Supplemental Appendix

Causal Effect of Chronic Pain on Mortality through Opioid prescriptions: Application of the Front-Door Formula

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eAppendix

1. Sample R code for g-computation of marginal structural model under front-door adjustment.

eText 1: The Front-Door Formula and Its Generalization

<u>Notation</u>

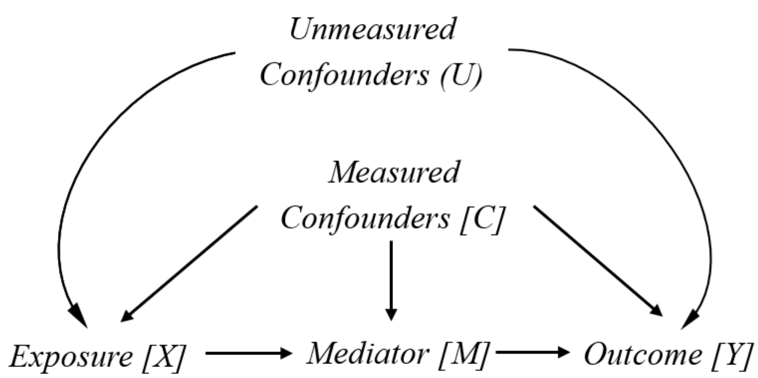
Let X denote the exposure of interest, M denote the mediator of interest, and Y denote the outcome of interest. Let C denote a set of measured confounders between the exposure and the outcome, and U denote a set of unmeasured confounders between the exposure and the outcome. Let x (index) and x^* (reference) denote two values of the exposure that we compare, and m (index) and m^* (reference) denote two values of the mediator that we compare. We assumed that C and U preceded X, and X preceded M, and M preceded Y.

Let M_x and Y_x denote the potential mediator and the potential outcome respectively if the exposure had taken value $X = x$; Y_{xm} denote the potential outcome if the exposure had taken value $X = x$ and the mediator had taken value $M = m$; $Y_{xM_{x^*}}$ denote the potential outcome if the exposure had taken value $X = x$ and M had been set to M_{x^*}. $Y_{x^*M_x}$ is defined similarly. Let Y_{XM_x} and $Y_{XM_{x^*}}$ denote the potential outcomes when the exposure had been set, perhaps contrary to fact, to x and x^* respectively at the M-stage, and M had been allowed to affect Y naturally following the X-intervention(s), and the direct effect of X on Y at the Y-stage is averaged over the observed marginal distribution of X. Let X' denote using X for confounding adjustment at the Y-stage of the front-door formula. Let $Y_{X'M_x}$ (= Y_{M_x}) and $Y_{X'M_{x^*}}$ (= $Y_{M_{x^*}}$) be similarly defined but without intervention on X at the Y-stage (hence, the use of X' instead of X in the subscript).

Pearl's Original Formulation and Assumptions[1-3]

Figure A1 presents a directed acyclic graph (DAG) representing a causal structure of Pearl's original formulation of the Front-door formula (FDF).

Figure A1. Causal diagram of the original Front-door formula proposed by Pearl.



X, exposure; M, mediator; Y, outcome; C, a set of measured confounders; U, a set of unmeasured confounders.

Assumptions needed for the original FDF include:

1) the mediator intercepts all directed paths from the exposure to the outcome

2) the causal path from the exposure to the mediator is not confounded given C; $M_x \perp\!\!\!\perp X \mid C$

3) the causal path from the mediator to the outcome is not confounded given X and C; $Y_m \perp\!\!\!\perp M \mid X, C$.

We also need the assumption of positivity (i.e., $P(X = x \mid C = c) > 0$, $P(M = m \mid X = x, C = c) > 0$ for all $P(C = c) > 0$), consistency (i.e., $M_x = M$ when $X = x$, $Y_x = Y$ when $X = x$, and $Y_{xm} = Y$ when $X = x$ and $M = m$), composition ($Y_x = Y_{xM_x}$ when $X = x$), no model misspecification, and no other sources of bias.

Under these assumptions, one can estimate the average total effect (TE) of X on Y by combining two effects (i.e., the effect of X on M and the effect of M on Y). The empirical analogue of the FDF can then be shown as follows:

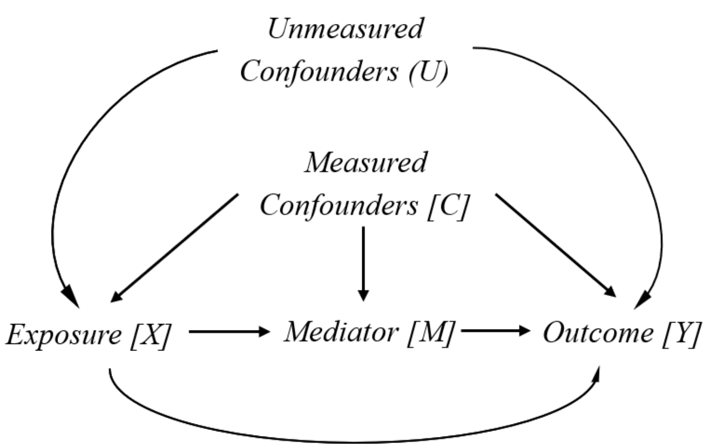
$$\begin{aligned}\text{TE} &= E(Y_x) - E(Y_{x^*}) \\ &= \Sigma_m P(M = m \mid X = x, C)\Sigma_{x',c} E(Y \mid M = m, X' = x', \text{C} = c)\text{P}(X' = x', C = c) \\ &- \Sigma_m P(M = m \mid X = x^*, C)\Sigma_{x',c} E(Y \mid M = m, X' = x', \text{C} = c)\text{P}(X' = x', C = c)\end{aligned}$$

where X' refers to using the measured X as a deconfounder in lieu (or proxy) of the unmeasured U on the backdoor between M and Y (**Figure A1**).

Fulcher et al's Generalization[4,5]

Fulcher et al. generalized the FDF to estimate the population intervention indirect effect (PIIE)—the indirect effect component of van der Laan and Hubbard's population intervention effect (PIE)—that can be identified in the presence of uncontrolled exposure-outcome confounding. As shown in **Figure A2**, this generalization formula does not require exclusion restriction assumptions: i.e., direct effect of exposure not mediated by intermediate variables.

Figure A2. Causal diagram of the generalized Front-door formula proposed by Fulcher et al.



X, exposure; *M*, mediator; *Y*, outcome; *C*, a set of measured confounders; *U*, a set of unmeasured confounders.

Empirical analogue of their generalized FDF can be shown as follows (on the risk difference scale):

PIIE($X = x^*$)

$= E(Y_{X'M_{X'}}) - E(Y_{X'M_{x^*}})$

$= E(Y) - \Sigma_m P(M = m \mid X = x^*, C)\Sigma_{x',c} E(Y \mid M = m, X' = x', C = c)\mathrm{P}(X' = x', C = c)$

<u>*Our Extension and Application of Pearl's FDF and Fulcher et al's Generalization*</u>

Our own work developed independent of Fulcher et al's work (Arah OA. *Estimating Causal Effects Using the Front-door Criterion.* UCLA and Caltech, March 3, 2014 [Unpublished Talk]) and can be seen as a further extension or generalization (**Figure A2**) to estimate what we call the path-specific front-door effect (PSFDE), i.e., effect of the X on Y through a specified front-door variable M. This PSFDE only equals the (pure and total or treatment-averaged) natural indirect effects under additional no U-M interaction assumption and restriction to the treated ($X = x$) or untreated ($X = x^*$) (see also Fulcher et al. 2019). PSFDE can be estimated by taking a contrast of Y_{M_x} and $Y_{M_{x^*}}$ (or equivalently, of $Y_{X'M_x}$ and $Y_{X'Mx^*}$) in the total population as well as among those with $X = x$ and $X = x^*$ using two computed outcomes that equal neither Y_x and Y_{x^*} (since the absence of U precludes identification of the total effect in the total population) nor $Y_{xM_{x^*}}$ and $Y_{xM_{x^*}}$ (since the absence of U precludes identification of the direct effect in the total population). In other words, the PSFDE captures the effect of the exposure X on the outcome Y that goes through the mediator M in a scenario where the total effect of X on Y is not identifiable but the effects of X on M and of M on Y are assumed identifiable.

Our generalized form of front-door formula can be applied based on the following assumptions: 1) the mediator (opioid prescriptions) intercepts the target causal path from the exposure (chronic pain) to the outcome (mortality), 2) the causal path from the exposure (chronic pain) to the mediator (opioid prescriptions) is not confounded given the abovementioned covariates (i.e. $M_{x^*} \perp\!\!\!\perp X \mid C$), and 3) the causal path from the mediator (opioid prescriptions) to the outcome (mortality) is not confounded given the exposure (chronic pain) and the abovementioned covariates (i.e. $Y_{xm} \perp\!\!\!\perp M_{x^*} \mid X, C$). In this formula, we allowed the model to have the direct pathway from the exposure (chronic pain) to the outcome (mortality); i.e., the exclusion restriction was not assumed to hold.

In addition, we required positivity assumptions: i.e. $f(X = x \mid C) > 0$ and $f(M = m \mid C, X) > 0$ where $f(.)$ is a probability density function. In other words, there should be 1) both participants with and without chronic pain at every combination of C, and 2) both participants with and without opioid prescriptions at every combination of X and C.

Another important assumption is consistency; i.e., $M_x = M$ when $X = x$, $Y_x = Y$ when $X = x$, and $Y_{xm} = Y$ when $X = x$ and $M = m$. In other words, an individual's potential outcome (M or Y in our scenario) under their exposure status (X or M in our scenario) is precisely their observed outcome. Beyond these assumptions, we also required other causal modeling assumptions including composition, well-defined variables (exposure, outcome, and covariates), no model misspecification, and no other sources of bias.

Under these assumptions, empirical analogues of our PSFDE can be shown as follows (on the risk difference scale):

PSFDE

$= E(Y_{M_x}) - E(Y_{M_{x^*}})$

$= \Sigma_m \mathrm{P}(M = m \mid X = x, C)\Sigma_{x',c} E\,(Y \mid M = m, X' = x', \mathrm{C} = c)\mathrm{P}(X' = x', \mathrm{C} = c)$

$\quad - \Sigma_m \mathrm{P}(M = m \mid X = x^*, C)\Sigma_{x',c} E\,(Y \mid M = m, X' = x', \mathrm{C} = c)\mathrm{P}(X' = x', \mathrm{C} = c)$

The odds ratio for the PSFDE was given by $odds[P(Y_{M_x} = 1)] \div odds[P(Y_{M_{x^*}} = 1)]$.

This estimand will be equal to the TANIE (treatment-averaged natural indirect effect) when the total and pure NIEs are averaged over the observed marginal distribution of X in the Y-stage:

$E(Y_{X'M_x}) - E(Y_{X'M_{x^*}}) = E(Y_{XM_x}) - E(Y_{XM_{x^*}})$ if no U-M and U-M-X interaction on the additive scale.

Two other versions of the PSFDE obtained by conditioning on $X' = x'$ or $X' = x'^*$ in the Y-stage expression:

a) Total PSFDE ($X' = x'$) = TNIE (total natural indirect effect) when $X = x$ in the *Y-stage*

   $E(Y_{x'M_x}) - E(Y_{x'M_{x^*}}) = E(Y_{xM_x}) - E(Y_{xM_{x^*}})$ if no U-M and U-M-X interaction on the additive scale.

b) Pure PSFDE ($X' = x'^*$) = PNIE (pure natural indirect effect) when $X = x^*$ in the *Y-stage*

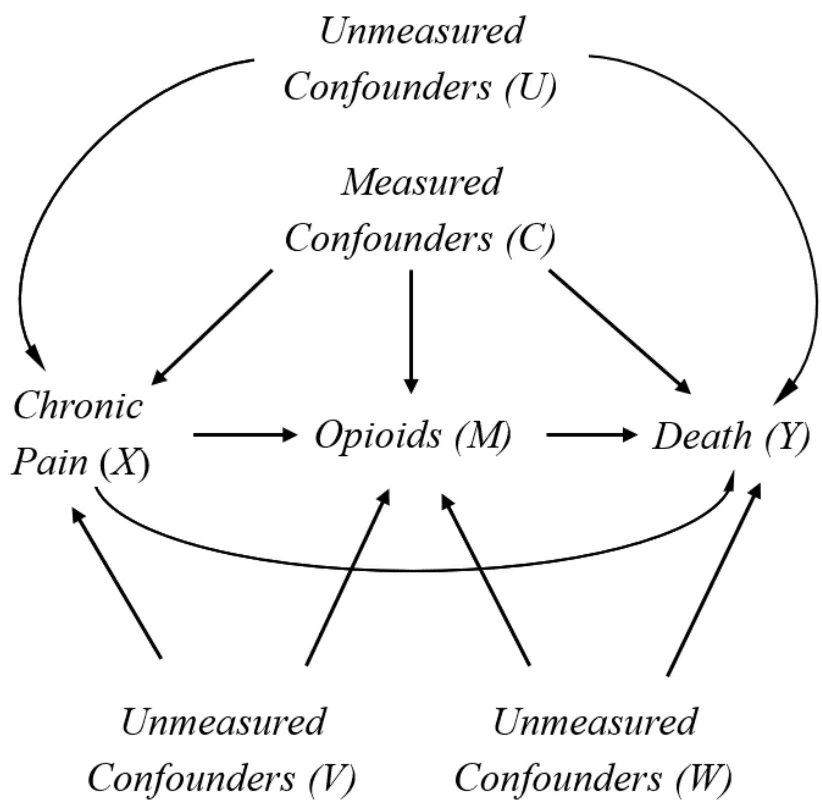
   $E(Y_{x'^*M_x}) - E(Y_{x'^*M_{x^*}}) = E(Y_{x^*M_x}) - E(Y_{x^*M_{x^*}})$ if no U-M interaction on the additive scale.

Using real-world data, we demonstrated the application of this method using the g-computation algorithm to estimate the PSFDE (**Table 1**). We also applied quantitative bias analysis to evaluate sensitivity to likely uncontrolled confounding between the exposure and the mediator or between the mediator and the outcome (see **eTable 1** and **eFigure 1**).

References:

1. Pearl J. Mediating Instrumental Variables. Technical Report R-210, Cognitive Systems Laboratory, UCLA Computer Science Department. 1993.
2. Pearl J. Causal diagrams for empirical research. Biometrika. 1995;82(4):669-88.
3. Pearl J. Causality. Cambridge university press; 2009.
4. Fulcher IR., Shpitser I, Marealle S, Tchetgen Tchetgen EJ. Robust inference on population indirect causal effects: the generalized front door criterion. Journal of the Royal Statistical Society: Series B (Statistical Methodology), 2020; 82(1), 199-214.
5. Fulcher IR, Shi X, Tchetgen Tchetgen EJ. Estimation of natural indirect effects robust to unmeasured confounding and mediator measurement error. Epidemiology. 2019;30(6):825-34.

eFigure 1. Directed acyclic graph for the plausible relations between chronic pain, opioid prescriptions, and mortality in the presence of measured and unmeasured confounders in our bias analyses.



eTable 1. Steps in the bias analysis in the front-door formula

Step 1. Assign OR_{MV}, P_{V1}, and P_{V0} where OR_{MV} is the odds ratio relating the unmeasured confounder *V* to opioid prescriptions *M*, conditional on chronic pain *X*; P_{V1} is the prevalence of *V* among those with chronic pain ($X = 1$); and P_{V0} is the prevalence of *V* among those without chronic pain ($X = 0$).
Step 2. Obtain Bias $factor_{XM}$ using the following equation: Bias $factor_{XM} = (OR_{MV}*P_{V1}+1-P_{V1})/(OR_{MV}*P_{V0}+1-P_{V0})$
Step 3. Obtain $OR_{XM\_adjusted}$ by dividing $OR_{XM\_preadjusted}$ by the Bias $factor_{XM}$ where $OR_{XM\_preadjusted}$ is the observed odds ratio; and $OR_{XM\_adjusted}$ is the odds ratio adjusted for the unmeasured confounder *V*.
Step 4. Assign OR_{YW}, P_{W1}, and P_{W0} where OR_{YW} is the odds ratio relating the unmeasured confounder *W* to all-cause mortality *Y*, conditional on opioid prescriptions *X*; P_{W1} is the prevalence of *W* among those with opioid prescriptions ($X = 1$); and P_{W0} is the prevalence of the unmeasured confounder among those without opioid prescriptions ($X = 0$).
Step 5. Obtain Bias $factor_{MY}$ using the following equation: Bias $factor_{MY} = (OR_{YW}*P_{W1}+1-P_{W1})/(OR_{YW}*P_{W0}+1-P_{W0})$
Step 6. Obtain $OR_{MY\_adjusted}$ by dividing $OR_{MY\_preadjusted}$ by the Bias $factor_{MY}$ where $OR_{MY\_preadjusted}$ is the observed odds ratio; and $OR_{MY\_adjusted}$ is the odds ratio adjusted for the unmeasured confounder.
Step 7. Obtain potential outcome Y_X by repeating steps in Table 1 using $OR_{XM\_adjusted}$ and $OR_{MY\_adjusted}$ instead of $OR_{XM\_preadjusted}$ and $OR_{MY\_preadjusted}$

eTable 2. Odds ratio (95% CI) for the estimated effects of chronic pain on opioid prescriptions with NHANES survey weights applied.

	***N* of opioids use / *N* of participants**		**Adjusted Odds ratio (95% CI)**	
	Pain (+)	**Pain (—)**	**Age + Sex adjusted**	**Main model [a]**
Total opioids	382/2168	301/11716	7.58 (6.22-9.24)	6.14 (4.99-7.55)
Opioids equivalent to or stronger than morphine [b]	223/2009	137/11552	9.50 (7.35-12.28)	7.37 (5.58-9.56)

[a] Adjusted for age, sex, education levels, poverty-income ratio, health insurance coverage, marital status, smoking, alcohol intake, and anti-depressant medication prescriptions.
[b] Total N is different from total opioids because opioids weaker than morphine were excluded from this analysis.

eTable 3. Odds ratio (95% CI) for the estimated effects of opioid prescriptions on all-cause mortality at 3 and 5 years according to the presence of chronic pain at enrollment.

	Adjusted OR of total opioids on mortality (95% CI) [a, b]		**P for interaction**
	Pain (+)	**Pain (─)**	
3-year mortality	1.17 (0.75-1.72)	1.86 (1.29-2.60)	0.06
5-year mortality	1.22 (0.90-1.63)	1.37 (1.03-1.82)	0.39

	Adjusted OR of opioids equivalent to or stronger than morphine on mortality (95% CI) [a, b]		**P for interaction**
	Pain (+)	**Pain (─)**	
3-year mortality	1.25 (0.76-2.02)	2.22 (1.24-3.44)	0.08
5-year mortality	1.27 (0.82-1.81)	1.68 (1.07-2.49)	0.22

[a] 1000 iterations were performed for bootstrapping to estimate 95% confidence interval.
[b] Adjusted for age, gender, education levels, poverty-income ratio, health insurance coverage, marital status, smoking, alcohol intake, anti-depressant medication prescription and chronic pain.

eTable 4. Odds ratio (95% CI) for the estimated effects of opioids on all-cause mortality at 3 and 5 years with NHANES survey weights applied.

	N of death / *N* of participants		Adjusted Odds ratio (95% CI) [a]	
	Opioids (+)	**Opioids (−)**	**Age + Sex adjusted**	**Main model** [a]
A) Total opioids				
3-year mortality	77/683	641/13201	1.87 (1.23-2.86)	1.53 (0.97-2.41)
5-year mortality	117/683	1143/13915	1.60 (1.19-2.15)	1.28 (0.95-1.71)
B) Opioids equivalent to or stronger than morphine [b]				
3-year mortality	36/360	641/13201	1.83 (1.00-3.36)	1.51 (0.79-2.87)
5-year mortality	56/360	1143/13195	1.77 (1.18-2.64)	1.42 (0.96-2.10)

[a] Adjusted for age, gender, education levels, poverty-income ratio, health insurance coverage, marital status, smoking, alcohol intake, anti-depressant medication prescription and chronic pain.
[b] Total N is different from total opioids because opioids weaker than morphine were excluded from this analysis.

eTable 5. Risk difference (95% CI) for the estimated path-specific front-door effects of chronic pain on all-cause mortality at 3 and 5 years using the front-door adjustment.

	N of death / *N* of participants		Adjusted risk difference (95% CI) [a,b]	
	Pain (+)	**Pain (−)**	**Through total opioids**	**Through opioids equivalent to or stronger than morphine**
3-year mortality	157/2168	561/11716	+0.27 (0.07-0.51) percentage points	+0.21 (0.02-0.41) percentage points
5-year mortality	261/2168	999/11710	+0.28 (0.05-0.51) percentage points	+0.26 (0.04-0.48) percentage points

[a] Adjusted for age, gender, education levels, poverty-income ratio, health insurance coverage, marital status, smoking, alcohol intake, and anti-depressant medication prescription.
[b] 1000 iterations were performed for bootstrapping to estimate 95% confidence interval.

eTable 6. Odds ratio (95% CI) for the estimated path-specific front-door effects of chronic pain on all-cause mortality through opioid prescriptions (total opioids), per pain location.

	Adjusted Odds ratio (95%CI) [a, b]				
All-cause Mortality	**Back pain**	**Legs/feet pain**	**Headache/ migraine**	**Arms/hands pain**	**Others** [c]
3-year mortality	1.06 (1.00-1.13)	1.08 (1.02-1.16)	1.06 (1.01-1.13)	1.08 (1.03-1.16)	1.12 (1.04-1.23)
5-year mortality	1.03 (1.00-1.08)	1.04 (1.00-1.08)	1.03 (0.99-1.06)	1.04 (1.00-1.09)	1.05 (1.00-1.12)

[a] Adjusted for age, gender, education levels, poverty-income ratio, health insurance coverage, marital status, smoking, alcohol intake, and anti-depressant medication prescriptions.
[b] 1000 iterations were performed for bootstrapping to estimate 95% confidence interval.
[c] Abdominal, face/teeth, or chest pain.

eTable 7. Odds ratios (95% CI) for the estimated path-specific front-door effects of chronic pain on all-cause mortality at 3 and 5 years using the front-door adjustment including a multiplicative interaction term between chronic pain and opioid prescriptions.

Total opioids	***N* of death / *N* of participants**				**Adjusted OR (95% CI)** [a,b]
	Pain (+)		**Pain (−)**		
	Opioid (+)	**Opioid (−)**	**Opioid (+)**	**Opioid (−)**	
3-year mortality	39/382	118/1786	38/301	523/11415	1.08 (0.96-1.22)
5-year mortality	66/382	195/1786	51/301	948/11409	1.04 (0.95-1.14)
Opioids equivalent to or stronger than morphine	***N* of death / *N* of participants**				**Adjusted OR (95% CI)** [a,b]
	Pain (+)		**Pain (−)**		
	Opioid (+)	**Opioid (−)**	**Opioid (+)**	**Opioid (−)**	
3-year mortality	22/223	118/1786	14/137	523/11415	1.07 (0.96-1.20)
5-year mortality	36/223	195/1786	20/137	948/11409	1.03 (0.94-1.14)

[a] Adjusted for age, gender, education levels, poverty-income ratio, health insurance coverage, marital status, smoking, alcohol intake, and anti-depressant medication prescription.
[b] 1000 iterations were performed for bootstrapping to estimate 95% confidence interval.

eTable 8. Odds ratios (95% CI) for the estimated effects of chronic pain on all-cause mortality through opioid prescription at 3 and 5 years using the front-door formula vs. the mediation analysis.

	***N* of death / *N* of participants**		**Adjusted Odds ratio (95% CI)** [a, b]	
	Pain (+)	**Pain (−)**	**PSFDE by our front-door formula**	**NIE by the mediation analysis**
3-year mortality	157/2168	561/11716	1.06 (1.01-1.11)	1.13 (1.04-1.22)
5-year mortality	261/2168	999/11710	1.03 (1.01-1.06)	1.07 (1.02-1.14)

PSFDE, path-specific front-door effect; NIE, natural indirect effect

[a] Adjusted for age, gender, education levels, poverty-income ratio, health insurance coverage, marital status, smoking, alcohol intake, and anti-depressant medication prescription.

[b] 1000 iterations were performed for bootstrapping to estimate 95% confidence interval.

eTable 9. Odds ratio (95% CI) for the estimated path-specific front-door effects of chronic pain on all-cause mortality in a complete case analysis (N = 12,037).

	***N* of death / *N* of participants**		**Adjusted Odds ratio (95% CI)** [a, b]	
	Pain (+)	**Pain (−)**	**Through total opioids**	**Through opioids equivalent to or stronger than morphine**
3-year mortality	126/1931	473/10106	1.05 (1.01-1.11)	1.04 (1.00-1.09)
5-year mortality	216/1931	842/10101	1.03 (1.00-1.06)	1.02 (0.99-1.05)

[a] Adjusted for age, gender, education levels, poverty-income ratio, health insurance coverage, marital status, smoking, alcohol intake, and anti-depressant medication prescription.
[b] 1000 iterations were performed for bootstrapping to estimate 95% confidence interval.

eTable 10. Odds ratio (95% CI) for the estimated path-specific front-door effects of chronic pain on all-cause mortality among those without a history of cancer (n=12,637).

	***N* of death / *N* of participants**		**Adjusted Odds ratio (95% CI)** [a, b]	
	Pain (+)	**Pain (−)**	**Through total opioids**	**Through opioids equivalent to or stronger than morphine**
3-year mortality	104/1885	426/10752	1.04 (1.00-1.09)	1.03 (0.99-1.07)
5-year mortality	187/1885	760/10746	1.02 (0.99-1.05)	1.02 (0.99-1.05)

[a] Adjusted for age, gender, education levels, poverty-income ratio, health insurance coverage, marital status, smoking, alcohol intake, and anti-depressant medication prescription.
[b] 1000 iterations were performed for bootstrapping to estimate 95% confidence interval.

eTable 11. Odds ratio (95% CI) for the estimated path-specific front-door effects of chronic pain on all-cause mortality additionally adjusting for comorbidities related to pain and illicit drug use among participants aged 20-59 years (N = 8,629).

	***N* of death / *N* of participants**		**Adjusted Odds ratio (95% CI)** [a, b]	
	Pain (+)	**Pain (−)**	**Through total opioids**	**Through opioids equivalent to or stronger than morphine**
3-year mortality	23/1310	53/7319	1.07 (0.98-1.26)	1.06 (0.97-1.23)
5-year mortality	50/1310	108/7317	1.02 (0.97-1.10)	1.02 (0.97-1.08)

[a] Adjusted for age, gender, education levels, poverty-income ratio, health insurance coverage, marital status, smoking, alcohol intake, and anti-depressant medication prescriptions, comorbidities related to pain (cardiovascular diseases, cancer, and arthritis), and illicit drug use.
[b] 1000 iterations were performed for bootstrapping to estimate 95% confidence interval.

eTable 12. Odds ratios (95% CI) for the estimated path-specific front-door effects of chronic pain on all-cause mortality at 3 and 5 years using the front-door adjustment (assuming antidepressant use occurred after chronic pain).

	***N* of death / *N* of participants**		**Adjusted Odds ratio (95% CI)** [a, b]	
	Pain (+)	**Pain (−)**	**Through total opioids**	**Through opioids equivalent to or stronger than morphine**
3-year mortality	157/2168	561/11716	1.06 (1.02-1.11)	1.05 (1.00-1.10)
5-year mortality	261/2168	999/11710	1.04 (1.00-1.07)	1.04 (1.00-1.07)

[a] Adjusted for age, gender, education levels, poverty-income ratio, health insurance coverage, marital status, smoking, alcohol intake in M-stage regression, and additionally anti-depressant medication prescription in the Y-stage regression.
[b] 1000 iterations were performed for bootstrapping to estimate 95% confidence interval.

eTable 13. Odds ratio (95% CI) for the estimated path-specific front-door effects of chronic pain on all-cause mortality at 3-year through total opioids with bias analyses.[a,b,c]

I) $P_{V0}=0.4$, $P_{V1}=0.6$, $P_{W0}=0.4$, $P_{W1}=0.6$		OR_{YW} **1.0**	**1.5**	**2.0**
OR_{MV}	**1.0**	1.057 (1.010-1.105)	1.043 (1.004-1.102)	1.036 (1.000-1.083)
	1.5	1.052 (1.016-1.098)	1.038 (1.001-1.086)	1.032 (0.998-1.078)
	2.0	1.049 (1.010-1.092)	1.036 (1.003-1.078)	1.029 (0.998-1.073)
II) $P_{V0}=0.05$, $P_{V1}=0.1$, $P_{W0}=0.1$, $P_{W1}=0.2$		OR_{YW} **1.0**	**1.5**	**2.0**
OR_{MV}	**1.0**	1.057 (1.010-1.105)	1.048 (1.008-1.109)	1.043 (1.002-1.093)
	1.5	1.055 (1.017-1.104)	1.046 (1.005-1.097)	1.041 (1.003-1.092)
	2.0	1.053 (1.011-1.101)	1.045 (1.007-1.091)	1.039 (1.003-1.088)

[a] Adjusted for age, gender, education levels, poverty-income ratio, health insurance coverage, marital status, smoking, alcohol intake, and anti-depressant medication prescription.
[b] ORs are described with three decimal points to show the difference in each cell. 1000 iterations were performed for bootstrapping to estimate 95% confidence interval.
[c] Notations are described in eTable 1. Examples from our dataset: smoke, $P_{V0}=0.46$, $P_{V1}=0.59$, $OR_{MV}=1.3$, $P_{W0}=0.47$, $P_{W1}=0.60$, $OR_{YW}=1.9$; antidepressant use, $P_{V0}=0.06$, $P_{V1}=0.17$, $OR_{MV}=1.6$, $P_{W0}=0.07$, $P_{W1}=0.24$, $OR_{YW}=1.7$.

eTable 14. Odds ratio (95% CI) for the estimated path-specific front-door effects of chronic pain on all-cause mortality at 3 and 5 years through total opioids assuming the misclassification of the mediator among participants with chronic pain.

	Percentage of participants who might not report opioid prescriptions among those with chronic pain		
	0.0% (no misclassification)	***5.0%***	***10.0%***
		Adjusted OR (95% CI) [a,b]	
3-year mortality	1.06 (1.01-1.11)	1.07 (1.02-1.13)	1.08 (1.02-1.15)
5-year mortality	1.03 (1.01-1.06)	1.04 (1.01-1.08)	1.05 (1.01-1.10)

[a] Adjusted for age, gender, education levels, poverty-income ratio, health insurance coverage, marital status, smoking, alcohol intake, and anti-depressant medication prescription.
[b] 1000 iterations were performed for bootstrapping to estimate 95% confidence interval.

eAppendix 1. Sample R code for g-computation of marginal structural model under front-door adjustment.

```
####################################################################################################
# Manuscript title:
# Causal Effect of Chronic Pain on Mortality through Opioids: An Application of the Front-Door Formula
# Program created by: Kosuke Inoue (koinoue@ucla.edu)
# Data in the paper: NHANES 1999-2004 linked to mortality data in 2015
# available at https://www.cdc.gov/nchs/nhanes/index.htm
# An example of R code for front-door formula
####################################################################################################

set.seed(12345)

#Set variables
d$exp <- d$pain        #exposure
d$med <- d$opioid    #mediator
d$out <- d$mortality #outcome

#Create temporary exposure and mediator
d$exptemp <- d$exp
d$medtemp <- d$med

#Run a logistic regression model (exposure -> mediator)
reg1  <- glm(med ~ as.factor(exptemp) + covariates, data=d, family=binomial(link="logit"))

#Run a logistic regression model (mediator -> outcome)
reg2 <- glm(out ~ as.factor(medtemp) + as.factor(exp) + covariates, data=d, family=binomial(link="logit"))

#Create a potential outcome model (exposure -> mediator)
#Create combined datasets: 1) everyone set to exp=0, and 2) everyone set to exp=1
levelsofexp <- unique(d$exp)
d1 <- d
d2 <- d
d1$expstar <- levelsofexp[1] #exp=0
d2$expstar <- levelsofexp[2] #exp=1
newmyd1 <- rbind(d1, d2)

N1 <- nrow(newmyd1)
newmyd1$exptemp <- newmyd1$expstar
newmyd1$med_po <- rbinom(N1, size = 1, prob=1/(1+exp(-predict(reg1,newdata=newmyd1))))
reg1_po <- glm(med_po ~ as.factor(exptemp), data=newmyd1, family=binomial(link="logit"))

#Create a potential outcome model (mediator -> outcome)
#Create combined datasets: 1) everyone set to med=0, and 2) everyone set to med=1
levelsofmed<-unique(d$med)
d3 <- d
d4 <- d
d3$medstar<- levelsofmed[1] #med=0
```

```
d4$medstar<- levelsofmed[2] #med=1
newmyd2<-rbind(d3, d4)

N2<-nrow(newmyd2)
newmyd2$medtemp <- newmyd2$medstar
newmyd2$out_po <- rbinom(N2, size = 1, prob=1/(1+exp(-predict(reg2, newdata=newmyd2))))
reg2_po <- glm(out_po~ as.factor(medtemp), data=newmyd2, family=binomial(link="logit"))

##Front-door adjustment
#Y=death, M=Opioid, X=Pain

#Path-specific front-door effect
newmyd1$medtemp <- newmyd1$med_po
newmyd1$po <- rbinom(N1, size = 1, prob=1/(1+exp(-predict(reg2, newdata=newmyd1))))
summary(glm(po ~ as.factor(exptemp), data=newmyd1, family=binomial(link="logit")))

#Bootstrap can be used to obtain 95% confidence intervals.
```