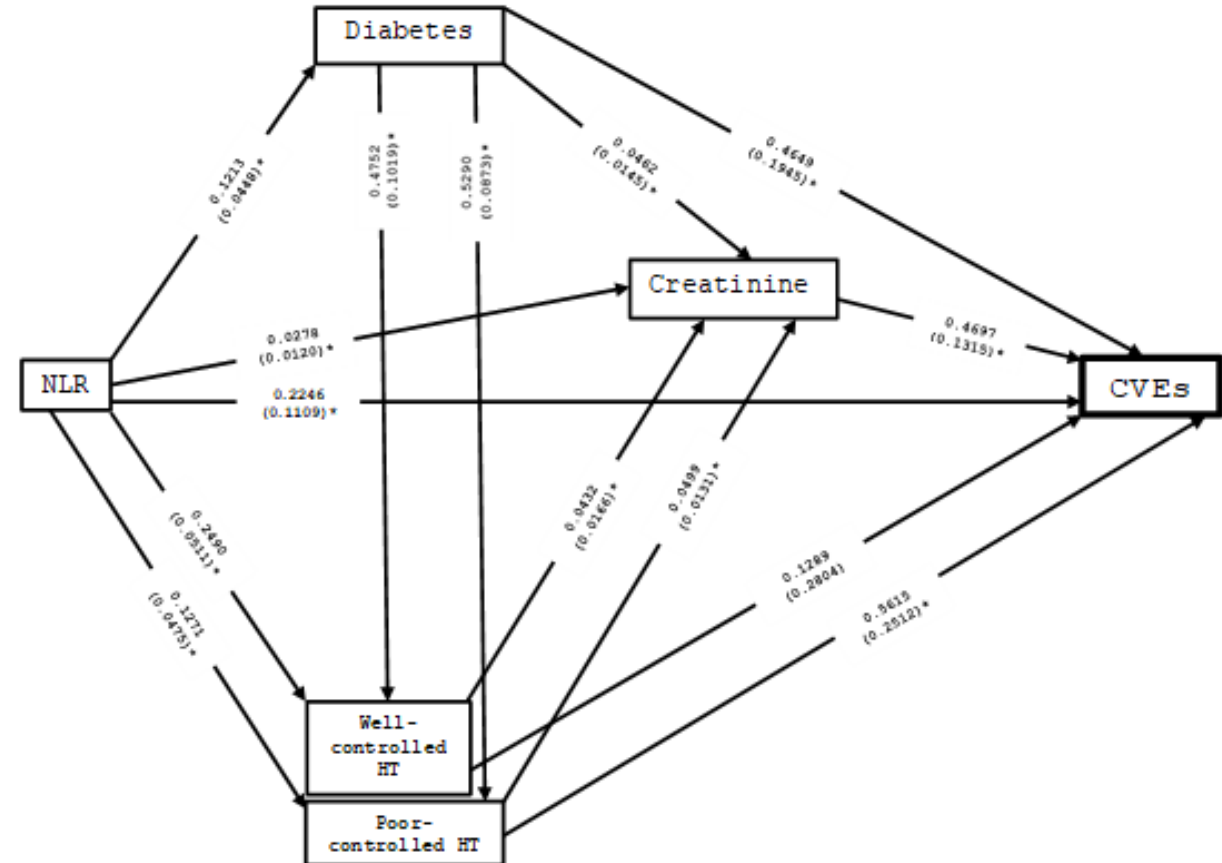
Pathway B

Path	Effect	SE	z	P-value	Bootstrapping		Odds Ratio	95% CI	Proportion mediated(%)
					Bias	Corrected 95%CI			
Direct effect	0.2246	0.1298	4.20	<0.001		0.1235,0.3306	1.2518	1.1315,1.3918	43.71
Indirect effects									
Overall	0.2892	0.1344	2.21	0.027		0.0759,0.5896	1.3318	1.0327,1.7175	56.29
Through DM	0.1052	0.0407	2.58	0.010		0.0434,0.2159	1.1109	1.0211,1.2008	20.47
Through Cr	0.0264	0.0065	4.06	<0.0001		0.0146, 0.0399	1.0267	1.0147,1.0408	5.15
Through HT ₁	0.0457	0.0005	0.61	0.541		-0.1050,0.1875	1.0468	0.8921,1.2015	8.90
Through HT ₂	0.1119	0.0020	2.56	0.010		0.0458,0.2145	1.1184	1.0236,1.2131	21.77
One mediator model									
NLR→DM→CVEs	0.0564	0.0250	2.25	0.024		0.0203,0.1209	1.0580	1.0205,1.1285	10.98
NLR→Cr→CVEs	0.0131	0.0040	3.25	0.001		0.0052,0.0212	1.0131	1.0052,1.0214	2.55
NLR→HT ₁ →CVEs	0.0321	0.0615	0.52	0.602		-0.0919,0.1513	1.0326	0.9122,1.1633	6.25
NLR→HT ₂ →CVEs	0.0714	0.0314	2.23	0.026		0.0243, 0.1502	1.0739	1.0246,1.1621	13.89
Two mediators model									
NLR→DM→Cr→CVEs	0.0026	0.0013	2.07	0.039		0.0009, 0.0062	1.0026	1.0009,1.0062	0.51
NLR→DM→HT ₁ →CVEs	0.0074	0.0146	0.51	0.612		-0.0183,0.0401	1.0075	0.9819,1.0409	1.44
NLR→DM→HT ₂ →CVEs	0.0360	0.0166	2.17	0.030		0.0135, 0.0818	1.0367	1.0136,1.0853	7.01
NLR→HT ₁ →Cr→CVEs	0.0051	0.0018	2.80	0.005		0.0019, 0.0089	1.0051	1.0019,1.0089	0.99
NLR→HT ₂ →Cr→CVEs	0.0029	0.0012	2.43	0.015		0.0011, 0.0056	1.0029	1.0011,1.0056	0.56
Three mediators model									
NLR→DM→HT ₁ →Cr→CVEs	0.0012	0.0006	2.08	0.038		0.0004, 0.0027	1.0012	1.0004, 1.0027	0.23
NLR→DM→HT ₂ →Cr→CVEs	0.0015	0.0007	2.22	0.027		0.0006, 0.0032	1.0015	1.0006, 1.0032	0.29
Total effect	0.5138	0.1343	3.81	<0.001		0.2669,0.7872	1.6671	1.2813,2.1692	100

PATHWAY A



Pathway B



MEDIATION ANALYSIS

- The role of indirect effect of well-controlled HT was not significant in the parallel multiple model.
 - It became a significant indirect effect in pathway B when creatinine was the next mediator.
- For two mediators in pathway B, poor-controlled HT became significantly indirect effect when creatinine was the next mediator.
- The causal chain of three mediators,
 - ***“NLR-Diabetes-HT(Well- or Poor-controlled)-Creatinine-CVEs”***,
 - was the only path that achieved a substantial indirect effect of NLR on CVEs.
- Participants with higher creatinine from well- or poor-controlled hypertension and high NLR would have higher risk of CVEs.

MAIN FINDINGS

- About 55% of the NLR effect operates independently of known metabolic risk factor pathways while the remaining effect (~45%) was influenced by NLR directly.
- Approximately 21.9, 20.5 and 4.9 % of total NLR effects on CVEs were mediated by poor-controlled HT, diabetes and creatinine mediators, respectively.
- The effect of NLR on CVEs was explained by the combination of direct NLR effect and mediated results of diabetes, creatinine and hypertension
 - Poor-controlled HT and diabetes have the strongest mediation effects.
- The higher NLR was, the more it would contribute to have diabetes, hypertension and higher creatinine level, which would together result in having higher CVEs.
- For hypertensive patients with well-controlled blood pressure, this causal pathway can still be used and explained, particularly in the case of having high serum creatinine level or worsening renal function thereafter.

CLINICAL APPLICATION

- Make us concern and implement an intensive intervention on modifying lifestyle and improving medication treatment in the prevention of worsening renal function of hypertensive patients.
- **Microalbuminuria measurement as quantitative data might give clearer causal pathways and better prediction.**
- **Focus on putting this inexpensive biomarker in existing CVD predicting models, particularly local risk models.**
- Testing the mediation model with other possible mediators, which may have similar effect on relationship of NLR and CVEs.
- Cost-effectiveness analysis of using and comparing NLR level with other circulating biomarkers of primary CVEs, for example C-reactive protein, fibrinogen, apolipoprotein B, etc.

CONCLUSION

- Our study demonstrates a direct relationship between the NLR and CVEs, as well as indirectly through DM, HT and Cr.
- However, nearly half of the NLR effect operates independently from the 3 established cardiometabolic risk factors modelled here, raising the possibility that healthy individuals with elevated NLR levels are at risk for CVEs and should receive primary prevention.
- The mediated effect of NLR through well-controlled HT was noted in patients with worsening renal function.
- Based on our limited data, we strongly recommend exploring this relationship with other possible mediators and confirm this causal relationship in other datasets.

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Mediation Effect of Neutrophil Lymphocyte Ratio on Cardiometabolic Risk Factors and Cardiovascular Events

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Teeran An [Angkananard](#)^{1,2}, Thunyarat [Anothaisintawee](#)^{1,3}, Atiporn [Ingsathit](#)¹, Mark [McEvoy](#)⁴, Kongpop [Silapat](#)⁵, John [Attia](#)^{4,6}, Piyamitr [Sritara](#)⁷ & Ammarin [Thakkinstian](#)¹

Neutrophil to lymphocyte ratio (NLR), an inflammatory biomarker, is associated with cardiovascular events (CVEs), but its causal pathway is unknown. We aimed to explore the extent to which NLR is directly associated with CVEs or mediated through diabetes mellitus (DM), hypertension (HT) and creatinine (Cr). The study used data on 2,501 subjects from the Electricity Generating Authority of Thailand cohort 2002–2012. Two causal pathways A: $NLR \rightarrow (DM \rightarrow Cr \rightarrow HT) \rightarrow CVEs$ and B: $NLR \rightarrow (DM \rightarrow HT \rightarrow Cr) \rightarrow CVEs$ were constructed. A generalized structural equation model and 1,000-replication bootstrapping were applied. The incidence rate of CVE was 8.8/1000/year. Prevalence rates of HT, DM, and chronic kidney disease were 45.1%, 23.6%, and 16.5%, respectively. The total effect of NLR on CVEs was explained partly (44%) by a direct effect and partly (56%) by an indirect effect through DM, HT and Cr. For pathway A, the direct OR of NLR on CVE was 1.25 (95% CI 1.12, 1.38); the ORs for the indirect effects of NLR on CVEs mediated through DM, Cr, and poor-controlled HT were 1.06 (1.01, 1.11), 1.01 (1.00, 1.02), and 1.07 (1.01, 1.14) respectively. Results were similar for pathway B. Our findings demonstrate that roughly half of the relationship between NLR and CVEs may be mediated through DM, HT and Cr.

**THANK YOU FOR YOUR KIND
ATTENTION**

