Universal Causal Inference in a Topos of Sheaves

Sridhar Mahadevan (Adobe Research, UMass Amherst)

NeurIPS 2025 Spotlight Paper

High-Level Intuition

- A causal intervention on a model creates a "submodel".
  - Intervening on the US economy by raising interest rates
  - Taking a pill to relieve a headache
  - Drinking red wine or eating dark chocolate as a way to improve your health
- A submodel in a Topos Causal Model (TCM) is defined by a subobject classifier Ω
- Causality is defined "locally" on a sheaf, and then "glued" together to discover what is globally j-stable
  - `oecd.org` is the Organization for Economic Cooperation and Development comprising of over 100 countries
  - They publish datasets and issue guidelines that estimate the effect of causal interventions

Health Benefits of Drinking Red Wine Article

molecules

MDPI

Review

Red Wine Consumption and Cardiovascular Health

Luigi Castaldo [1,2], Alfonso Narváez [1], Luana Izzo [1], Giulia Graziani [1], Anna Gaspari [1], Giovanni Di Minno [2] and Alberto Ritieni [1,*]

[1] Department of Pharmacy, Faculty of Pharmacy, University of Naples "Federico II", Via Domenico Montesano 49, 80131 Naples, Italy; luigi.castaldo2@unina.it (L.C.); alfonsonsimon@gmail.com (A.N.); luana.izzo@unina.it (L.I.); giulia.graziani@unina.it (G.G.); annagaspari@virgilio.it (A.G.)

[2] Department of Clinical Medicine and Surgery, University of Naples "Federico II", Via S. Pansini 5, 80131 Naples, Italy; diminno@unina.it

* Correspondence: alberto.ritieni@unina.it; Tel.: +39-081-678-652; Fax: +39-081-678-107

Academic Editors: Susana M. Cardoso and Alessia Fazio
Received: 16 September 2019; Accepted: 7 October 2019; Published: 8 October 2019

check for updates

Abstract: Wine is a popular alcoholic beverage that has been consumed for hundreds of years. Benefits from moderate alcohol consumption have been widely supported by the scientific literature and, in this line, red wine intake has been related to a lesser risk for coronary heart disease (CHD). Experimental studies and meta-analyses have mainly attributed this outcome to the presence in red wine of a great variety of polyphenolic compounds such as resveratrol, catechin, epicatechin, quercetin, and anthocyanin. Resveratrol is considered the most effective wine compound with respect to the prevention of CHD because of its antioxidant properties. The mechanisms responsible for its putative cardioprotective effects would include changes in lipid profiles, reduction of insulin resistance, and decrease in oxidative stress of low-density lipoprotein cholesterol (LDL-C). The aim of this review is to summarize the accumulated evidence correlating moderate red wine consumption with prevention of CHD by focusing on the different mechanisms underlying this relationship. Furthermore, the chemistry of wine as well as chemical factors that influence the composition of the bioactive components of red wine are also discussed.

Keywords: red wine; resveratrol; polyphenols; alcohol; cardioprotective; antioxidants

1. Introduction

Coronary heart disease (CHD) and stroke are the leading causes of mortality, disability, and death in developed countries [1]. Most CHDs are due to atherosclerosis, a degenerative

Democritus Causal Summary

Top-Tier Causal Claim:

- Moderate red wine consumption reduces the risk of cardiovascular disease by enhancing endothelial function and increasing HDL cholesterol levels.

Democritus Causal Summary

Top-Tier Causal Claim:

- Moderate red wine consumption reduces the risk of cardiovascular disease by enhancing endothelial function and increasing HDL cholesterol levels.
- Supported by: Association between moderate red wine intake and longevity; Definition and historical origins of the French paradox; Reduced risk of atherosclerosis through improved endothelial function; french paradox; moderate red wine consumption

Democritus Causal Summary

Top-Tier Causal Claim:

- Moderate red wine consumption reduces the risk of cardiovascular disease by enhancing endothelial function and increasing HDL cholesterol levels.
- Supported by: Association between moderate red wine intake and longevity; Definition and historical origins of the French paradox; Reduced risk of atherosclerosis through improved endothelial function; french paradox; moderate red wine consumption

More Speculative Causal Claim:

- Improved endothelial function due to moderate red wine intake influences vascular health by enhancing nitric oxide bioavailability.

Democritus Causal Summary

Top-Tier Causal Claim:

- Moderate red wine consumption reduces the risk of cardiovascular disease by enhancing endothelial function and increasing HDL cholesterol levels.
- Supported by: Association between moderate red wine intake and longevity; Definition and historical origins of the French paradox; Reduced risk of atherosclerosis through improved endothelial function; french paradox; moderate red wine consumption

More Speculative Causal Claim:

- Improved endothelial function due to moderate red wine intake influences vascular health by enhancing nitric oxide bioavailability.
- Supported by: Reduced risk of atherosclerosis through improved endothelial function

Theory of Sheaves

- A *sheaf* is a *data structure* attached to a mathematical object.
- For example, suppose we are given a topological space defined by a set S and a collection of subsets $\mathcal{U} = \{U | U \subseteq S\}$ called "open sets", such that $\bigcup_i U = S$ forms a "cover".
- Any finite intersection $\bigcap_i U$ should be an "open" set as well, and any arbitrary union $\bigcup_i U$ should also be open.
- Now, imagine we "attach" a Transformer T_U object to each open set U.
- Now, if two open sets U and V intersect, their intersection $U \cap V$ defines an associated Transformer object $T_{U \cap V}$.
- How can we ensure that if we define a Transformer for each open set T_U, there is exactly one unique Transformer T_S for the whole space S?

Classical Do-Calculus

Definition

A **structural causal model** (SCM) is defined as the triple $\langle U, V, F \rangle$ where $V = \{V_1, \ldots, V_n\}$ is a set of *endogenous* variables, U is a set of *exogenous* variables, F is a set $\{f_1, \ldots, f_n\}$ of "local functions" $f_i : U \cup (V \setminus V_i) \to V_i$ whose composition induces a unique function F from U to V.

Definition

Let $M = \langle U, V, F \rangle$ be a causal model defined as an SCM, and X be a subset of variables in V, and x be a particular realization of X. A **submodel** $M_x = \langle U, V, F_x \rangle$ of M is the causal model $M_x = \langle U, V, F_x \rangle$, where $F_x = \{f_i : V_i \notin X\} \cup \{X = x\}$.

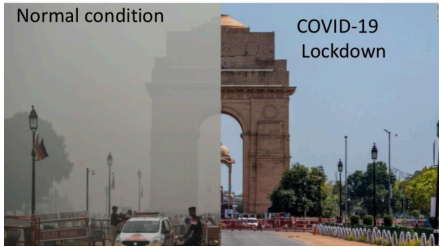
[Pearl, Causality, 2009]

Do-Calculus over Sheaves

- We can define a sheaf of SCMs by "attaching" an SCM $\mathcal{M}_i$ defined by a "local function" $f_i : U \cup (V \setminus V_i) \to V_i$
- Note Pearl's condition that the composition of local functions f_i "glue" together to form a unique global function $F : U \to V$ is exactly the sheaf condition!
- Pearl's solution was somewhat ad-hoc: force the composition to exist by defining the SCM over a directed acyclic graph (DAG) model.
- Topos causal models (TCMs) generalizes SCMs by building on the topos theory of sheaves.
- Instead of "graph surgery" (where we force some variable $X = x$), we define interventions using a "subobject classifier" in a topos.

Universal Causality (Mahadevan, Entropy, 2023)

Pollution in New Delhi, India



Categorical Framework

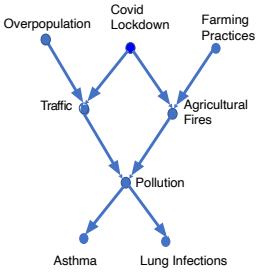
- **Objects:** Variables or Causal Models or Sheaves
- **Arrows:** Interventions or Observations
- **Diagrams:** Functors like pullback ($\bullet \to \bullet \leftarrow \bullet$) that map to concrete causal model.

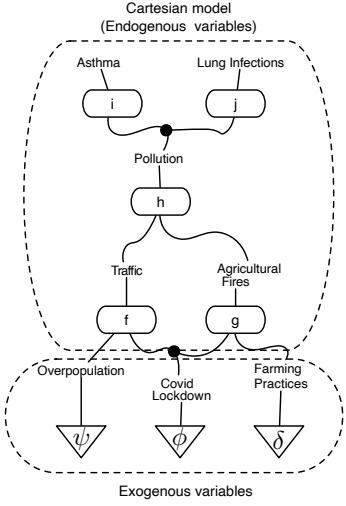
$$\mathcal{C}(\mathrm{T}, \mathrm{P}) \cong \mathbf{Nat}(\mathcal{C}(-, \mathrm{T}), \mathcal{C}(-, \mathrm{P}))$$

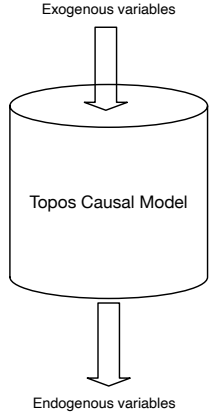
Yoneda embedding: $\mathcal{C} \mapsto \mathbf{Set}^{\mathcal{C}^{op}}$

$$\underbrace{P(\text{Pollution} \mid \text{Traffic})}_{\text{observational}} \neq \underbrace{P(\text{Pollution} \mid \mathrm{do}(\text{No-traffic}))}_{\text{interventional}}$$

Three Examples of Topos Causal Models







Judo Calculus: Intuitionistic *j*-do-calculus in TCM

Characteristic	**Classical do-calculus**	**Judo Calculus**
Logic	Causal claims are globally true or false	Intuitionistic logic: truth is *local*
Context	Uses"average" treatment effect	Local truth is "glued" together
Interventions	"Surgery" of a causal graph	Subobject classifier
Identification	Axioms define three rules	More general axiomatic framework

Table: Some of the salient differences between classical do-calculus and judo calculus.

Sridhar Mahadevan, *Intuitionistic j-do-calculus for Topos Causal Models*, Arxiv

Do-Calculus

Definition

Let M be an SCM, X be a set of variables in V, and x be a particular realization of X. The **effect** of an action $\text{do}(X = x)$ on M is given by the submodel M_x.

Definition

Let Y be a variable in V, and let X be a subset of V. The **potential outcome** of Y in response to an action $\text{do}(X = x)$, denoted $Y_x(u)$, is the solution of Y for the set of equations F_x.

Do-Calculus

1. **Rule 1 (Insertion/Deletion of Observations).** If $(Y \perp Z \mid X, W)_{G_{\bar{X}}}$, then

$$P(Y \mid \mathrm{do}(X), Z, W) \;=\; P(Y \mid \mathrm{do}(X), W).$$

2. **Rule 2 (Action/Observation Exchange).** If $(Y \perp Z \mid X, W)_{G_{\bar{X},\underline{Z}}}$, then

$$P\left(Y \mid \mathrm{do}(X), \mathrm{do}(Z), W\right) \;=\; P\left(Y \mid \mathrm{do}(X), Z, W\right).$$

3. **Rule 3 (Insertion/Deletion of Actions).** If $(Y \perp Z \mid X, W)_{G_{\bar{X},\overline{Z(W)}}}$, then

$$P\left(Y \mid \mathrm{do}(X), \mathrm{do}(Z), W\right) \;=\; P\left(Y \mid \mathrm{do}(X), W\right).$$

Universal Causality

Definition

A **universal property** of an object $c \in C$ in a category C is expressed by a representable functor F together with a universal element $x \in Fc$ that defines a natural isomorphism $C(-, c) \simeq F$. The collection of morphisms $C(-, c)$ into an object c is called the **presheaf**, and from the Yoneda Lemma, forms a universal representation of the object.

Theorem

Causal Reproducing Property: *All causal influences between any two objects c and d can be derived from its presheaf functor objects, namely*

$$\mathbf{Hom}_{\mathcal{C}}(c, d) \simeq \mathbf{Nat}(\mathbf{Hom}_{\mathcal{C}}(-, c), \mathbf{Hom}_{\mathcal{C}}(-, d))$$

Universal Causality

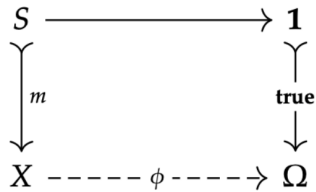
Theorem

Universality of Diagrams in UC: *In the functor category of presheaves* $\mathbf{Set}^{\mathcal{C}^{op}}$, *every functor object* F *is the colimit of a diagram of representable objects, in a canonical way.*

Topos Causal Models

- The category $\mathcal{C}_{\mathcal{TCM}}$ of topos causal models is defined as a collection of objects $c \in \mathcal{C}_{\mathcal{TCM}}$.
  - each object is a triple $\langle U, V, F \rangle$ where $V = \{V_1, \ldots, V_n\}$ is a set of *endogenous* variables, U is a set of *exogenous* variables, and F is a function from U to V.
- The arrows $\mathcal{C}_{\mathcal{TCM}}(c, d)$ are defined through commutative diagrams, where f and f' are the global functions induced by the TCM objects c and d, respectively, such that $d \circ f = f' \circ c$.
- A submodel $c' = \langle U', V', F' \rangle$ of c is any subobject of c. The effect of an intervention on c is given by some submodel c'.
- Finally, let Y be a variable in V, and let X be a subset of V. The potential outcome in response to an intervention on X modeled by a submodel $c' \hookrightarrow c$ is the solution of Y in the submodel c'.

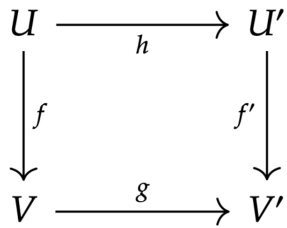
Causal Interventions as Subobject Classifiers



- A **subobject classifier** is a $\mathcal{C}$-object Ω, and a $\mathcal{C}$-arrow **true** : $\mathbf{1} \to \Omega$, such that to every monic arrow $S \hookrightarrow X$ in $\mathcal{C}$, there is a unique arrow ϕ that forms the above pullback square.
- Example: The Covid-19 causal intervention of **No-Traffic** produces a *subobject* of the original causal model of pollution in New Delhi, India.

Structural Causal Models are Topos Causal Models

- A **topos** is a category that is *Cartesian closed*, has a *terminal object*, and has a *subobject classifer*.
- A structural causal model $\mathcal{M}$ (SCM) defines a unique function $F : U \to V$ from *exogenous* variables into *endogenous variables*
- SCMs forms a topos, where each object is an SCM model $\langle U, V, F \rangle$, and arrows are given by *commutative diagrams*:



The Topos of Directed Graphs

As we saw earlier in the semester, any directed graph can be defined as a set-valued functor.
Let us define the category Γ as consisting of two objects N and A, and two non-identity arrows $s : N \to A$ and $t : N \to A$.

$$N \underset{t}{\overset{s}{\rightrightarrows}} A$$

The presheaf category $\mathbf{Sets}^{\Gamma^{op}}$ is now the category of graphs. Each object in this category is a specific graph.

[Vigna, A Guided Tour in the Topos of Graphs, Arxiv]

Why is the Topos of Graphs a Topos?

- See Vigna's Arxiv paper for a detailed proof.
- The empty graph is the initial object denoted as 0, where $0(N) = \emptyset$ and $0(A) = \emptyset$
- The single node graph is the terminal object $\mathbf{1}$, where $\mathbf{1}(N) = \mathbf{1}(A) = \bullet$
- Products of graphs $G \times H$ is simply defined as the graph whose node set is $G(N) \times H(N)$, and the edge set is defined as $(x, y) \to (x', y')$ if there is an edge $x \to y$ in G and an edge $x' \to y'$ in H.
- In a presheaf category, limits and colimits are computed "locally" over each object.

Representable Functors in the Topos of Graphs

Recall that a representable functor in a category $\mathcal{C}$ is defined as a set-valued functor $\mathcal{C}(-, c)$. So, for our topos of graphs, we have two representable functors:

$$\Gamma(-, N) \qquad \Gamma(-, A)$$

Note $\Gamma(N, N) = \{\mathbf{1}_N\}$, and $\Gamma(A, N) = \emptyset$.

Also, $\Gamma(N, A) = \{s, t\}$ and $\Gamma(A, A) = \{\mathbf{1}_A\}$

We can succinctly denote this by $s \overset{A}{\rightarrow} t$

Subobject Classifier in the Topos of Graphs

Since $\mathbf{Sets}^{\Gamma^{op}}$ is a presheaf category, it is a topos by a general result shown in Mac Lane and Moerdkik's book (Sheaves in Logic and Geometry: An Introduction to Topos Theory).

The exponential object Y^X in the presheaf category $\mathbf{Sets}^{\mathcal{C}^{op}}$ is defined as

$$Y^X(Z) = \mathrm{Nat}(\mathcal{C}(-, Z) \times X, Y) = \mathbf{Sets}^{\mathcal{C}^{op}}(\mathcal{C}(-, Z) \times X, Y)$$

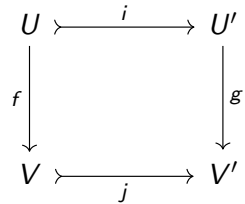
The subobject classifier for the general presheaf category $\mathbf{Sets}^{\mathcal{C}^{op}}$ is given as

$$\Omega(X) = \{S | S \text{ is a subobject of } \mathcal{C}(-, X))\}$$

SCMs are TCMs

Theorem

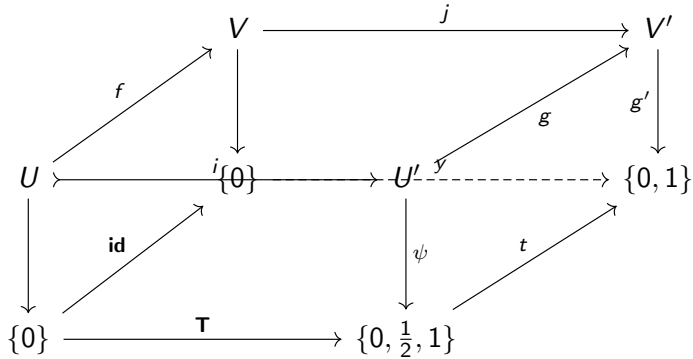
The category $\mathcal{C}_{\mathcal{SCM}}$ forms a topos.



An element $x \in U'$, which is a particular realization of the exogenous variables in U', can be classified in three ways by defining a characteristic function ψ:

1. $x \in U$ – here we set $\psi(x) = \mathbf{1}$.
2. $x \notin U$ but $g(x) \in V$ – here we set $\psi(x) = \frac{\mathbf{1}}{\mathbf{2}}$.
3. $x \notin U$ and $g(x) \notin V$ – we denote this by $\psi(x) = \mathbf{0}$.

Subobject Classifier for SCMs



Universal Property of Topos Causal Models

1. A causal model is a functor that maps from a structure domain category to a semantic co-domain category
2. **Structure Category:** Examples include symmetric monoidal categories with a "copy-delete" comonoidal structure on each object (aka Markov category)
3. **Semantics Category:** Examples include **Prob**, where objects are measurable spaces, and arrows are measure-preserving maps.

Theorem

Any causal functor $F : \mathcal{C} \to \mathcal{E}$ from a structural causal category $\mathcal{C}$ (such as a Markov category) to a semantic cocomplete category $\mathcal{E}$ (such as **Prob***) factors uniquely through a TCM structure defined by the Yoneda embedding.*

Grothendieck Topology

Definition

A **sieve** for any object x in any (small) category $\mathcal{C}$ is a subobject of its Yoneda embedding $\mathcal{C}(-, x)$. If S is a sieve on x, and $h : y \to x$ is any arrow in category $\mathcal{C}$, then

$$h^*(S) = \{g \mid \mathrm{cod}(g) = D, hg \in S\}$$

Definition

A **Grothendieck topology** on a category $\mathcal{C}$ is a function J which assigns to each object x of $\mathcal{C}$ a collection $J(x)$ of sieves on x such that

1. the maximum sieve $t_x = \{f | \mathrm{cod}(f) = x\}$ is in $J(x)$.
2. If $S \in J(x)$ then $h^*(S) \in J(y)$ for any arrow $h : y \to x$.
3. If $S \in J(x)$ and R is any sieve on x, such that $h^*(R) \in J(y)$ for all $h : y \to x$, then $R \in J(C)$.

Sheaves and Sites

Definition

A **site** is defined as a pair $(\mathcal{C}, J)$ consisting of a small category $\mathcal{C}$ and a Grothendieck topology J on $\mathcal{C}$.

Definition

The **subobject classifier** Ω is defined on any topos $\mathbf{Sets}^{\mathcal{C}^{op}}$ as subobjects of the representable functors:

$$\Omega(x) = \{S | S \text{ is a subobject of } \mathcal{C}(-, x)\}$$

and the morphism $\mathbf{true} : 1 \to \Omega$ is $\mathbf{true}(x) = x$ for any representable x.

Causal Functors

Definition

A causal functor $F : \mathcal{C} \to \mathbf{Prob}$ maps from a general symmetric monoidal category $\mathcal{C}$ with a comonoidal "copy-delete" structure to the category of probability spaces **Prob**, where each object $(\Omega, \mathcal{F}, \mathbb{P})$ is a probability space, and the arrows are measure-preserving maps, namely $\mathbf{Prob}(c, d)$, where $c = (\Omega_c, \mathcal{F}_c, \mathbb{P}_c)$ and $d = (\Omega_d, \mathcal{F}_d, \mathbb{P}_d)$, where $f \in \mathbf{Prob}(c, d)$ is such that $\mathbb{P}_c(f^{-1}(A)) = \mathbb{P}_d(A)$ for all $A \in \mathcal{F}_d$.

Theorem

The symmetric monoidal category **Prob** *has all colimits of non-empty diagrams.*

TCMs are Universal

Theorem

Any causal functor $F : \mathcal{C} \to \mathcal{E}$ from a structural causal category $\mathcal{C}$ (such as a Markov category) to a semantic cocomplete category $\mathcal{E}$ (such as **Prob***) factors uniquely through a TCM structure defined by the Yoneda embedding.*

Lawvere-Tierney Topology

Definition (Lawvere–Tierney topology)

Let $\mathcal{E}$ be an elementary topos with subobject classifier Ω. A *topology* on $\mathcal{E}$ is a Lawvere–Tierney topology $j : \Omega \to \Omega$ satisfying:

$$j(\top) = \top, \qquad j(p \wedge q) = j(p) \wedge j(q), \qquad j(j(p)) = j(p),$$

where $\top =$ **true**

Topos Causal Models define an internal intuitionistic logic

- The internal language of a TCM is intuitionistic (constructive): law of the excluded middle does not hold.
- The semantics of the logic is defined by a topology on the arrows:
  - *Grothendieck topology*: open sets map to *sieves*
  - *Lawvere-Tierney topology*: specified by a modal operator $j : \Omega \to \Omega$ on the subobject classifier that defines "local" truth.
- **Syntax:** defined by the Mitchell-Bénabou Language
- **Semantics:** defined by Kripke-Joyal possible worlds

Rules of Judo Calculus

Each premise means: there exists a j-cover $\mathcal{S} = \{S_i \to U\}_i$ such that the stated CI holds on *every* chart S_i after the indicated graph surgery.

[j-Rule 1: insert/delete observations]

$$\Big(Y \perp Z \mid X, W \text{ in } \mathcal{G}_{\overline{X}} \text{ on a } j\text{-cover of } U\Big) \implies \mathrm{P}(y \mid \mathrm{do}(x), z, w) = \mathrm{P}(y \mid \mathrm{do}(x), w).$$

[j-Rule 2: action/observation exchange]

$$\Big(Y \perp Z \mid X, W \text{ in } \mathcal{G}_{\overline{X},\underline{Z}} \text{ on a } j\text{-cover of } U\Big) \implies \mathrm{P}(y \mid \mathrm{do}(x), \mathrm{do}(z), w) = \mathrm{P}(y \mid \mathrm{do}(x), z, w).$$

[j-Rule 3: insert/delete actions]

$$\Big(Y \perp Z \mid X, W \text{ in } G_{\overline{X},\overline{Z(W)}} \text{ on a } j\text{-cover of } U\Big) \implies \mathrm{P}(y \mid \mathrm{do}(x), \mathrm{do}(z), w) = \mathrm{P}(y \mid \mathrm{do}(x), w).$$

Decentralized Causal Discovery in Judo Calculus

- A significant advantage of judo calculus is that it is *sheaf*-based and highly decentralized.
- A J-cover $\mathcal{S} = \{ V_i \hookrightarrow U \}_{i=1}^{E}$ turns a global causal discovery problem into E *independent* subproblems plus a light-weight aggregation. This matches a map–reduce pattern:

$$\underbrace{\textsc{Discover}(U)}_{\text{pooled}} \quad \rightsquigarrow \quad \{ \underbrace{\textsc{Discover}(V_i)}_{\text{per-env/chart}} \}_{i=1}^{E} \text{ then } \underbrace{\textsc{Glue}(\{A_i\})}_{j\text{-aggregation}}.$$

- Preliminary Experiments with j-stable GES, ψ-FCI and DCDI show significant benefits of TCM framework.

  Sridhar Mahadevan, *Decentralized Causal Discovery in Judo Calculus*, Arxiv

Experimental Results with TCM-enabled Methods

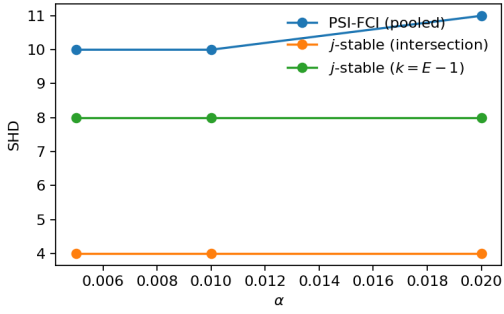


Figure: j-stable ψ-FCI outperforms pooled version by a wide margin.

Experimental Results with TCM-enabled Methods

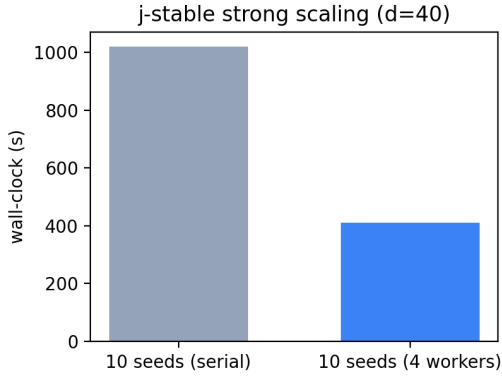


Figure: *j*-stable DCDI scales far better than standard DCDI.

Combining Multiple Causal Studies

molecules

MDPI

Review

Red Wine Consumption and Cardiovascular Health

Luigi Castaldo [1,2], Alfonso Narváez [1], Luana Izzo [1], Giulia Graziani [1], Anna Gaspari [1], Giovanni Di Minno [2] and Alberto Ritieni [1,*]

1 Department of Pharmacy, Faculty of Pharmacy, University of Naples "Federico II", Via Domenico Montesano 49, 80131 Naples, Italy; luigi.castaldo2@unina.it (L.C.); alforsonsimon@gmail.com (A.N.); luana.izzo@unina.it (L.I.); giulia.graziani@unina.it (G.G.); annagaspari@virgilio.it (A.G.)

2 Department of Clinical Medicine and Surgery, University of Naples "Federico II", Via S. Pansini 5, 80131 Naples, Italy; diminno@unina.it

* Correspondence: alberto.ritieni@unina.it; Tel.: +39-081-678-652; Fax: +39-081-678-107

Academic Editors: Susana M. Cardoso and Alessia Fazio
Received: 16 September 2019; Accepted: 7 October 2019; Published: 8 October 2019

check for updates

Abstract: Wine is a popular alcoholic beverage that has been consumed for hundreds of years. Benefits from moderate alcohol consumption have been widely supported by the scientific literature and, in this line, red wine intake has been related to a lesser risk for coronary heart disease (CHD). Experimental studies and meta-analyses have mainly attributed this outcome to the presence in red wine of a great variety of polyphenolic compounds such as resveratrol, catechin, epicatechin, quercetin, and anthocyanin. Resveratrol is considered the most effective wine compound with respect to the prevention of CHD because of its antioxidant properties. The mechanisms responsible for its putative cardioprotective effects would include changes in lipid profiles, reduction of insulin resistance, and decrease in oxidative stress of low-density lipoprotein cholesterol (LDL-C). The aim of this review is to summarize the accumulated evidence correlating moderate red wine consumption with prevention of CHD by focusing on the different mechanisms underlying this relationship. Furthermore, the chemistry of wine as well as chemical factors that influence the composition of the bioactive components of red wine are also discussed.

Keywords: red wine; resveratrol; polyphenols; alcohol; cardioprotective; antioxidants

1. Introduction

Coronary heart disease (CHD) and stroke are the leading causes of mortality, disability, and death in developed countries [1]. Most CHDs are due to atherosclerosis, a degenerative process of the arteries which is triggered by oxidative stress and chronic inflammatory status [2,3]. Smoking, arterial hypertension, hypercholesterolemia, diabetes mellitus, overweight/obesity, lack of physical activity, and genetic factors are known to play a role in determining cardiovascular risk [4].

Although excessive alcohol intake is associated with the development of chronic diseases and other serious problems, a wealth of data from scientific evidence support an inverse relationship between moderate alcohol consumption and the risk of CHD [5]. Moderate alcohol consumption is defined in the Dietary Guidelines for Americans 2015–2020 as up to one unit of alcohol per day for

biomedicines

MDPI

Review

Resveratrol: A Double-Edged Sword in Health Benefits

Bahare Salehi [1,2], Abhay Prakash Mishra [3], Manisha Nigam [4], Bilge Sener [5], Mehtap Kilic [5], Mehdi Sharifi-Rad [6,*], Patrick Valere Tsouh Fokou [7,*], Natália Martins [8,9,*] and Javad Sharifi-Rad [10,11,*]

1 Medical Ethics and Law Research Center, Shahid Beheshti University of Medical Sciences, Tehran 88777539, Iran; bahar.salehi0078@gmail.com
2 Student Research Committee, Shahid Beheshti University of Medical Sciences, Tehran 22439789, Iran
3 Department of Pharmaceutical Chemistry, H. N. B. Garhwal (A Central) University, Srinagar Garhwal 246174, Uttarakhand, India; abhayapharmachem@hnbgu@gmail.com
4 Department of Biochemistry, H. N. B. Garhwal (A Central) University, Srinagar Garhwal 246174, Uttarakhand, India; m.nigam@hnbgu.ac.in
5 Gazi University Faculty of Pharmacy Department of Pharmacognosy, Ankara 06330, Turkey; bilgesener11@gmail.com (B.S.); klcmehtap89@gmail.com (M.K.)
6 Department of Medical Parasitology, Zabol University of Medical Sciences, Zabol 61663335, Iran
7 Antimicrobial and Biocontrol Agents Unit, Department of Biochemistry, Faculty of Science, University of Yaounde 1, Ngoa Ekelle, Annex Fac. Sci, P.O. Box. 812, Yaounde-Cameroon
8 Faculty of Medicine, University of Porto, Alameda Prof. Hernâni Monteiro, Porto 4200-319, Portugal
9 Institute for Research and Innovation in Health (i3S), University of Porto, Porto 4200-135, Portugal
10 Phytochemistry Research Center, Shahid Beheshti University of Medical Sciences, Tehran 11369, Iran
11 Department of Chemistry, Richardson College for the Environmental Science Complex, The University of Winnipeg, Winnipeg, MB R3B 2G3, Canada
* Correspondence: mehdi_sharifrad@yahoo.com (M.S.-R.); tsouh80@yahoo.fr (P.V.T.S.); ncmartins@med.up.pt (N.M.); javad.sharifirad@gmail.com (J.S.-R.); Tel.: +98-54-322-51-790 (M.S.-R.); +237-675623503 (P.V.T.F.); +35-12-2551-2100 (N.M.); +98-21-8820-0164 (J.S.-R.)

Received: 14 August 2018; Accepted: 7 September 2018; Published: 9 September 2018

check for updates

Abstract: Resveratrol (3,5,4′-trihydroxy-trans-stilbene) belongs to polyphenols' stilbenoids group, possessing two phenol rings linked to each other by an ethylene bridge. This natural polyphenol has been detected in more than 70 plant species, especially in grapes' skin and seeds, and was found in discrete amounts in red wines and various human foods. It is a phytoalexin that acts against pathogens, including bacteria and fungi. As a natural food ingredient, numerous studies have demonstrated that resveratrol possesses a very high antioxidant potential. Resveratrol also exhibit antitumor activity, and is considered a potential candidate for prevention and treatment of several types of cancer. Indeed, resveratrol anticancer properties have been confirmed by many in vitro and in vivo studies, which shows that resveratrol is able to inhibit all carcinogenesis stages (e.g., initiation, promotion and progression). Even more, other bioactive effects, namely as anti-inflammatory, anticarcinogenic, cardioprotective, vasorelaxant, phytoestrogenic and neuroprotective have also been reported. Nonetheless, resveratrol application is still being a major challenge for pharmaceutical industry, due to its poor solubility and bioavailability, as well as adverse effects. In this sense, this review summarized current data on resveratrol pharmacological effects.

Keywords: resveratrol; physiological effects; pharmacological activity; antioxidant; anticancer; antimicrobial

1. Introduction

Among many phytochemicals, phytoestrogens have been reported to contain several bioactive molecules, mostly found in soy, vegetables and fruits. These compounds can be classified into four main

cSQL: Causal Databases

Property	RAG Systems	Knowledge Graphs	IE Pipelines	cSQL
Primary goal	Answer generation	Structured facts	Entity / relation extraction	Causal analysis
Input	Text chunks	Curated triples	Annotated text	Unstructured documents
Schema	None (implicit)	Predefined ontology	Fixed schema	**Induced from discourse**
Causality support	None	Implicit / informal	Pairwise only	**Weighted causal relations**
Uncertainty	None	Rare / ad hoc	None	**Aggregated model support**
Conflicting claims	Not supported	Manual resolution	Not supported	**Preserved and quantified**
Compositionality	Prompt-based	Limited graph traversal	Limited	**SQL joins and aggregations**
Counterfactuals	No	No	No	**Supported via causal structure**
Output format	Generated text	Graph database	Triples / tables	**Relational causal database**
Execution model	Neural inference	Symbolic querying	Batch extraction	**Deterministic SQL**

cSQL Query Semantics

- **Backbone extraction:** Identify the most credible causal relations by ordering edges by `score_sum`.
- **Causal hubs:** Identify nodes with large outgoing score mass.
- **Downstream influence:** Join edges transitively to analyze multi-step causal paths.
- **Disagreement analysis:** Compare `score_max` and `score_mean` to detect fragile claims.

Pullback definition (hard equality)

The pullback object is

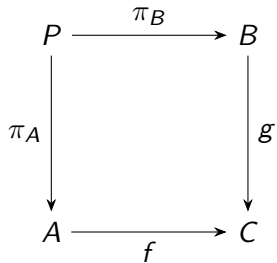
$$P = A \times_C B = \{(a, b) \in A \times B \ : \ f(a) = g(b)\}.$$

It comes with projections:

$$\pi_A : P \to A, \quad \pi_B : P \to B,$$

such that the square commutes:

$$f \circ \pi_A = g \circ \pi_B.$$



Soft pullback reconciliation: resveratrol ⇒ mitochondrial biogenesis

Soft pullback consensus (A $\times_C$ B):

rel	src	dst	score_joint
INCREASES	resveratrol	mitochondrial biogenesis ...	6.892

Witness evidence (top focus patches):

Atlas A: Cardiovascular Health (PMC6804046)

- **25.15** (r=3) Antioxidant effects of resveratrol on cellular aging
- **8.86** (r=2) Attenuation of cardiac fibrosis via TGF-β/Smad signaling inhibition
- **8.42** (r=2) Resveratrol and polyphenol-mediated cardioprotective pathways in red wine
- **8.42** (r=3) Enhancement of endothelial function and nitric oxide bioavailability

Atlas B: Resveratrol review (PMC6164842)

- **26.07** (r=2) Anti-inflammatory effects of resveratrol
- **25.70** (r=1) Resveratrol
- **25.63** (r=2) Resveratrol pharmacological effects
- **25.26** (r=2) Anti-inflammatory effects and cytokine modulation

Takeaway: Soft pullback glues two atlases and returns both the aligned claim and auditable provenance.

Soft pullback reconciliation: resveratrol ⇒ endothelial function

Soft pullback consensus (A $\times_C$ B):

rel	src	dst	score_joint
INCREASES	resveratrol	endothelial function ...	4.305

Witness evidence (top focus patches):

Atlas A: Cardiovascular Health (PMC6804046)

- **8.86** (r=2) Attenuation of cardiac fibrosis via TGF-β/Smad signaling inhibition
- **8.42** (r=2) Resveratrol and polyphenol-mediated cardioprotective pathways in red wine
- **8.42** (r=3) Enhancement of endothelial function and nitric oxide bioavailability
- **7.98** (r=3) Resveratrol's anti-inflammatory effects through NF-κB and TNF-α suppression

Atlas B: Resveratrol review (PMC6164842)

- **25.63** (r=2) Resveratrol pharmacological effects
- **24.82** (r=3) Age-related inflammation (inflammaging) and resveratrol's anti-inflammatory efficacy
- **24.78** (r=2) Improvement in insulin sensitivity and glucose metabolism
- **24.37** (r=3) Cardioprotective effects and endothelial function improvement

Takeaway: Soft pullback recovers a shared mechanism and provides auditable witnesses from both atlases.

Tylenol/Paracetomol Useage during Pregnancy

Prenatal paracetamol exposure and child neurodevelopment: a systematic review and meta-analysis

Francesca D'Antonio*, Maria Elena Flacco*, Lorenza Della Valle, Smriti Prasad, Lamberto Manzoli, Athina Samara, Asma Khalil

Summary

Background Concerns have emerged about the impact of paracetamol use in pregnancy on child neurodevelopment, particularly in relation to autism spectrum disorder. We aimed to synthesise available evidence to investigate associations between prenatal paracetamol exposure and autism spectrum disorder, attention-deficit hyperactivity disorder (ADHD), and intellectual disability.

Methods For this systematic review and meta-analysis, we searched MEDLINE, Embase, ClinicalTrials.gov, and the Cochrane Library from inception to Sept 30, 2025, for cohort studies reporting adjusted estimates of the risk of autism spectrum disorder, ADHD, and intellectual disability. Eligible studies used validated questionnaires or medical records to define outcomes, reported maternal comorbidities and treatments, and compared pregnancies with and without paracetamol exposure, whereas unadjusted studies were excluded. Quality assessment of the included studies was conducted using the Quality In Prognosis Studies (QUIPS) tool. The primary outcomes were the associations between prenatal paracetamol exposure and the likelihood of autism spectrum disorder, ADHD, and intellectual disability. Analyses were restricted to sibling-comparison studies with adjusted estimates, and odds ratios (OR) were calculated. Random-effects meta-analyses used the generic inverse variance method. Subgroup analyses were performed when possible (trimester, duration of use, offspring sex, and follow-up length). This study was registered with PROSPERO, CRD42025156690.

Findings 43 studies were included in the systematic review, and 17 studies in the meta-analysis. When considering sibling comparison studies, paracetamol exposure during pregnancy was not associated with the risk of autism spectrum disorder (OR 0·98, 95% CI 0·93–1·03; p=0·45), ADHD (0·95, 0·86–1·05; p=0·31), or intellectual disability (0·93, 0·69–1·24; p=0·63). There was also no association between paracetamol intake during pregnancy and autism spectrum disorder (OR 1·03, 95% CI 0·86–1·23; p=0·78), ADHD (0·97, 0·89–1·05; p=0·49), or intellectual disability (1·11, 0·92–1·34; p=0·28) when considering only studies at low risk of bias according to QUIPS. This absence of association persisted when considering all studies with adjusted estimates and those with more than 5 years of follow-up.

Interpretation Current evidence does not indicate a clinically important increase in the likelihood of autism spectrum disorder, ADHD, or intellectual disability in children of pregnant individuals who use paracetamol as directed, supporting existing recommendations on its safety.

Funding None.

The Lancet

Lancet Obstet Gynaecol Womens Health 2026

Published Online January 18, 2026 https://doi.org/10.1016/S3059-5018(25)00211-0

See Online/Comment https://doi.org/10.1016/S3059-5018(25)00212-2

*Joint first authors

Center for Fetal Care and High-Risk Pregnancy, University of Chieti, Chieti, Italy (F D'Antonio PhD); Department of Environmental and Preventive Sciences, University of Ferrara, Ferrara, Italy (M E Flacco PhD); Fetal Medicine Unit, Liverpool Women's University Hospital, University of Liverpool, Liverpool, UK (L D Valle MBBS, Prof A Khalil FRCOG); Fetal Medicine Unit, Department of Obstetrics and Gynaecology (S Prasad MRCOG, Prof A Khalil) and Vascular Biology Research Centre, Molecular and Clinical Sciences Research Institute (Prof A Khalil), St George's University Hospitals NHS Foundation Trust, London, UK; Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy (L Manzoli PhD); Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden (A Samara PhD); Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden (A Samara); FUTURE, Centre for Functional Tissue Reconstruction, Department of Biotechnology, University of Oslo, Oslo, Norway (A Samara)

Correspondence to: Prof Asma Khalil, Fetal Medicine Unit, Department of Obstetrics and Gynaecology, St George's University Hospitals NHS Foundation Trust, London SW17 0QT, UK **asma.khalil@stgeorges.nhs.uk**

Introduction

Paracetamol, or acetaminophen, is the most commonly used analgesic and antipyretic during pregnancy, recommended globally as a first-line option for pain relief and fever reduction. Its safety profile is generally more favourable than that of non-steroidal anti-inflammatory drugs and opioids, making it the preferred choice in obstetric care.[1,2] However, concerns have arisen regarding its potential impact on child neurodevelopment, including conditions such as autism spectrum disorder.[3-5]

The public debate gained traction in September, 2025, when the US Government suggested that prenatal exposure to paracetamol might contribute to autism, citing a review linking acetaminophen use in pregnancy to neurodevelopmental outcomes.[6,7] This review was more limited by data variability and significant differences in how studies defined exposure and outcomes. Despite these concerns, major professional organisations, such as the American College of Obstetricians and Gynecologists (USA) and the Royal College of Obstetricians and Gynaecologists (UK), continue to endorse the safe use of paracetamol during pregnancy when used appropriately.[8,9]

Conflicting findings in the literature stem from variability in evaluating neurodevelopmental outcomes and the timing of acetaminophen use.[10-13] A 2024 meta-analysis[14] suggested small associations between prenatal paracetamol exposure and increased risks of autism spectrum disorder and attention-deficit hyperactivity disorder (ADHD), but these were often based on studies prone to biases. More rigorous studies, including a

---

No Link Between Acetaminophen in Pregnancy and Autism, a New Study Finds

The review looked at more than three dozen studies and found no evidence that acetaminophen increased the risk of neurodevelopmental disorders in children.

Listen to this article · 6:00 min Learn more

Share full article

Justin Sullivan/Getty Images

By Azeen Ghorayshi

Published Jan. 16, 2026 Updated Jan. 17, 2026, 12:29 p.m. ET

A scientific review of 43 studies on acetaminophen use during pregnancy concluded that there was no evidence that the painkiller increased the risk of autism or other neurodevelopmental disorders.

"We found no clinically important increase in the risk of autism, A.D.H.D. or intellectual disability," Dr. Asma Khalil, a professor of obstetrics and maternal fetal medicine at St. George's Hospital,

Soft pullback reconciliation: Tylenol/paracetamol ⇒ neurodevelopment

Soft pullback consensus edge (NYT $\times_C$ Lancet):

`acetaminophen use during pregnancy INCREASES risk of neurodevelopmental disorders in offspring`

(sim = 100.0, score_joint = 7.294, LCMs: NYT=14, Lancet=20)

Witness evidence (top focus patches):

Atlas A (NYT)

- 6.897 (r=3) Placental transfer and fetal exposure to acetaminophen
- 6.011 (r=3) Pharmacokinetics of acetaminophen during pregnancy
- 5.125 (r=3) Potential association between prenatal acetaminophen and neurodevelopmental outcomes
- 6.011 (r=3) acetaminophen use in pregnancy

Atlas B (Lancet meta-analysis)

- 11.484 (r=2) Mechanisms of paracetamol crossing the placental barrier
- 11.041 (r=3) Maternal factors influencing paracetamol metabolism during pregnancy
- 11.041 (r=2) Interaction between prenatal paracetamol and genetic susceptibility
- 10.598 (r=2) Dose-response relationships in prenatal paracetamol use

Takeaway: Hard pullback fails on surface form differences; soft pullback glues mechanistically aligned claims (placental transfer, exposure, and downstream neurodevelopment).

Pushout witnesses: merged evidence for a glued claim

Glued claim (origin = AB):

`resveratrol INCREASES mitochondrial biogenesis`

Top provenance witnesses from the merged support table:

Atlas B (Resveratrol review)

- 26.070 (r=2) anti-inflammatory effects of resveratrol
- 25.703 (r=1) resveratrol
- 25.627 (r=2) resveratrol pharmacological effects
- 25.259 (r=3) Enhancement of mitochondrial biogenesis and energy metabolism

Atlas A (Cardiovascular health)

- 25.146 (r=3) Antioxidant effects of resveratrol on cellular aging

Point: After pushout gluing, the reconciled atlas retains auditable witnesses across sources for the same consensus mechanism.

Pushout witnesses: resveratrol ⇒ endothelial function

Glued claim (origin = AB):

`resveratrol INCREASES endothelial function` (AB:11156366169706253341)

Top provenance witnesses (shown per atlas):

Atlas A (Cardiovascular health)

- 8.420 (r=3) Enhancement of endothelial function and nitric oxide bioavailability
- 8.420 (r=2) Resveratrol and polyphenol-mediated cardioprotective pathways in red wine
- 7.977 (r=3) Resveratrol's anti-inflammatory effects through NF-κB and TNF-α suppression

Atlas B (Resveratrol review)

- 25.627 (r=2) resveratrol pharmacological effects
- 24.373 (r=3) Cardioprotective effects and endothelial function improvement
- 24.816 (r=3) Age-related inflammation (inflammaging) and resveratrol's anti-inflammatory efficacy

Note: `score_raw` scales may differ across atlas builds; the key point is merged, auditable provenance for the same glued claim.

Subobject classifier Ω for causal claims

Idea (topos intuition). A *subobject* is a selected subset of claims (e.g., "consensus claims"). A *subobject classifier* assigns each claim a truth-value: $\chi : \texttt{pushout\_edges} \to \Omega$. Here Ω is a small set of qualitative truth values computed from provenance and match quality.

Practical Ω (4-valued):

- **CONSENSUS**: glued AB edge with high similarity (e.g., sim ≥ 90)
- **WEAK_CONSENSUS**: glued AB edge but weaker match (sim < 90)
- **A_ONLY**, **B_ONLY**: study-specific claims

Ω value	# edges
A_ONLY	298
B_ONLY	266
CONSENSUS	1
WEAK_CONSENSUS	1

Takeaway: χ turns a merged causal atlas into a logic-valued object: we can query the *CONSENSUS subobject* (equalizer) or inspect disagreements systematically.

Summary

- Topos Causal Models (TCM) introduce a new framework for causal inference.
- Causal interventions are modeled as *subobjects* and induce an intutionistic *j*-do calculus (aka "judo" calculus)
- Judo calculus has an axiomatic set of rules for drawing inferences.
- Preliminary experimental results show significant benefits of judo calculus over classical do-calculus
- Sridhar Mahadevan, "Intutionistic *j*-do-calculus for Topos Causal Models (Arxiv)
- Sridhar Mahadevan, "Decentralized Causal Discovery with Judo Calculus" (Arxiv)