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DOCTORADO EN SALUD PÚBLICA

UNIVERSIDAD DE CHILE
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EXPOSICIÓN AL ARSÉNICO INORGÁNICO Y EL ÍNDICE DE MASA CORPORAL: ESTUDIO DE COHORTE RETROSPECTIVA EN NIÑOS DE ARICA

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Profesora Guía: Dra. Verónica Iglesias Álamos

Análisis de factores de riesgo y situación de salud

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Resumen

Introducción: La ciudad de Arica se ubica en una zona geográfica donde el arsénico se distribuye de manera natural en el agua. Además, la población ha estado expuesta involuntariamente a tóxicos ambientales, entre ellos arsénico de origen antropogénico. La exposición temprana al arsénico es un factor de riesgo para varios trastornos en la infancia, que a su vez pueden derivar en enfermedades crónicas posteriores e incluso un mayor riesgo de mortalidad. Se ha planteado que la inflamación, el estrés oxidativo y la modificación epigenética podrían ser mecanismos biológicos que explican cómo la exposición al arsénico influye en el desarrollo de trastornos metabólicos. Estos mismos mecanismos podrían también estar relacionados con la aparición de obesidad en la niñez, por lo que se ha propuesto que la exposición prenatal al arsénico esté asociada con un mayor z score del índice de masa corporal infantil.

Objetivo: Evaluar la asociación entre la exposición prenatal al arsénico inorgánico y el z score del índice de masa corporal en niños de Arica.

Métodos: Esta tesis abordó dos componentes. En primer lugar, se realizó una revisión sistemática de la literatura en PubMed y Scopus hasta diciembre de 2024, siguiendo las directrices PRISMA (Preferred reporting items for systematic reviews and meta-analyses) y el marco PECO (Population, Exposure, Comparator, and Outcome). Se incluyeron estudios observacionales que midieron la exposición al arsénico durante el embarazo o la infancia y presentaron desenlaces antropométricos. El riesgo de sesgo se evaluó utilizando la herramienta de la Office of Health Assessment and Translation (OHAT), considerando 10 preguntas distribuidas en 7 dominios.

En segundo lugar, se constituyó una cohorte retrospectiva en base a datos secundarios de dos estudios. El primero “Prevalencia de arsénico en gestantes y plomo en recién nacidos del Hospital Dr. Juan Noé Crevani, Arica 2013-2016” realizado por la SEREMI

de Salud Arica y Parinacota evaluó a 1644 binomios gestantes-recién nacidos. De esta base se obtuvo la información de la concentración prenatal de arsénico en orina. El segundo estudio corresponde al proyecto FONIS “Exposición a arsénico y su asociación con citoquinas proinflamatorias en niños nacidos entre 2013 y 2016 en la ciudad de Arica”. Este es un estudio de diseño transversal que utilizó una muestra de 451 de los 1644 binomios gestantes-recién nacidos. De este estudio se obtuvo información del z score del índice de masa corporal (IMC) para la edad de los niños. Ambos estudios proporcionaron datos sobre covariables sociodemográficas y de salud. Para evaluar la asociación entre la exposición prenatal al arsénico y el z score del IMC, se ajustaron modelos de regresión lineal. Adicionalmente, se aplicó el enfoque de ponderación inversa de la probabilidad de exposición (IPTW) para ajustar por variables confusoras basales.

Resultados: La revisión sistemática incluyó 26 estudios, de los cuales siete reportaron asociaciones estadísticamente significativas entre la exposición al arsénico y desenlaces antropométricos como peso, talla y puntajes z. Estos estudios fueron principalmente cohortes prospectivas, con mediciones de arsénico en orina y ajuste adecuado por variables de confusión. Sin embargo, la mayoría no encontró asociación. La evaluación de la exposición se basó frecuentemente en una única medición sin especiación para diferenciar las formas orgánicas e inorgánicas del arsénico, y sin mediciones repetidas que permitan capturar variaciones a lo largo del tiempo. Asimismo, se identificaron diferencias en las matrices biológicas utilizadas, en los desenlaces antropométricos evaluados y en las edades de seguimiento, lo que dificulta la comparación directa de los resultados entre estudios y podría explicar parte de la heterogeneidad observada. La cobertura geográfica fue limitada, concentrándose la mayoría de las investigaciones en Asia del Sur, con pocos estudios en América Latina o la región Asia-Pacífico.

En el análisis de la cohorte, la mediana de edad de los niños fue de 8 años (IQR: 7–8), y la mediana de concentración prenatal de arsénico fue 16 µg/L (IQR: 10–23). Se identificó que el 4,7% de los niños estaban en riesgo de desnutrición o desnutridos, y el 33,3% fueron clasificados como obesos. Tras ajustar por el IMC materno, etnia, nivel educacional y edad materna, se encontró una asociación inversa entre el arsénico inorgánico urinario prenatal y el z score del IMC infantil (β= -0,20; IC 95%: -0,37; -0,03). Los modelos ajustados por IPTW mostraron un efecto similar, con un promedio ponderado de los estimadores β para cada quintil de exposición (β= -0,18; IC 95%: -0,26; -0,09), lo que refuerza la evidencia de una asociación negativa entre la exposición prenatal al arsénico y el crecimiento infantil.

Conclusión: Esta tesis aporta evidencia complementaria sobre la relación entre la exposición temprana al arsénico y el crecimiento infantil. La revisión sistemática no encontró una asociación concluyente entre la exposición al arsénico durante la etapa prenatal y postnatal y las medidas antropométricas en la infancia, aunque los estudios de mayor calidad metodológica tendieron a mostrar asociaciones en dirección negativa. Por su parte, el análisis de la cohorte retrospectiva en Arica mostró que una mayor exposición prenatal a arsénico inorgánico se asoció de forma inversa con el z score del IMC infantil, en contraste con la hipótesis inicial de un efecto positivo. En conjunto, estos hallazgos sugieren que la exposición prenatal al arsénico podría influir de manera compleja en el metabolismo y el crecimiento de los niños, posiblemente favoreciendo trayectorias de menor ganancia ponderal en la infancia. Se requieren estudios longitudinales con mediciones repetidas de la exposición y especiación de arsénico para comprender mejor esta asociación y orientar estrategias de prevención en poblaciones vulnerables.

1. Introducción

El desarrollo de la obesidad es atribuible a una serie de factores de riesgo cuyo mecanismo inicial es un desbalance energético positivo producto de la interacción entre factores ambientales y predisposición genética [1]. En las últimas décadas, se ha reconocido que este proceso puede originarse desde etapas tempranas del desarrollo [2], cuando las exposiciones prenatales pueden modular la programación metabólica del feto, alterando de manera permanente los mecanismos de regulación energética [3]. Así, la susceptibilidad a desarrollar obesidad a lo largo de la vida comienza en la etapa prenatal, donde se han identificado diversos factores de riesgo como el IMC de la madre [4], la ganancia de peso durante el embarazo [5], la diabetes gestacional [6], la exposición al humo de tabaco y a contaminantes ambientales [7].

El arsénico es un contaminante que se encuentra distribuido de manera natural en el ambiente y es motivo de preocupación por su toxicidad y potencial de exposición [8]. En su forma inorgánica, tiene la capacidad de incorporarse al organismo a través del agua de bebida, los alimentos y el polvo ambiental. Una vez ingerido, la exposición intrauterina al arsénico inorgánico ocurre dada su capacidad de circular a través de la placenta de la madre al feto. [9] La evidencia disponible sugiere una relación inversa entre la exposición prenatal al arsénico y el crecimiento fetal, reportándose resultados que lo asocian con mayor riesgo de mortalidad fetal e infantil, parto prematuro, disminución del peso al nacer [10-13] y con menor crecimiento postnatal [14-16].

Sin embargo, a diferencia de lo reportado en estudios previos, en el norte de Chile y en el sur de Perú se han descrito resultados que sugieren un efecto distinto del arsénico sobre el crecimiento fetal. En Arica, estudios realizados en embarazadas han mostrado

que mayores concentraciones de arsénico urinario se asocian con un mayor peso al nacer [17, 18], hallazgo también descrito en Tacna, Perú [19]. Estos resultados, junto con la alta prevalencia de obesidad infantil observada en Arica [20], plantean la posibilidad de que en este contexto el arsénico podría estar relacionado con un aumento del IMC en la infancia, más que con una restricción del crecimiento.

El rol del arsénico en la obesidad infantil ha sido poco estudiado. La mayor parte de la evidencia se ha centrado en la exposición al arsénico y su relación con el deterioro de indicadores de crecimiento infantil [14-16, 21-24]. En cambio, los estudios que han evaluado específicamente su asociación con un mayor IMC no han reportado resultados concluyentes [25-29]. Aunque se ha descrito una relación entre la exposición al arsénico y un mayor perímetro de brazo y de cintura [30], considerados indicadores de exceso de adiposidad, esta evidencia proviene de un único estudio transversal, lo que impide establecer si el arsénico ejerce un rol causal en la obesidad.

Entre los posibles mecanismos de acción del arsénico sobre la obesidad, se encuentran la formación de especies reactivas de oxígeno y la producción de citoquinas proinflamatorias, que pueden desencadenar una disfunción metabólica generalizada, resultando en la acumulación de tejido adiposo [31, 32]. Asimismo, se ha postulado que la exposición al arsénico en el útero podría inducir alteraciones fisiológicas permanentes que alteran el metabolismo de los lípidos y la producción hormonal, lo que a su vez podría dar lugar a fenotipos de obesidad caracterizados por aumento de masa grasa corporal e intolerancia a la glucosa [33]. Estas alteraciones epigenéticas y metabólicas proveen una base biológica para vincular la exposición prenatal a arsénico con un mayor IMC en la infancia, además de explicar la relación entre la exposición prenatal al arsénico y el desarrollo de enfermedades crónicas en la vida adulta [34].

La exposición al arsénico en el norte de Chile ha sido bien documentada, siendo el agua potable la principal fuente de exposición [35-37]. En particular, en la ciudad de Arica, la preocupación por la exposición al arsénico se originó por la presencia de 20.901 toneladas de residuos tóxicos (barros con contenido metálico) abandonados en la zona industrial de la ciudad en la década de los 80, sector donde años más tarde se construyeron viviendas sociales [38]. Estudios realizados previamente en Arica han descrito que la exposición al arsénico no se asocia significativamente con vivir en el sitio contaminado sino más bien con el consumo de agua potable [39, 40]. Asimismo, se ha reportado la exposición temprana al arsénico [41] e incluso existe evidencia de los efectos de la exposición en la salud en niños de Arica [42-44].

Los antecedentes expuestos junto con la alta prevalencia de obesidad infantil observada en Arica [20], plantean la hipótesis de que, en este contexto, el arsénico podría actuar como un factor de riesgo que favorece un mayor índice de masa corporal en la infancia, en lugar de restringir el crecimiento**.** Dado que se cuenta con datos de dos estudios transversales realizados de manera independiente, el primero conducido desde la Secretaría Regional Ministerial de Arica y Parinacota (SEREMI) entre los años 2013 y 2016 (n= 1667), y el segundo, un proyecto FONIS realizado durante el 2023 que consideró una submuestra de 451 niños del primer estudio, existe una oportunidad única para evaluar esta hipótesis mediante un diseño de cohorte retrospectiva que considere la exposición prenatal al arsénico inorgánico y el z score del índice de masa corporal, en niños de Arica.

En adelante, se presenta el marco conceptual de la tesis que resume las principales características del arsénico, sus fuentes de exposición, los métodos para estimar la

exposición, su toxicocinética e impacto en la salud humana, en particular, sobre el índice de masa corporal en la niñez. Esta sección concluye con la justificación de la investigación. Luego, se plantea la pregunta de investigación, hipótesis, objetivos y los métodos propuestos para llevar a cabo el estudio. A continuación, se presentan los resultados en formato manuscrito y una discusión final.

2. Marco teórico

2.1 Arsénico

El arsénico (As) es un metaloide presente en el medio ambiente que puede existir en cuatro estados de oxidación -3, 0, 3 y 5, cuyas formas se clasifican en orgánicas e inorgánicas. Los compuestos orgánicos del arsénico mantienen enlaces unidos a carbono e hidrógeno y las formas más comunes son la arsenobetaína, la arsenocolina, arsenoazúcares y arsenolípidos. Mientras, las formas inorgánicas incluyen al arsenito (As^{III}) y al arseniato (As^{V}), los cuales presentan estados de valencia 3 y 5, respectivamente. Ambas formas se consideran tóxicas para el ser humano y se encuentran en rocas, suelo y agua, siendo el As^{V} la forma con mayor predominio en el medio ambiente [45].

El arsénico forma parte de la corteza terrestre, aunque su concentración es baja, es un elemento ubicuo [45]. En general, el arsénico inorgánico se encuentra unido a minerales de sulfuro, óxidos y oxihidróxidos metálicos que constituyen las rocas, y su liberación al medio ambiente puede ocurrir por procesos geogénicos como la oxidación de sulfuros, erosión, adsorción y lixiviación. Estos procesos dependen de reacciones naturales como la meteorización, el clima, la actividad biológica, tectónica y volcánica [46].

También, la exposición al arsénico inorgánico puede ocurrir mediante actividades antropogénicas como la minería, el procesamiento de combustibles fósiles, el uso de pesticidas arsenicales, la aplicación de preservantes de madera y como aditivo en la industria de alimentos de aves de corral [8]. Sin embargo, los problemas ambientales relacionados a la presencia de arsénico inorgánico en agua y suelo son originados

principalmente por factores naturales [47]. Es así que en América Latina la contaminación natural por arsénico inorgánico ocurre en su mayoría por la actividad asociada a la tectónica de placas y al vulcanismo. En particular, las zonas afectadas se concentran en los países que se ubican en el cinturón de fuego del Pacífico (Figura 1) [48]. En estas áreas, la contaminación natural de las aguas subterráneas y superficiales se debe a las condiciones reductoras y de pH que favorecen la movilización de arsénico de los sedimentos al medio acuático [49].

Figura 1. Regiones y localidades de 20 países de América Latina con concentraciones elevadas de arsénico en aguas subterráneas.

Fuente: elaboración propia en base a información de artículo de Bundschuh J et al [48].

Numerosos estudios han reportado altas concentraciones de arsénico en aguas del norte de Chile [48, 50-53], lugar que reúne las condiciones que explican la contaminación natural, pues los recursos hídricos de la zona tienen su origen en la Meseta Altiplano-Puna de los Andes Central en el que el clima árido, la actividad hidrotermal, la presencia de salares y las formaciones volcánicas afectan la calidad de las aguas subterráneas y superficiales [54].

2.2 Exposición al arsénico en Arica

La ciudad de Arica se ubica en la región más septentrional de Chile y se caracteriza por aridez extrema y bajas precipitaciones. Como es habitual en las ciudades del norte del país, los recursos hídricos dependen de las precipitaciones que ocurren en la cordillera de los Andes en época estival, de ahí nacen las principales cuencas hidrográficas; los ríos San José y Lluta, que abastecen los suministros de agua potable de la ciudad de Arica y tienen una alta demanda en la zona rural tanto para el consumo como para la actividad agrícola. Otras cuencas de la región utilizadas para la actividad agropecuaria y, en menor medida para el consumo, son las Altiplánicas y Río Camarones [55].

En cuanto a la caracterización de la concentración de arsénico en agua proveniente de las cuencas de la región, un estudio del año 2021, analizó 90 muestras de las cuencas Altiplánicas, Camarones, Lluta y San José; entre sus hallazgos, el 72% contenía concentraciones de arsénico sobre el umbral establecido por la Organización Mundial de la Salud (OMS) de 0,01 mg/L, siendo el As^{V} la especie dominante. Asimismo, en muestras de agua destinadas para el consumo humano, el 44% presentó concentraciones >0,01 mg/L, superando hasta 22 veces la norma [53].

Por su parte, en la ciudad de Arica, entre los años 1984 y 1989, ocurrió la importación de residuos mineros provenientes de Suecia, los cuales fueron depositados en terrenos destinados originalmente a actividades productivas. Luego, en la década de los 90, se construyeron conjuntos habitacionales en las cercanías de esta zona. En el año 2008, se realizó una evaluación química de los suelos urbanos de la ciudad de Arica y se encontró que el 4,1% de las muestras superaban el límite establecido por la norma holandesa de 55 mg/kg de arsénico, específicamente en el sector puerto, maestranza y junto a la zona donde fueron acumulados los residuos de Suecia, denominada Sitio F [56]. Cabe señalar que los residuos fueron trasladados y se realizó el recubrimiento del lugar [38]. Sin embargo, mediciones de muestras de suelo tomadas en el Sitio F en el año 2017 indican que la concentración de arsénico en suelo continúa siendo una preocupación, dado que la concentración del 95% del nivel superior del intervalo de confianza[1] fue de 84,27 mg/kg, valor que supera el límite de referencia utilizado (55 mg/kg) [57].

Respecto a la concentración de arsénico en agua potable, la SEREMI de Salud de Arica y Parinacota detectó valores de arsénico superiores a 0,01 mg/L en el 45% de las muestras tomadas de distintos puntos de la ciudad durante el mes de enero de 2015. Estas muestras correspondían al suministro de agua proveniente del estanque Cerro Chuño. Es importante destacar que este suministro abarca aproximadamente el 60% de la población de la ciudad de Arica [58].

[1] El cálculo del 95% del nivel superior de confianza del promedio [95% Upper Confidence Limit (UCL)], representa el valor por debajo del cual, con un 95% de confianza, se encuentra el verdadero valor de exposición promedio. De modo que, con un 95% de confianza, el promedio real es igual o inferior a este valor.

Pese al historial de contaminación por polimetales, la exposición al arsénico inorgánico en Arica ocurre por su presencia en agua y alimentos [39, 40]. De modo que no solo las personas que vivieron cerca de los sitios contaminados podrían resultar expuestas, sino que la exposición podría ser relevante para la población general. Además, es probable que exista un nivel constante de exposición en la población, ya que las principales fuentes de exposición tienden a no cambiar sustancialmente a lo largo del tiempo.

2.3 Metabolismo

En la población general, la exposición al arsénico inorgánico se produce en su mayoría por la ingestión de agua y alimentos. Tan pronto ingresa al organismo, más del 90% se absorbe en el sistema gastrointestinal y su metabolismo ocurre principalmente en el hígado. Básicamente, el metabolismo consiste en la biotransformación de las especies de arsénico inorgánico en metabolitos monometilados y dimetilados que son excretados fácilmente a través de la orina [8]. La vía metabólica convencional involucra reacciones alternadas de reducción y metilación oxidativa en el que participan glutatión (GSH) como agente reductor y S-adenosilmetionina (SAM) como donante de metilo. En esta vía, los metabolitos pentavalentes se reducen a compuestos monometilados y dimetilados trivalentes [59]. Por otro lado, se ha descrito una vía metabólica alternativa de metilación reductora en la que se forman complejos de As^{III} con GSH. A diferencia de la vía convencional, los metabolitos trivalentes se convierten en compuestos pentavalentes menos tóxicos (Figura 2) [60].

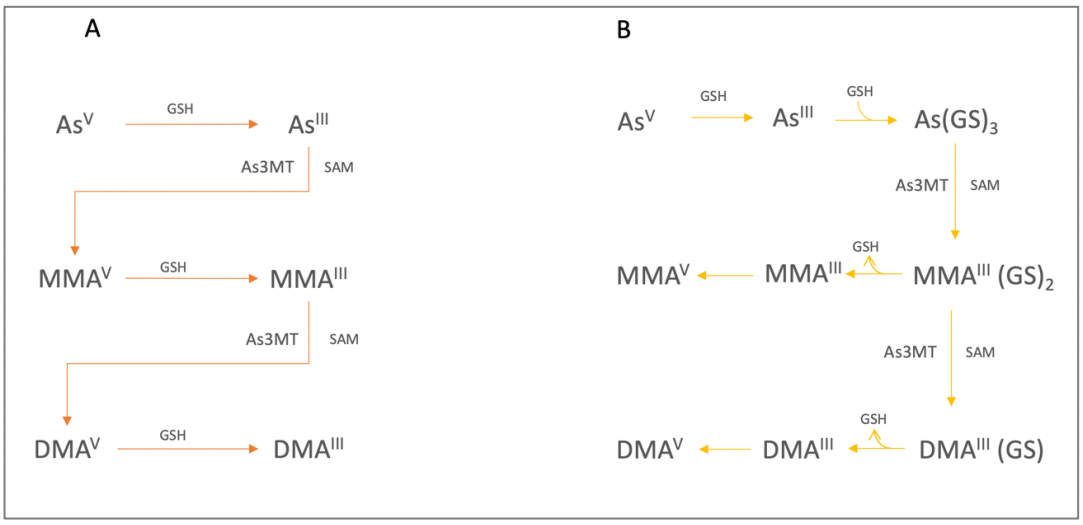


Figura 2. Vías metabólicas del arsénico inorgánico.

El arseniato (As^V) absorbido se reduce a arsenito (As^{III}). El esquema A ilustra la vía metabólica convencional de reacciones secuenciales de reducción y metilación oxidativa mediadas arsénico metiltransferasa (As3MT) que utiliza S-adenosilmetionina (SAM) como donante de metilo y glutatión (GSH) como cofactor, resultando en la metilación de As^{III} en ácido monometilarsónico (MMA^V), la reducción a ácido monometilarsenoso (MMA^{III}), la metilación a ácido dimetilarsínico (DMA^V) y la reducción a ácido dimetilarsenoso DMA^{III}. En el esquema B, el As^{III} se conjuga con GSH dando lugar al arsénico triglutation [$As(GS)_3$] que es metilado a monometilarsenodiglutation [$MMA^{III}(GS)_2$] y dimetilarsenoglutation [$DMA^{III}(GS)$], que luego se oxidan a MMA^V y DMA^V. Fuente: elaboración propia.

Independiente de la vía de metabolización, los productos finales del arsénico inorgánico se excretan en su mayoría a través de la orina; entre un 10-20% corresponde a especies de arsénico inorgánico (As^{III} y As^V), 10-20% ácido monometilarsénico (MMA) y 60-80% ácido dimetilarsénico (DMA) [61-63]. No obstante, la proporción relativa de especies de arsénico inorgánico en la orina puede variar entre individuos en función de la eficiencia de metilación, que está dada por una mayor proporción de DMA y menor de MMA [61]. Varios factores pueden influir en la eficiencia de metabolización, entre ellos, el grado de

exposición al arsénico, la edad, el sexo, características genéticas y el estado de nutrientes [64].

2.4 Biomarcadores de exposición

La concentración de arsénico en orina es el biomarcador más utilizado para aproximarse a los niveles de absorción y determinar la exposición directa. Este método permite medir la concentración total de arsénico inorgánico y sus especies (As^{III}, As^{V}, DMA y MMA). Para su determinación, se requiere de una muestra de orina que puede ser obtenida mediante la recolección durante 24 horas, la primera micción de la mañana o una muestra puntual [65].

Para estimar la exposición concurrente, se ha descrito que la concentración de arsénico en orina no varía sustancialmente entre los diferentes métodos de obtención de muestras [66-68]. Incluso, la variabilidad de la concentración de arsénico en muestras puntuales recolectadas en días consecutivos en un mismo individuo es baja en relación con la variabilidad entre individuos [66, 69]. También se ha observado que los patrones de metilación intraindividual se mantienen estables durante largos periodos [62, 70]. Por ejemplo, en un estudio de seguimiento de 10 años, se encontró que la proporción relativa de especies de arsénico (%MMA y %DMA) medidas en tres ocasiones en 60 sujetos se mantuvo constante. Se observó que la mayor parte de la variabilidad en los patrones de metilación se debió a las diferencias entre los sujetos, con un coeficiente de correlación intraclase (ICC) de 0,80 para %MMA y 0,77 para %DMA, lo que sugiere que la eficiencia de metilación podría estar influenciada por factores que se mantienen estables en el tiempo [62].

Además de obtener la fracción de especies de arsénico inorgánico, las muestras puntuales de orina presentan la ventaja de ser de fácil obtención en comparación con los otros métodos. Sin embargo, es necesario controlar por la variabilidad asociada a la hidratación que puede influir en la dilución de arsénico en orina [71]. En general, se utiliza la concentración de creatinina urinaria como método de ajuste de la dilución de dos maneras: al dividir la concentración de arsénico por la concentración de creatinina urinaria (expresada como arsénico en µg/gramo de creatinina), o incorporando la creatinina como covariable independiente en el modelo de asociación. Estos enfoques asumen que la tasa de excreción de creatinina en la orina es constante, lo que implica que las concentraciones de creatinina y de arsénico en orina estarían diluidas proporcionalmente en individuos bien hidratados [71]. No obstante, se ha descrito que los niveles de creatinina varían de acuerdo a la edad, sexo, etnia, composición corporal y la función renal, por lo tanto, ambos enfoques pueden dar lugar a estimaciones sesgadas cuando la variable de interés está relacionada con la concentración de creatinina [71-73].

Otros métodos de ajuste de la concentración de arsénico en orina incluyen la osmolalidad, la gravedad específica y la tasa de flujo urinario. La osmolalidad y la gravedad específica cuantifican la cantidad de partículas disueltas en la orina y se utilizan como divisor de la concentración de arsénico en orina o como una covariable independiente en el modelo de asociación [71]. Aunque se consideran medidas de dilución más robustas que la concentración de creatinina, ambos indicadores están relacionados con la composición corporal y la función renal [73, 74], lo que puede resultar en asociaciones espurias cuando estas variables son respuestas de interés. Por su parte, la tasa de flujo urinario, que mide la cantidad de orina producida durante un periodo de tiempo específico (volumen de orina/tiempo entre micciones), se puede utilizar multiplicándola por la concentración de arsénico o como una covariable independiente en el modelo de

asociación [71]. Sin embargo, este método tiene la limitación de depender del autorreporte de los sujetos sobre el intervalo de tiempo entre micciones, lo que puede carecer de precisión en estudios epidemiológicos y, en particular, en estudios que involucren a niños [73].

Por lo anterior, se ha propuesto un método denominado estandarización ajustada por covariables que efectúa la corrección de dilución de biomarcadores de exposición tomando en cuenta las relaciones causales entre la exposición, la creatinina u otro biomarcador y el resultado en salud mediante el uso de grafos acíclicos dirigidos (DAG) [75, 76]. Este método consta de dos etapas, primero se modela la creatinina en escala logarítmica en función de las variables que afectan a la creatinina definidas en un marco causal usando DAG, así se obtienen los valores ajustados o predichos de creatinina. Luego, se dividen los valores observados por los valores ajustados de creatinina para estimar la razón de creatinina, que representa el efecto residual de la hidratación sobre la creatinina [72]. La razón de creatinina se utiliza como denominador de la concentración de arsénico en orina, lo que permite obtener una medida ajustada por dilución para evaluar su efecto en salud [72, 73].

También, es viable determinar la concentración de arsénico en muestras de sangre, aunque debido al corto periodo de circulación en esta matriz, solo se utiliza para cuantificar exposiciones agudas. Este método permite obtener la concentración total de arsénico, incluyendo la fracción inorgánica, pero no es posible el análisis de las especies de arsénico a bajos niveles de exposición [65, 77]. En los últimos años, se ha propuesto el análisis de muestras de saliva como un método para el monitoreo biológico de arsénico, que tiene la característica de ser menos invasivo, de fácil obtención y presenta una buena correlación con la concentración total de arsénico en orina [78]. Sin embargo, la

cuantificación de las especies de arsénico es imprecisa, por ello no es un método adecuado para evaluar la fracción inorgánica o la capacidad de metilación [79].

Por otro lado, para evaluar la exposición prolongada al arsénico, se pueden utilizar muestras de pelo y uñas, que tienen la característica de ser tejidos ricos en queratina, lo que resulta en la acumulación de arsénico por su afinidad a los grupos sulfhidrilo. Además, tanto en el pelo como en las uñas, es posible obtener las fracciones de arsénico inorgánico especiado. No obstante, se requiere una cantidad de muestra suficiente (>500 mg) [80], sobre todo para la especiación, lo que es difícil de alcanzar cuando se evalúan niños [81]. Otra limitación de esta matriz es la contaminación por exposición externa, es decir, el arsénico que no ingresó al organismo y que se adhiere al cabello por contacto directo con agua o suelo contaminado con arsénico [65].

2.5 Exposición al arsénico y efectos en salud

Históricamente se reconoce al arsénico inorgánico como un potente veneno, la dosis letal aguda para humanos se ha estimado en 0,6 mg/kg/día. Los signos y síntomas de la exposición aguda son principalmente gastrointestinales: vómitos, dolor abdominal y diarrea, lo que resulta en una deshidratación severa e hipovolemia que conduce a la insuficiencia circulatoria [8].

Sin embargo, la preocupación por el arsénico se debe a su presencia en el medio ambiente y su gran potencial de exposición humana. En ese sentido, se destacan tres importantes cuerpos de evidencia epidemiológica de arsenicosis endémica con gran impacto en la salud de la población. La primera evidencia se reportó en la costa suroeste de Taiwán, lugar en que se observó una alta prevalencia de cáncer de piel y de

enfermedad cardiovascular periférica, conocida como enfermedad de pie negro, cuya principal complicación es la amputación de las extremidades afectadas. Este fenómeno se observó en habitantes que utilizaban agua de pozos artesianos con concentraciones de arsénico entre 0,1 y 1,82 mg/L [82]. Otros efectos identificados de la exposición al arsénico incluyen el cáncer de pulmón, de vejiga e hígado [83] cardiopatía isquémica [84], ateroesclerosis [85], diabetes e hipertensión [86-88].

Una segunda fuente importante de evidencia proviene de los estudios realizados en la ciudad de Antofagasta, norte de Chile, donde el cambio en las fuentes de obtención de agua potable trajo consigo una alta exposición al arsénico, con concentraciones de hasta 0,8 mg/L. Esto derivó en la aparición temprana de trastornos respiratorios y cardiovasculares [89, 90], así como en un aumento del 24% de la tasa de mortalidad infantil [12]. Además, se observó un incremento en la mortalidad por cáncer de pulmón, vejiga y riñón incluso después de 40 años de haber interrumpido la exposición al arsénico [91]. También, se ha reportado una mayor posibilidad de desarrollar diabetes e hipertensión en la población afectada [92, 93].

Luego, la evidencia proveniente de estudios realizados en Bangladesh, donde la instalación de pozos entubados con el objetivo de prevenir la transmisión de enfermedades gastrointestinales derivadas del consumo de aguas superficiales, resultó en una exposición a altos niveles de arsénico en más de la mitad de su población [94]. Numerosos estudios han reportado un mayor riesgo de lesiones cutáneas [95, 96], enfermedades cardiovasculares [97], diabetes mellitus [98-100], problemas respiratorios [101-103], déficit cognitivo [104, 105] y exceso de mortalidad [106-108] en las personas expuestas a niveles elevados de arsénico.

La amplia evidencia de estudios epidemiológicos realizados en Taiwán, Chile, Bangladesh y otros países con altos niveles de arsénico de origen natural [109-112], han demostrado que la exposición se asocia con una amplia variedad de enfermedades crónicas. La Agencia Internacional para la Investigación del Cáncer (IARC) clasifica al arsénico inorgánico (As^{III} y As^{V}) como un cancerígeno (grupo 1), debido a la suficiente evidencia en humanos que establece que la exposición causa cáncer de pulmón, vejiga y de piel, además de estar relacionado con cáncer de riñón, hígado y próstata. Asimismo, la IARC clasificó los metabolitos DMA y MMA como posibles cancerígenos para los humanos (grupo 2B) [113].

Por su parte, se ha observado de manera consistente que la exposición crónica al arsénico inorgánico también se asocia con resultados no cancerígenos, como las enfermedades cardiovasculares y la diabetes mellitus, que son muy prevalentes en la actualidad [114]. Aunque establecer relaciones causales es difícil debido a la presencia de múltiples factores de confusión [115], los resultados de estudios que utilizaron metodología de metaanálisis han demostrado que el arsénico incrementa el riesgo de padecer estas enfermedades [116, 117].

2.5.1 Exposición prenatal al arsénico y salud infantil

El arsénico atraviesa la barrera placentaria [9] y la evidencia señala una asociación entre la exposición prenatal y riesgo de aborto espontáneo, muerte fetal, mortalidad neonatal e infantil y bajo peso al nacer [118]. La exposición materna al arsénico se asocia con una disminución del peso al nacer, de la longitud al nacer y del perímetro cefálico [119, 120], aunque también se han reportado resultados contradictorios [13, 120]. En un estudio de cohorte en Estados Unidos, se observó una disminución del perímetro cefálico asociado

a la concentración de arsénico inorgánico en la orina materna; sin embargo, en los niños encontraron una asociación positiva con la longitud al nacer [121]. Otro estudio realizado en Tacna, Perú, reveló que las gestantes que residían en los distritos con mayor concentración de arsénico en agua potable (> 0,1 mg/L) presentaron una prevalencia más baja de recién nacidos pequeños para la edad gestacional (8,03%) comparado con los distritos de concentración ≤ 0,01 mg/L (11,5%) [19].

La exposición prenatal al arsénico se ha asociado con marcadores de la función endotelial en recién nacidos [122], con cardiopatía congénita [123] y con una mayor susceptibilidad a infecciones respiratorias en la infancia [124]. Otros efectos de la exposición intrauterina al arsénico incluyen la disminución de la función pulmonar [125] y del coeficiente intelectual [104]. Además, la exposición prenatal se ha asociado con el retraso de la edad de la menarquía en niñas [126], así como con niveles elevados de testosterona en niños y, durante el periodo de seguimiento, con una progresión más lenta de la maduración sexual en los niños [127].

Incluso, se ha establecido una asociación entre la concentración de arsénico en orina medida durante el embarazo (µg/L) y un incremento en la presión arterial sistólica (β 3,69 mmHg; IC 95%: 0,74; 6,63) y diastólica (β 2,91 mmHg; IC 95%: 0,41; 5,42) en niños de 4,5 años de edad [128]. Asimismo, en adolescentes entre 14 y 17 años, la concentración de arsénico en orina materna, utilizada como proxy de exposición durante la infancia temprana (un año antes del nacimiento hasta <5 años de edad), se asoció con el aumento de la presión arterial sistólica (β 0,7 mmHg; IC 95%: 0,05; 1,4), siendo este efecto mayor (β 1,6; IC 95%: 0,6; 2,6) en los adolescentes con un IMC sobre la mediana (> 17,7 kg/ mt^2) [129].

Por lo tanto, el IMC podría actuar como un factor modificador en la relación entre la exposición prenatal al arsénico y la presión arterial en adolescentes. Estos hallazgos también se han observado en población adulta, incluyendo otros resultados metabólicos [93, 130, 131]. La amplia evidencia que respalda el efecto del arsénico sobre enfermedades cardiovasculares y metabólicas ha llevado a plantear la hipótesis de que la exposición al arsénico podría tener un efecto en el exceso de peso, dado que los mecanismos patológicos del arsénico sobre aquellas enfermedades también podrían influir en el desarrollo de obesidad [132]. No obstante, la relación entre la exposición al arsénico y el índice de masa corporal en población infantil ha sido poco explorada, y los resultados obtenidos hasta ahora no han sido concluyentes [21, 23-26, 30, 133].

2.5.2 Exposición prenatal al arsénico y el índice de masa corporal infantil

El índice de masa corporal (IMC) es una medida antropométrica que se utiliza en la evaluación del estado nutricional, el cual se define como el estado fisiológico de un individuo derivado del balance entre los requerimientos nutricionales y la ingesta de nutrientes [134]. Este indicador se calcula a partir de la razón entre el peso (gramos) y la estatura al cuadrado (metros). El diagnóstico del estado nutricional se realiza mediante la comparación de la medida individual con el patrón de crecimiento específico para la edad y sexo, que han sido desarrollados tanto por la Organización Mundial de la Salud como por los Centros para el Control y la Prevención de Enfermedades (CDC) [135, 136]. La malnutrición infantil, que abarca el riesgo de desnutrir, la desnutrición, el sobrepeso y la obesidad, se asocia con un mayor riesgo de morbilidad y mortalidad [137, 138].

Después del nacimiento, el IMC experimenta un rápido incremento, alcanzando su punto máximo entre los 6 y 12 meses de edad. Luego, entre los 4 y 6 años de edad, desciende

hasta su punto mínimo y vuelve a aumentar [139]. Un rápido crecimiento implica que estas variaciones de las trayectorias del IMC ocurren antes y, se ha demostrado, que los niños con bajo peso al nacer experimentan un rápido crecimiento en la primera infancia y, posteriormente, un mayor porcentaje de grasa corporal y obesidad en la niñez [140]. Además, el rápido crecimiento y la obesidad durante la infancia también se observa en los recién nacidos con mayor tamaño al nacer [141]. Esta dinámica está influenciada por factores prenatales como la obesidad materna y la diabetes gestacional [142], y se postula que la exposición prenatal al arsénico también podría ejercer un rol mediante la modificación epigenética [143].

La mayoría de los estudios se han centrado en evaluar los efectos de la exposición prenatal al arsénico en el deterioro del crecimiento pondoestatural en la infancia. Un estudio de cohorte en zonas rurales de Bangladesh reveló una disminución del peso y la estatura alcanzados a los 2 años de edad, asociada con la exposición pre y postnatal al arsénico. Sin embargo, tras el ajuste, las asociaciones se mantuvieron solo en las niñas con un OR de 1,57 (IC 95% 1,02; 2,40) para bajo peso y un OR de 1,58 (IC 95% 1,05; 2,37) para retraso del crecimiento en el cuarto quintil de exposición postnatal (46-96 µg/L), en comparación con el quintil de menor exposición (< 16 µg/L) [16].

Posteriormente, cuando los niños de esta cohorte fueron medidos a los 5 años de edad, no se encontró una asociación entre la exposición prenatal al arsénico y el deterioro del crecimiento. Sin embargo, se observó una diferencia en el peso a los 5 años de edad en los niños expuestos al arsénico (concurrente) por encima del percentil 95 de -0,33kg (IC 95% -0,60; -0,06), en comparación con los niños con menor exposición (percentil 5 o menos). Por su parte, se observaron asociaciones positivas y significativas entre el porcentaje de MMA y todas las medidas antropométricas [14]. Según los autores, estos

resultados contradictorios tendrían relación con la hipótesis de que los niños con mejores trayectorias de crecimiento tendrían mayor requerimiento de grupos metilos para el crecimiento y por ello, la disponibilidad para la metilación de MMA para formar DMA estaría limitada [14]. Resultados en esa misma dirección, también se observaron en un estudio de cohorte en Estados Unidos, donde la concentración del logaritmo natural de arsénico inorgánico en orina prenatal, se asoció con un leve aumento en las medidas repetidas de longitud de los niños hasta el primer año de edad (β 0,05; IC 95%: 0,00; 0,09) [144].

En cambio, la evidencia sobre los efectos del arsénico prenatal en la obesidad es limitada. En una cohorte de niños españoles expuestos a arsénico en orina total prenatal, no se observó una asociación con el z score del IMC en los niños a los 7 años de edad (β= -0,01; IC 95%: -0,29; 0,26) y (β= -0,05; CI 95%: -0,34; 0,24) para el segundo y tercer, respectivamente) [25]. De forma similar, en una cohorte de niños mexicanos no se evidenció asociación entre el arsénico en sangre prenatal y el z score del IMC medido entre los 4 y 6 años de edad (β= 0,04; IC 95%: -0,18; 0,26) [26]. De igual manera, en una cohorte estadounidense, no se halló relación entre el arsénico en eritrocitos maternos y el z score del IMC a los 3 años (β= -0,01; IC 95%: -0,05; 0.04), 8 años (β= 0,03; IC 95%: -0,03; 0,08), y 13 años (β= -0,03; IC 95%: -0,09; 0,03) [27]. Asimismo, los estudios que evaluaron la exposición postnatal también reportaron resultados nulos: un estudio transversal en niños canadienses no encontró asociación entre DMA y obesidad en los grupos de 3–5 años (OR= 0,98; IC 95%: 0,92; 1,05) y 6–11 años (OR= 1,01; IC 95%: 0,96; 1,06) [28], y un estudio de casos y controles en España tampoco halló relación con sobrepeso/obesidad en niños de 6 a 12 años (OR= 1,17; IC 95%: 0,75; 1,82) [29].

En síntesis, la evidencia indica que el arsénico puede tener un efecto en el crecimiento infantil, aunque los resultados no son completamente claros en cuanto a la dirección de este efecto. En los estudios que analizaron distintos momentos de exposición, los efectos solo se encontraron con la exposición concurrente o fueron más pronunciados con la exposición postnatal en comparación con la exposición prenatal [14, 16]. En cuanto al IMC y la obesidad, la evidencia es escasa y, en general, no muestra asociaciones significativas ni para la exposición prenatal ni para la postnatal [25-28]. Esto podría tener relación con consideraciones metodológicas, ya que en otros eventos en la infancia se ha observado una mayor susceptibilidad tanto en la exposición prenatal al arsénico como en la primera infancia [102, 104, 124]. Además, es importante tener en cuenta que el período crítico de exposición al arsénico para el desarrollo de enfermedades a largo plazo comienza en la gestación y continúa durante la infancia temprana [34, 145], momento en que los niños alcanzan su mayor potencial de crecimiento y desarrollo.

2.5.3 Mecanismo de acción del arsénico sobre el crecimiento pondoestatural y el índice de masa corporal infantil

Durante el embarazo, la exposición al arsénico se ha asociado con marcadores de estrés oxidativo, así como con el aumento de citoquinas proinflamatorias y niveles de leptina en la placenta [146, 147]. Tales factores podrían conducir a una disfunción en el tejido placentario, afectando la capacidad de suministrar oxígeno y nutrientes al feto [146, 147 148, 149]. Además, el arsénico puede influir en el crecimiento infantil al alterar la respuesta inmunológica a través de la expresión de genes relacionados con la activación de las células T [146, 150], lo que incrementaría la susceptibilidad de los niños a infecciones que, a su vez, podrían impactar negativamente en el crecimiento [13]. Estos efectos podrían explicar una de las vías por las cuales el arsénico influye en el bajo peso al nacer y en

el crecimiento durante los primeros meses de vida [147]. Cabe señalar que el bajo peso al nacer es un factor de riesgo para desarrollar obesidad y trastornos cardio metabólicos en la vida posterior [31, 34].

Por otra parte, el arsénico podría contribuir en la fisiopatología de la obesidad por múltiples vías (Figura 3). Los estudios en modelos animales han proporcionado evidencia de los posibles mecanismos involucrados. Las revisiones de estudios experimentales han sistematizado una serie de efectos de la exposición al arsénico inorgánico sobre el riesgo de obesidad, como la disminución de expresión de la proteína perilipina en el tejido adiposo, el aumento del depósito de grasa ectópica perivascular en el músculo esquelético, la reducción de la capacidad de diferenciación de las células precursoras (preadipocitos) para convertirse en adipocitos maduros y la disminución de la expresión de la proteína transportadora de glucosa GLUT4. Además, la exposición en el útero al As^{III} se ha asociado con la disminución de los niveles de adiponectina y el aumento del peso corporal después del nacimiento [31, 130, 151].

El arsénico puede influir en el desarrollo de trastornos metabólicos mediante la modificación epigenética, como la metilación del ADN y la modificación de histonas [32]. Por ejemplo, se han observado marcas de metilación de ADN asociadas a la exposición al arsénico en el linaje materno, que se relacionan con enfermedades metabólicas de los hijos [152]. Además, la exposición temprana al arsénico se vinculó con la disminución de la expresión del gen que codifica el receptor γ activado por el proliferador de peroxisomas (PPARγ) en recién nacidos y niños. Este gen, es el principal regulador de la diferenciación de adipocitos, y la disminución de su expresión puede alterar la homeostasis y metabolismo de los lípidos, lo que puede contribuir al desarrollo de obesidad y otros trastornos metabólicos [153].

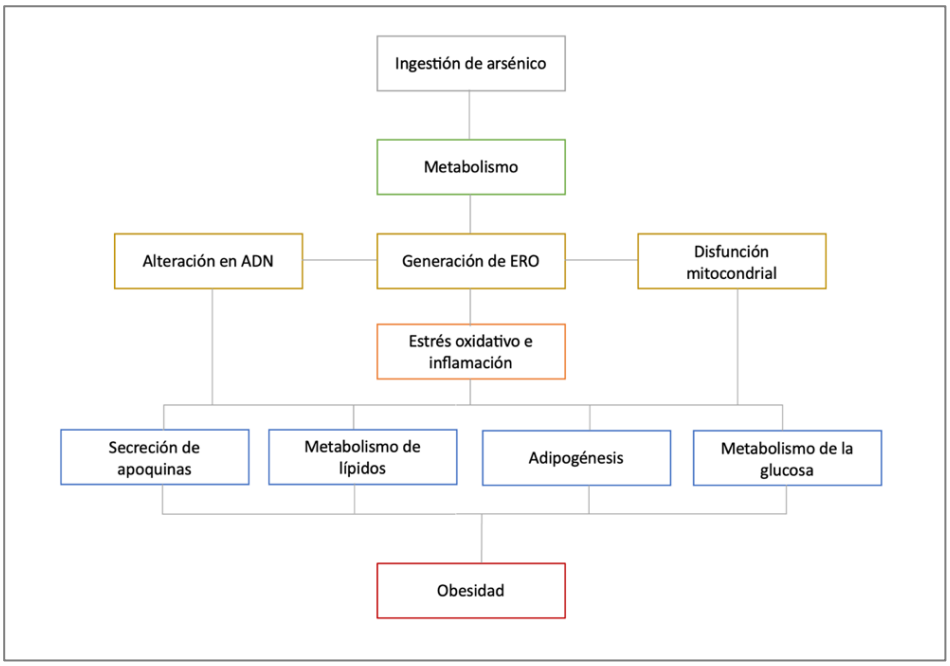


Figura 3. Posibles mecanismos de los efectos de la exposición a arsénico inorgánico en el desarrollo de obesidad.

Luego de la exposición e ingestión del arsénico ocurre un proceso metabólico que da lugar a una reacción directa en el tejido adiposo o indirecta a través de efectos moleculares y celulares que desencadena la formación de especies reactivas de oxígeno. Estas especies promueven la producción de citoquinas proinflamatorias que podrían contribuir al desarrollo de la obesidad al influir en procesos fisiopatológicos. Fuente: elaboración propia.

2.6 Contexto y justificación del estudio

La exposición al arsénico se reconoce como un problema de salud pública cuyo potencial de exposición humana está dado principalmente por su presencia en el agua potable, lo que puede dar lugar a una exposición acumulada a lo largo de la vida. La población infantil es especialmente susceptible a los efectos del arsénico, pues los

mecanismos necesarios para metabolizar y eliminar contaminantes se encuentran en desarrollo. Por ello, el efecto del arsénico sobre la disminución del crecimiento fetal e infantil ha sido ampliamente estudiado, aunque los resultados no han sido consistentes [13, 14, 16, 19, 119-121]. En cambio, la relación entre la exposición al arsénico y el aumento del IMC o la presencia de sobrepeso y obesidad en la niñez ha sido menos estudiada, y la evidencia disponible muestra resultados nulos tanto para la exposición prenatal como para la postnatal [25-29].

En este sentido, los mecanismos de acción descritos anteriormente sustentan la hipótesis de este estudio. La exposición prenatal al arsénico inorgánico podría influir en el estado nutricional infantil a través de procesos como el estrés oxidativo, el aumento de citoquinas proinflamatorias y alteraciones epigenéticas que afectan la diferenciación de adipocitos y la homeostasis lipídica [31, 151, 153]. Estas vías biológicas permiten plantear que la exposición prenatal al arsénico podría asociarse con un mayor z score del índice de masa corporal infantil.

En la actualidad, un 26% de los escolares chilenos que asisten a establecimientos educacionales financiados por el Estado presenta obesidad. La situación de los niños y niñas de Arica es similar, en donde la prevalencia de obesidad infantil es de 28,4% [20]. En relación con la exposición al arsénico, un estudio realizado en el año 2012 reveló que el 10,8% de las embarazadas tenían concentraciones de arsénico inorgánico en orina superiores a 35 µg/L, con una mediana de arsénico en orina de 14,6 µg/L [154]. Asimismo, en las embarazadas que atendieron sus partos en el Hospital de Arica entre 2013 y 2016, la mediana de arsénico inorgánico en orina fue similar (15 µg/L) [155], indicando una estabilidad en la situación de exposición a lo largo del tiempo.

Hasta ahora, las hipótesis que han guiado los estudios epidemiológicos plantean una asociación inversa entre la exposición al arsénico sobre el crecimiento infantil y el IMC de los niños. Sin embargo, estudios previos realizados en Arica con embarazadas, han mostrado que la exposición prenatal al arsénico está vinculada a un mayor peso al nacer. Por ejemplo, en el estudio que evaluó embarazadas en 2014, se identificó una asociación positiva entre la concentración de arsénico inorgánico en orina y el peso al nacer. Además, el análisis de mediación realizado en dicho estudio no mostró un efecto directo e indirecto del arsénico mediado por la edad gestacional, la edad materna y el sexo del recién nacido [17]. Por su parte, en el análisis de las embarazadas que atendieron sus partos en el Hospital de Arica entre 2013 y 2016, se observó un efecto indirecto del logaritmo natural (Ln) de arsénico en orina (µg/L) en el peso al nacer, mediado por la edad gestacional (β 49,8 gramos; IC 95%: 23,8; 75,8), aunque no se evidenció un efecto directo y total del Ln arsénico prenatal en el peso al nacer [18]. Es importante destacar que, en ambos estudios, el IMC materno al inicio del embarazo mostraba una asociación positiva tanto con la concentración prenatal de arsénico en orina como con el peso al nacer.

En base a lo expuesto, en esta tesis se propuso evaluar la asociación entre la exposición prenatal al arsénico inorgánico y el z score del índice de masa corporal en niños entre 7 y 10 años de edad de Arica. Se empleó un enfoque alternativo para controlar la confusión que podría ser causada por el IMC materno al inicio del embarazo, con el propósito de contribuir a mejorar la comprensión de la vía a través de la cual el arsénico afecta el IMC de los niños, especialmente en el contexto actual de aumento de la obesidad infantil. Para ello, se utilizó información de un estudio previo del cual se dispuso de la base de datos a la luz del convenio de colaboración existente entre la SEREMI de Salud Pública de Arica y Parinacota y la Facultad de Medicina de la Universidad de Chile. Además, se

integraron datos del estudio FONIS SA22I0119 “Exposición a arsénico y su asociación con citoquinas proinflamatorias en niños nacidos entre 2013-2016 de la ciudad de Arica”. De este último, se obtuvieron las medidas para calcular el IMC de los niños, las cuales fueron tomadas específicamente para el desarrollo de esta tesis. Asimismo, la tesista, nutricionista de profesión, elaboró el manual de procedimiento para la toma de medidas antropométricas en terreno y capacitó al personal de trabajo de campo encargado de ejecutarlas.

Dada la falta de claridad sobre el impacto de la exposición al arsénico en el estado nutricional infantil, esta tesis incluyó una revisión sistemática de la literatura para profundizar la comprensión de esta asociación.

3. Pregunta de investigación

¿Cuál es el efecto de la exposición prenatal al arsénico inorgánico sobre el incremento del z score del IMC de los niños?

4. Hipótesis

La mayor exposición prenatal al arsénico inorgánico se asocia con mayor z score del índice de masa corporal infantil.

5. Objetivos

5.1 Objetivo general

Evaluar la asociación entre la exposición prenatal al arsénico inorgánico y el z score del índice de masa corporal (IMC) en los niños

5.2 Objetivos específicos

1. Analizar la evidencia epidemiológica disponible sobre la asociación entre la exposición al arsénico en la vida temprana (prenatal y en la infancia) y las medidas antropométricas de los niños.
2. Describir el estado nutricional de los niños de acuerdo a variables sociodemográficas y de salud.
3. Estimar la asociación entre la concentración de arsénico inorgánico prenatal y el z score del IMC.

6. Métodos

A continuación, se presenta el diseño de la revisión sistemática de la literatura (sección 6.1). Luego se presenta el diseño de estudio que aborda tanto el objetivo general como los objetivos específicos 2 y 3 (sección 6.2).

6.1 Revisión sistemática

Se llevó a cabo una revisión sistemática con el propósito de abordar el objetivo 1, el cual consiste en analizar la evidencia epidemiológica disponible sobre la asociación entre la exposición al arsénico en la vida temprana (prenatal y en la infancia) y las medidas antropométricas de los niños.

6.1.1 Pregunta de investigación

La pregunta de investigación que se respondió en la revisión sistemática fue: ¿Cuál es el efecto de una mayor exposición al arsénico en la vida temprana (prenatal y en la infancia) en los resultados antropométricos en la niñez?

La revisión se realizó siguiendo la guía de formulación PECO (Population, Exposure, Comparator, and Outcome) [156], con el fin de garantizar un proceso estructurado y replicable en la selección y síntesis de la evidencia. Los componentes se definieron de la siguiente manera:

P (Población): En niños, cuál es el efecto de

E (Exposición): la mayor exposición al arsénico en la vida temprana (prenatal y en la infancia)

C (Comparador): frente a la menor exposición al arsénico en la vida temprana (prenatal y en la infancia)

O (Outcome): alteración de resultados antropométricos en la niñez

Asimismo, los métodos para llevar a cabo la revisión sistemática se realizaron de acuerdo a las pautas de la declaración PRISMA (Preferred reporting items for systematic reviews and meta-analyses) [157].

6.1.2 Estrategia de búsqueda

La búsqueda de artículos se realizó en las bases de datos PubMed y Scopus utilizando términos de búsqueda en inglés, los cuales están especificados en la Tabla 1 como palabras clave.

Tabla 1. Palabras clave de búsqueda para identificar artículos.

Base de datos	Término de búsqueda	Resultado
Pubmed		
#1	(Arsenate[tw] OR Arsenic[tw] OR "Arsenic Drinking Water"[tw] OR "Arsenic Poisoning"[Mesh] OR "Arsenic Trioxide"[tw] OR Arsenicals[tw] OR Arsenite[tw] OR Arsenosis[tw] OR "Blood arsenic"[tw] OR "Chronic arsenic exposure"[tw] OR "Hair arsenic"[tw] OR "Inorganic arsenic exposure"[tw] OR "Nail arsenic*"[tw] OR "Toenail arsenic*"[tw] OR "Urinary arsenic"[tw])	
#2	("Anthropometry"[Mesh] OR "Body Height"[Mesh] OR "Body Mass Index"[tiab] OR "Body Size"[Mesh] OR "Body Weight"[Mesh] OR "Body Weights and Measures"[Mesh] OR Growth[tiab] OR "Growth trajector*"[tiab] OR Height[tiab] OR "Nutrition Disorders"[Mesh] OR Obesity[tiab] OR Overweight[tiab] OR Stunting[tiab] OR Thinness[tiab] OR Underweight[tiab] OR Wasting[tiab] OR Weight[tiab] OR	

	"Weight-for-height"[tiab] OR "height-for-age z-score"[tiab] OR "BMI-for-age z-score"[tiab] OR "BMI z-score"[tiab])	
#3	("Child, Preschool"[MeSH] OR Adolescent[tiab] OR Childhood[tiab] OR Child[tiab] OR Children[tiab] OR Infant*[tiab] OR "Maternal Exposure/adverse effects"[MAJR] OR "Prenatal Exposure Delayed Effects/epidemiology"[MAJR] OR Newborn[tiab] OR Pregnancy[tiab] OR Preschool[tiab] OR Prenatal[tiab])	
#4	#1 AND #2 AND #3	
Scopus		
	(TITLE-ABS-KEY (arsenate) OR TITLE-ABS-KEY (arsenic) OR TITLE-ABS-KEY (arsenic AND drinking AND water) OR TITLE-ABS-KEY (arsenic AND poisoning) OR TITLE-ABS-KEY (arsenic AND trioxide) OR TITLE-ABS-KEY (arsenicals) OR TITLE-ABS-KEY (arsenite) OR TITLE-ABS-KEY (arsenosis) OR TITLE-ABS-KEY (blood AND arsenic) OR TITLE-ABS-KEY (chronic AND arsenic AND exposure) OR TITLE-ABS-KEY (hair AND arsenic) OR TITLE-ABS-KEY (inorganic AND arsenic AND exposure) OR TITLE-ABS-KEY (nail AND arsenic) OR TITLE-ABS-KEY (nails AND arsenic) OR TITLE-ABS-KEY (toenail AND arsenic) OR TITLE-ABS-KEY (toenails AND arsenic) OR TITLE-ABS-KEY (urinary AND arsenic) AND TITLE-ABS-KEY (body AND heigh) OR TITLE-ABS-KEY (body AND mass AND index) OR TITLE-ABS-KEY (body AND size) OR TITLE-ABS-KEY (body AND weight) OR TITLE-ABS-KEY (body AND weights AND measures) OR TITLE-ABS-KEY (growth) OR TITLE-ABS-KEY (growth AND trajectory) OR TITLE-ABS-KEY (growth AND trajectories) OR TITLE-ABS-KEY (height) OR TITLE-ABS-KEY (nutrition AND disorders) OR TITLE-ABS-KEY (obesity) OR TITLE-ABS-KEY (overweight) OR TITLE-ABS-KEY (stunting) OR TITLE-ABS-KEY (thinness) OR TITLE-ABS-KEY (underweight) OR TITLE-ABS-KEY (wasting) OR TITLE-ABS-KEY (weight) OR TITLE-ABS-KEY (weight-for-height) OR TITLE-ABS-KEY (height-for-age AND z-score) OR TITLE-ABS-KEY (bmi-for-age AND z-score) OR TITLE-ABS-KEY (bmi AND z-score) TITLE-ABS-KEY (child AND preschool) OR TITLE-ABS-KEY (adolescent) OR TITLE-ABS-KEY (childhood) OR TITLE-ABS-KEY (child) OR TITLE-ABS-KEY (children) OR TITLE-ABS-KEY (infant) OR TITLE-ABS-KEY (infants) OR TITLE-ABS-KEY (newborn) OR TITLE-ABS-KEY (pregnancy) OR TITLE-ABS-KEY (preschool) OR TITLE-ABS-KEY (prenatal) OR TITLE-ABS-KEY (preschool))	

6.1.3 Criterios de inclusión y exclusión

La selección de artículos se realizó revisando los títulos y los resúmenes, de acuerdo a los criterios de selección considerados en la guía PECO (Tabla 2).

Tabla 2. Criterios de inclusión y exclusión de títulos y resumen de artículos de acuerdo a la guía PECO.

	Inclusión	**Exclusión**
Population	Niños y niñas desde el nacimiento hasta antes de los 18 años de edad.	Estudios que incluyan exclusivamente a personas adultas, o investigaciones en tejido humano (células), animales u otros organismos no humanos.
Exposure	Exposición a arsénico durante el período prenatal y en la infancia medido a través del biomonitoreo de la concentración de arsénico en una muestra biológica (orina, sangre, leche materna, uña o pelo) o medición de arsénico en muestra de agua potable.	Mezclas de arsénico con otros metales sin evaluar su efecto independiente. Se excluyeron los estudios que no tengan una medición de la exposición en matriz biológica o en agua.
Comparator	Niños con mayor nivel de exposición al arsénico frente a niños con menor nivel de exposición al arsénico	Estudios sin grupo de comparación (reporte de caso, serie de casos o descriptivos). Ensayos clínicos o cuasi-experimentales.
Outcome	Alteración de medidas antropométricas que reflejen déficit o exceso en el crecimiento infantil. En menores de 5 años: peso para la edad, longitud para la edad, peso para la longitud y peso para la estatura. En niños y niñas de 5 años o más: estatura para la edad, peso para	Se excluyeron los estudios en los que las medidas antropométricas no constituyen la variable de resultado. Se excluyeron las medidas de crecimiento prenatal como el peso y la longitud al nacer.

	la edad, IMC para la edad y puntaje z del IMC.	
Otros	Se incluirán artículos en inglés.	No se consideraron cartas al editor, capítulos de libros, resúmenes de conferencias y trabajos no revisados por pares. Evaluaciones de riesgo ambiental que no incluyeron la medición directa de desenlaces en población humana.

6.1.4 Extracción de datos

Luego, se evaluó los artículos de texto completo seleccionados y la extracción de datos se realizó utilizando una planilla Excel que consideró información sobre: el diseño de estudio, características de la muestra (tamaño y país), la evaluación de la exposición de arsénico, la evaluación de los resultados antropométricos, las medidas de asociación e intervalo de confianza.

6.1.5 Evaluación de la calidad de los estudios

La calidad de los artículos se evaluó utilizando la herramienta de riesgo de sesgo desarrollada por la Oficina de Evaluación y Traducción de la Salud (OHAT: Office of Health Assessment and Translation) del Programa Nacional de Toxicología (NTP) [158]. Este instrumento consta de 10 preguntas diseñadas para evaluar fuentes de sesgo, incluyendo el sesgo de selección, confusión, desempeño, desgaste/exclusión, detección, informe selectivo y amenazas a la validez interna. Cada pregunta aplica a determinados diseños de estudios, y en este caso, se consideraron las preguntas destinadas a estudios observacionales, tales como estudios de cohorte, caso-control, y transversal, las cuales se detallan en el anexo 1. Es importante señalar que, aunque se

evaluó la calidad metodológica, no se excluyeron artículos en función del puntaje obtenido según la herramienta OHAT.

6.1.6 Síntesis de los resultados de los estudios

Se realizó un resumen de los resultados de forma narrativa y agrupado de acuerdo a las medidas antropométricas de interés.

6.2 Diseño de estudio

Para responder a la pregunta de investigación se constituyó una cohorte retrospectiva en base a información secundaria. Para ello se utilizó datos provenientes de dos fuentes: (1) Estudio “Prevalencia de arsénico en gestantes y plomo en recién nacidos del Hospital Dr. Juan Noé Crevani, Arica 2013 y 2016” realizado por la Secretaría Regional Ministerial (SEREMI) de Salud en la región de Arica y Parinacota. La base de datos de dicho estudio fue proporcionada en virtud de un convenio de colaboración firmado entre la SEREMI de Salud de Arica y Parinacota y la Facultad de Medicina de la Universidad de Chile. La información contenida en dicha base de datos corresponde al inicio del seguimiento de la cohorte; (2) Proyecto FONIS SA22I0119 “Exposición a arsénico y su asociación con citoquinas proinflamatorias en niños nacidos entre 2013-2016 de la ciudad de Arica” (Investigadora principal Dra. Paola Rubilar). Esta investigación considera la participación de una muestra de niños de la cohorte iniciada entre los años 2013 y 2016. La fase de recolección de datos se realizó entre junio y agosto del 2023.

6.2.1 Población y muestra

Corresponde a los hijos de 1644 gestantes que participaron en el estudio “Prevalencia de arsénico en gestantes y plomo en recién nacidos del Hospital Dr. Juan Noé Crevani” realizado por la SEREMI de Salud Arica y Parinacota entre los años 2013 y 2016. La edad de los niños fluctúa actualmente entre 7 a 10 años. De esta población, se consideró una muestra de 451 niños para el proyecto FONIS “Exposición a arsénico y su asociación con citoquinas proinflamatorias en niños nacidos entre 2013-2016 de la ciudad de Arica”. Se consideró como criterio de inclusión que la residencia actual se emplazara en la ciudad de Arica. Adicionalmente, se compararon las características maternas entre los niños que participaron en el estudio FONIS y aquellos que no participaron. No se observaron diferencias entre ambos grupos (anexo 2).

6.2.2 Poder estadístico de la muestra

Para este proyecto se utilizó la muestra reclutada en el estudio FONIS (n=451). Para determinar si el tamaño de muestra es suficiente para demostrar la asociación entre exposición al arsénico prenatal y el z score del IMC si este efecto existe, se consideró un análisis de regresión lineal múltiple, un coeficiente de determinación (R^2) hipotético de 0,04 (obtenido de la asociación entre el arsénico en orina y el índice de masa corporal del estudio de las gestantes), un valor $\alpha = 0,05$ para una prueba bilateral y un ajuste de 10 covariables. Con estos parámetros, el poder estadístico esperado para la asociación entre arsénico y z score del IMC es cercano a 80%.

Además, se realizó un análisis de potencia posterior, considerando el modelo final ajustado. Dicho modelo, que incluyó la exposición al arsénico inorgánico prenatal y cinco covariables de ajuste, presentó un R^2= 0,111 con un tamaño muestral de 435 observaciones. Considerando un nivel de significancia de 0,05 y seis predictores, la potencia estadística estimada fue de 1,00, lo que indica que el estudio tuvo suficiente poder para detectar la asociación observada.

6.2.3 Variables

6.2.3.1 Variable de exposición

Concentración prenatal de arsénico inorgánico en orina: la base de datos que contiene esta información fue proporcionada por la SEREMI de Salud de Arica y Parinacota y corresponde al estudio "Prevalencia de arsénico en gestantes y plomo en recién nacidos del Hospital Dr. Juan Noé Crevani, Arica 2013-2016". Las muestras de orina fueron recolectadas al ingreso de la madre al centro asistencial para la atención del parto. El análisis de las muestras se realizó en el Laboratorio de Salud Ocupacional del Instituto de Salud Pública (ISP) mediante espectrofotometría de absorción atómica. El límite de detección (LOD) fue de 5 µg/L. Para las concentraciones inferiores al LOD, se asignó un valor de 2,5 µg/L (LOD/2).

La variable se analizó en escala continua. Dado que se observó una relación no lineal con la variable respuesta, la concentración de arsénico se transformó a escala logarítmica (log2) y se calcularon quintiles de exposición.

El ajuste de la concentración prenatal de arsénico en orina se realizó con la concentración de creatinina (g/L) utilizando el método de estandarización ajustada por

covariables [75]. Para ello, se transformó la creatinina urinaria en escala logarítmica y se modeló en función de variables explicativas que tienen un efecto directo sobre la creatinina [71, 73, 75]. El modelo de regresión se describe mediante la siguiente ecuación:

$$\ln(creatinina) = \beta_0 + \beta_1 \times \chi + e$$

Donde $\ln(creatinina)$ expresa el logaritmo natural de la concentración de creatinina, β_0 representa el valor de creatinina cuando las covariables son iguales a cero, β_1 es el coeficiente de regresión, χ son las covariables que explican la concentración de creatinina y e es el término de error.

A partir del modelo, se obtuvieron los valores ajustados (predichos) de la concentración de creatinina, con los cuales se estimó la razón de creatinina. Esta medida representa el efecto residual de la hidratación sobre la creatinina y su fórmula es:

$$Razón\ de\ creatinina = \frac{Cr}{\widehat{Cr}}$$

Donde Cr es la concentración de creatinina observada, y $\widehat{Cr}$ la concentración de creatinina ajustada (predicha). Por último, para ajustar se utilizó el cociente de la razón de creatinina como denominador de la concentración de arsénico en orina [75].

6.2.3.2 Variable respuesta

La variable respuesta es el **z score del IMC** para la edad y sexo, que se considera como indicador de obesidad actual de los niños. Este indicador está especificado en la norma chilena para la evaluación nutricional de niños, niñas y adolescentes [159] y se calculó a partir de mediciones antropométricas realizada a los niños entre junio y agosto de 2023 (fase de terreno proyecto FONIS). Las medidas antropométricas utilizadas para la

construcción del indicador fueron el peso en gramos (g) y la estatura en centímetros (cm). Estas mediciones fueron realizadas por personal capacitado del estudio FONIS, siguiendo un protocolo estandarizado para la investigación elaborado por nutricionista. Para la medición del peso corporal, los niños vistieron ropa ligera y pies descalzos. El niño se ubicó de pie, quieto y con los brazos a los costados, en el centro de la balanza. El instrumento para realizar las mediciones fue una báscula de piso electrónica marca Seca bella 840, cuya sensibilidad es de 1 g.

La medición de estatura se obtuvo utilizando un tallímetro de pared Seca bodymeter 206, con una sensibilidad de 1 mm. El instrumento se fijó en una pared lisa y recta. Para la evaluación, los niños fueron medidos descalzos y dispuestos en posición vertical con los pies juntos, asegurando el ángulo de Frankfurt de 90°, es decir, trazando una línea imaginaria horizontal desde el canal auricular y el borde inferior de la órbita ocular, dispuesta en forma paralela con el piso y perpendicular a la pared donde se ubica el tallímetro.

El índice de masa corporal (IMC) se calculó mediante la razón entre el peso en kilogramos (kg) y la estatura en metros (m) al cuadrado (Kg/mt^2), cuya fórmula se describe a continuación:

Fórmula IMC:

$$IMC\ \left(\frac{kg}{m^2}\right) = \frac{Peso\ (kg)}{Talla\ (m)^2}$$

Se utilizó el patrón de referencia de crecimiento de niños entre 5 a 19 años de la Organización Mundial de la Salud del año 2007 [135], tal como lo establece la norma chilena de evaluación nutricional desde el nacimiento hasta la adolescencia [159]. Para la

clasificación nutricional se utilizaron los indicadores IMC para la edad y estatura para la edad considerando la edad cronológica de los niños aproximado por año, mes y día cumplido.

La clasificación nutricional en función del IMC para la edad se realizó considerando el Z score, también denominado puntaje de desviación estándar. El Z score describe qué tan lejos y en qué dirección se desvía la medida antropométrica (IMC) de un individuo respecto del valor de la mediana de la población de referencia. Los puntajes que se sitúan fuera del rango normal indican un déficit o un exceso nutricional, cuya severidad está dada por la distancia desde la mediana. La estimación del Z score del IMC para la edad y por sexo, se llevó a cabo utilizando el software estadístico RStudio, mediante el paquete “anthroplus”, que proporciona los Z scores de referencia de la OMS 2007 para niños y adolescentes de 5 a 19 años. La variable se analizó en escala continua y, para la clasificación del diagnóstico nutricional, se analizó en categorías de acuerdo a la ubicación del IMC dentro del intervalo de desviaciones estándar establecido por la OMS:

- Desnutrición: IMC/E ≤ -2 DE
- Riesgo de desnutrir: IMC/E ≤ -1 DE y > -2 DE
- Normal o eutrófico: IMC/E > -1 DE y < +1 DE
- Sobrepeso: IMC/E ≥ +1 DE y < +2 DE
- Obesidad: IMC/E ≥ +2 DE y < +3 DE
- Obesidad severa: IMC/E ≥ +3 DE

Dado que el IMC no distingue completamente la masa muscular de la masa grasa y solo se realizó una medida de peso y estatura, se evaluó la concordancia del IMC de los niños mediante la correlación con la medida de circunferencia de cintura. Para la

medición de la circunferencia de la cintura, se utilizó una cinta ergonómica para medir circunferencias marca Seca 201. El niño se posicionó de pie y con la zona abdominal descubierta. Se identificó y marcó el borde superior de la cresta ilíaca, que es el hueso saliente en la parte superior de la cadera. Luego, se extendió la cinta métrica alrededor de la cintura en línea horizontal, pasando por encima del ombligo y sobre la cresta ilíaca marcada. Se solicitó al niño que tomara aire y al final de la exhalación, con el abdomen relajado, se tomó la medida. La variable se utilizó en escala continua (cm).

6.2.3.3 Covariables

- ***Variables sociodemográficas**:* edad, sexo, etnia, nivel educacional de la madre y fuente de abastecimiento de agua potable.
- ***Variables relacionadas con salud:*** peso al nacer, semana gestacional, IMC de la madre al inicio del embarazo, y actividad física.

En la Tabla 3 se describen las variables en términos de la fuente de información y momento de medición.

Tabla 3. Descripción de las variables.

Variables /operacionalización	Fuente de información	Medición
Variable respuesta		
Z score del IMC • Variable categórica (desnutrición, riesgo de desnutrir, normal, sobrepeso, obesidad y obesidad severa) (objetivo 2). • Variable continua (Kg/m^2) (objetivo 3)	Estudio FONIS SA22I0119 "Exposición a arsénico y su asociación con citoquinas proinflamatorias en niños nacidos entre 2013-2016 de la ciudad de Arica"	Entre junio y agosto 2023
Variable independiente		
Concentración prenatal de arsénico inorgánico en orina • Variable continua (µg/L) • Variable categórica (quintiles)	Estudio SEREMI de Salud de Arica y Parinacota "Prevalencia de arsénico en gestantes y plomo en recién nacidos del Hospital Dr. Juan Noé Crevani, Arica 2013 y 2016"	Orina en gestantes medida entre octubre 2013 y enero 2016.
Covariables		
• Creatinina urinaria (g/L)* • IMC de la madre inicio embarazo (kg/m^2) * • Peso al nacer del niño * • Semana gestacional * • Grupo étnico (aimara, diaguita, quechua u otro) * • Nivel educacional de la madre (básica, media o superior) * • Fuente de agua potable * • Edad del niño (años) ** • Sexo del niño (hombre o mujer) ** • Actividad física (horas a la semana) **	* Estudio SEREMI de Salud de Arica y Parinacota "Prevalencia de arsénico en gestantes y plomo en recién nacidos del Hospital Dr. Juan Noé Crevani, Arica 2013 y 2016" ** Estudio FONIS SA22I0119 "Exposición a arsénico y su asociación con citoquinas proinflamatorias en niños nacidos entre 2013-2016 de la ciudad de Arica"	Entre octubre 2013 y enero 2016. Entre junio y agosto 2023

6.2.4 Análisis de los datos

Se realizó un análisis exploratorio de los datos para identificar posibles errores de codificación, datos faltantes y distribución de las variables. Se utilizaron estadísticas descriptivas para la caracterización de los niños, mediana y rango intercuartílico para las variables continuas, y proporciones y frecuencias relativa para las variables categóricas.
A continuación, se describe el análisis de los datos de acuerdo a los objetivos específicos 2 y 3.

Objetivo 2: Describir el estado nutricional de los niños de acuerdo a variables sociodemográficas y de salud

Se realizó un análisis bivariado del Z score del IMC para la edad, utilizando las categorías de diagnóstico nutricional construidas en base a este indicador (desnutrición, riesgo de desnutrir, normal, sobrepeso, obesidad y obesidad severa), de acuerdo a las variables sociodemográficas, de salud y de exposición al arsénico. Dado que las variables continuas no distribuyeron normal, para comparar entre las categorías del IMC, se utilizó la prueba de Kruskal-Wallis. La comparación de las categorías de diagnóstico nutricional entre variables categóricas se realizó con la Prueba Ji cuadrado.

Objetivo 3: Estimar la asociación entre la concentración de arsénico inorgánico prenatal y el z score del IMC.

Para estimar la asociación entre la concentración de arsénico inorgánico prenatal y el z score del IMC de los niños, se identificó, a través de la literatura, las potenciales variables

que podrían participar en la asociación. Estas variables incluyeron la edad de la madre, educación de la madre [160, 161], IMC de la madre al inicio del embarazo [133, 162], peso al nacer [119, 141], semana gestacional [163, 164], fuente de agua potable [39] y etnia[162, 165].

Luego, se utilizó un grafo acíclico dirigido (Figura 4) para evaluar la estructura de la relación de las variables. Dada la importancia del peso al nacer en el z score del IMC posterior [141] y su posible relación con la exposición al arsénico [119], se evaluó si se comportaba como un mediador. Para ello, se ajustó el z score del peso al nacer por la edad gestacional mediante las curvas integradas de crecimiento intrauterino chilenas de Alarcón y Pittaluga [166]. Se calculó la diferencia entre el peso al nacer (gramos) y el peso correspondiente a la mediana de la edad gestacional (semanas), dividiendo luego este valor por la desviación estándar para obtener el z score.

Para determinar si el z score del peso al nacer era un mediador, se examinó inicialmente la relación entre el arsénico en orina prenatal y el z score del peso al nacer. Aunque no se encontró una asociación significativa entre estas variables (β = -0.09; IC 95%: -0.26, 0.07), el z score del peso al nacer sí mostró una asociación significativa con el z score del IMC (β = 0.20; IC 95%: 0.10, 0.30). Por ello, se decidió proceder con el análisis de mediación (anexo 2).

A través del DAG (Figura 4), se seleccionó las variables etnia, nivel educacional e IMC de la madre al inicio del embarazo para realizar el ajuste mínimo necesario de un modelo de regresión lineal para la asociación:

$$\mathbb{E}[Y_{z\ score\ IMC}] = \beta_0 + \beta_1 As\ prenatal + \beta_2 etnia + \beta_3 IMC\ materno + \beta_4 Eduación\ materna + \beta_5 Edad\ materna + e$$

Donde $\mathbb{E}[Y_{z\ score\ IMC}]$ es el valor esperado del Z score del IMC, β_0 representa el valor de Z score de IMC cuando las covariables son iguales a cero, $\beta_1, \beta_2, \beta_3, \beta_4\ y\ \beta_5$ son los coeficientes de las variables arsénico prenatal, etnia, IMC materno, educación de la madre y edad materna, respectivamente. Finalmente, e es el error residual.

Cabe señalar que, se realizó el diagnóstico del modelo para verificar el cumplimiento de los supuestos de la regresión lineal: 1) linealidad: mediante un gráfico de dispersión que represente la relación entre la concentración de arsénico prenatal y el z score del IMC; 2) distribución normal de los residuos: para comprobar que los residuos distribuyen normal alrededor de cero, se realizó una inspección visual de los residuos del modelo de regresión a través de gráficos cuantil-cuantil. Además, se utilizó el test de normalidad de Shapiro-Wilk; 3) homocedasticidad: para verificar que la varianza de los residuos es constante alrededor de cero, se compararon los residuos estandarizados frente a los observados mediante una aproximación gráfica. Asimismo, se utilizó el test de homocedasticidad de Breusch-Pagan.

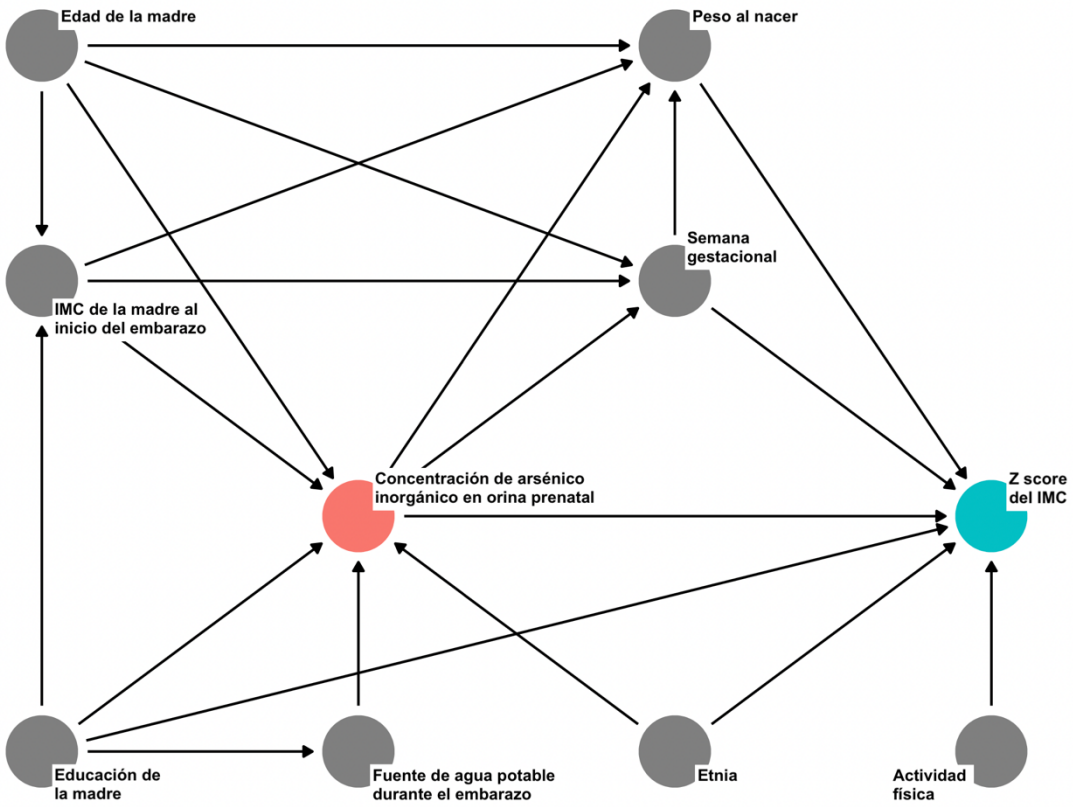


Figura 4. Relación entre exposición prenatal al arsénico y el z score del IMC.

Dado el desequilibrio en el IMC al inicio del embarazo entre los quintiles de exposición al arsénico prenatal, se empleó un enfoque alternativo para controlar la confusión. Este método se basa en la estimación del puntaje de propensión [167], el cual mide la probabilidad de asignación a una categoría de exposición al arsénico prenatal, considerando un conjunto de covariables basales observadas. Este enfoque asume que, al controlar dichas covariables, la exposición a una categoría específica de arsénico es independiente a los resultados potenciales [168].

Este análisis se realizó en tres pasos, siguiendo un proceso similar al descrito en un estudio previo [169]. Para ello, se consideró la generalización del puntaje de propensión para exposiciones con más de dos categorías [170, 171]. El primer paso, consiste en estimar el

puntaje de propensión mediante el ajuste de una regresión logística politómica [172] que considere la probabilidad de estar expuesto al arsénico (X) en uno de los quintiles de exposición $J \quad (j = 1, \dots, 5)$ dado un conjunto de covariables (Z). La ecuación general se presenta a continuación:

$$\Pr(X_i = j|Z) = \frac{e^{\beta_{0j}+\beta_j Z}}{1 + \Sigma_{k=1}^{J-1} e^{\beta_{0k}+\beta_k Z}}$$

Esta ecuación representa modelos separados para estimar la probabilidad de estar expuesto al arsénico en cada quintil $J - 1$, donde $\Pr(X_i = j|Z)$ es la probabilidad de que la observación i se ubique en el quintil j de exposición al arsénico, dada las covariables Z. El numerador, $e^{\beta_{0j}+\beta_j Z}$ representa al exponencial de la combinación lineal de las covariables Z ponderadas por los coeficientes β_j específicos para el quintil j. Por otro lado, el denominador $\Sigma_{j=1}^{J-1} e^{\beta_{0k}+\beta_k Z}$ es la suma de exponenciales de las combinaciones lineales de las covariables ponderadas por los coeficientes de todas las categorías j desde 1 hasta $J - 1$. En este modelo, el quintil de menor exposición se toma como la categoría de referencia.

La optimización del modelo se examinó mediante la evaluación de la bondad de ajuste de la regresión politómica, utilizando el criterio de información de Akaike (AIC) para seleccionar el mejor modelo predictivo, considerando distintas combinaciones de covariables y términos de interacción.

Luego, se realizó una verificación del balance del puntaje de propensión entre los quintiles de exposición al arsénico, mediante la estimación de estadísticas sumarias, la construcción de histogramas, y el cálculo de diferencias de medias estandarizadas (SMD).

En el segundo paso, se estimaron los pesos de la probabilidad inversa del puntaje de propensión para cada categoría j de la exposición al arsénico:

$$w_{iX=J} = \frac{1}{Pr(X_i = j|Z)}$$

El tercer paso consiste en realizar el ajuste de una regresión ponderada con la probabilidad inversa de puntaje de propensión, calculado para cada quintil. Este procedimiento permite estimar la asociación entre la exposición al arsénico prenatal y el z score del IMC, como se representa en la siguiente ecuación:

$$Y_{z\ score\ IMC} = \beta_0 + \beta_1 As\ prenatal + e$$

6.2.5 Aspectos éticos del estudio

Esta tesis se inserta en el estudio FONIS (#SA22I0119), el cual cuenta con la aprobación del Comité de Ética Científico de la Facultad de Medicina de la Universidad del Desarrollo. Este comité revisó y aprobó los procedimientos éticos relacionados con la recolección de datos, obtención de consentimientos informados y manejo de la información de los participantes.

De igual manera, esta tesis fue evaluada y aprobada por el Comité de ética de investigación de seres humanos de la Facultad de Medicina de la Universidad de Chile. El valor científico de la propuesta se sustenta en el diseño utilizado, una cohorte retrospectiva que corresponde al mejor diseño observacional para evaluar una asociación causal dada la temporalidad en la medición de la exposición. Asimismo, los resultados contribuirán a generar evidencia para la formulación de recomendaciones y dado que el contexto de exposición en que se desarrolla el estudio es compartido con otras ciudades en Chile y a nivel latinoamericano, los resultados podrían ser extrapolados a contextos similares.

7. Resultados

Los resultados de esta tesis se presentan en forma de dos manuscritos científicos. El primer manuscrito corresponde a una revisión sistemática que da respuesta al objetivo 1; cuyo propósito fue analizar la evidencia epidemiológica disponible sobre la asociación entre la exposición al arsénico durante la vida temprana (período prenatal e infancia) y las medidas antropométricas en niños. El segundo manuscrito aborda los principales resultados de los objetivos 2 y 3. Además, en este documento se incluye información complementaria que amplía los resultados obtenidos y que no fue incorporada en el manuscrito debido a restricciones de espacio.

7.1 Resultados objetivo 1

Para la revisión sistemática, se identificaron 1.498 registros en las bases de datos PubMed y Scopus. Después de eliminar 385 registros duplicados, se revisaron 1.113 títulos y resúmenes de los cuales 1.078 fueron excluidos por no cumplir con los criterios de inclusión. Las principales razones de exclusión fueron: revisiones, revisiones sistemáticas y metaanálisis (n= 193); publicaciones no originales como cartas, capítulos de libros, resúmenes de conferencias y estudios no revisados por pares (n= 11); estudios experimentales o ambientales en tejidos humanos, animales u otros organismos no humanos (n= 372); reportes de casos o estudios sin grupo de comparación (n= 38); estudios experimentales o cuasi-experimentales (n= 13); estudios no relacionados con exposición a arsénico (n= 59); estudios sin medición de arsénico en matriz biológica (n= 46); estudios donde el arsénico fue analizado solo como parte de una mezcla de metales (n= 1); estudios en que las medidas antropométricas no constituyeron la variable de resultado (n= 253); estudios que solo reportaron medidas de crecimiento prenatal como peso o talla al nacer

(n= 88) y estudios realizados exclusivamente en población adulta (≥18 años) (n= 4). Tras esta etapa, se revisaron 35 textos completos, de los cuales se excluyeron 9 artículos adicionales, quedando finalmente 26 estudios que fueron incluidos en la revisión sistemática.

7.1.1 Manuscrito 1

Early-life arsenic exposure and childhood anthropometric measures: a systematic review

Abstract:

Background: Early-life exposure to inorganic arsenic is a public health concern due to its potential to interfere with critical stages of development. Although adverse birth outcomes have been consistently reported, the association with anthropometric measures in childhood remains unclear.

Objectives: To synthesize epidemiological evidence on the association between arsenic exposure during pregnancy or childhood and anthropometric outcomes.

Methods: A systematic review was conducted in PubMed and Scopus through December 2024, following PRISMA guidelines and the PECO framework. Observational studies assessing arsenic exposure during pregnancy or childhood and reporting anthropometric outcomes were included. Risk of bias was evaluated using the Office of Health Assessment and Translation (OHAT) tool, applying 10 questions covering 7 risk-of-bias domains.

Results: Twenty-six studies met the inclusion criteria. Seven reported statistically significant associations between arsenic exposure and anthropometric outcomes, including weight, height, and standardized z-scores. These studies were mostly prospective cohorts with urinary arsenic measurements and adjustment for confounders. However, many studies found no association, and exposure assessment frequently relied on a single measurement without arsenic speciation or repeated sampling. Risk of bias was generally lower in prospective cohort studies, but higher in many cross-sectional studies. Geographic coverage was limited, with most research conducted in South Asia and few studies from Latin America or the Asia-Pacific region.

Conclusion: Evidence remains inconsistent regarding the association between prenatal or childhood arsenic exposure and anthropometric outcomes. Future research should prioritize longitudinal designs, repeated biomonitoring with speciation, and inclusion of underrepresented regions to better elucidate the potential effects of early-life arsenic exposure.

keywords: Arsenic exposure, child growth, anthropometry, prenatal exposure, systematic review.

1. Introduction

Exposure to environmental contaminants during critical periods of human development, such as the prenatal stage and early childhood, is increasingly recognized as a determinant of child health and health trajectories throughout life [173]. Among these contaminants, arsenic stands out due to its high prevalence in groundwater and its potential for exposure through the consumption of drinking water [8]. It has been documented that inorganic arsenic can cross the placenta, leading to early intrauterine exposure with potential effects during childhood [145]. Several studies have associated this exposure with a higher risk of fetal and infant mortality, preterm birth, low birth weight [10-13], and reduced postnatal growth [14-16]. At later stages, elevated urinary arsenic concentrations have been linked to higher blood pressure and insulin resistance in adolescents, with more pronounced effects among those with obesity [129, 174].

Exposure to arsenic during pregnancy and the early years of life may interfere with fundamental processes of growth and development. These alterations can be indirectly assessed through anthropometric indicators such as weight, height, and body mass index (BMI), which are widely used as markers of nutritional status and child development [135].

Despite the growing evidence on the effects of arsenic on child health, the specific relationship between early-life exposure and anthropometric outcomes during childhood has been scarcely reviewed in a systematic manner.

It has been proposed that prenatal exposure to inorganic arsenic may affect child nutritional status through mechanisms such as oxidative stress, increased proinflammatory cytokines, and altered immune response [146], which would increase susceptibility to infections that could limit growth [13]. Likewise, this exposure has been linked to epigenetic modifications that affect adipocyte differentiation and lipid homeostasis, which could contribute to a higher body mass index in childhood [31, 151, 153]. These biological pathways suggest that arsenic may influence both impaired growth and accelerated weight gain trajectories.

To date, the only systematic review that addressed the relationship between early-life arsenic exposure and child growth was published in 2017 [13]. That study evaluated the available evidence on exposure during fetal life or early childhood and its association with growth, birth weight, and child morbidity. Although some negative associations were identified, the results were inconsistent and based on a limited number of studies, most of which were conducted in Bangladesh. Since then, no new systematic reviews have been published to update this evidence or to focus specifically on anthropometric measures during childhood as primary outcomes.

Epidemiological evidence on the relationship between arsenic exposure and childhood body mass index remains limited and inconclusive, with only one systematic review available, which is now outdated. Individual studies have not observed consistent associations between biomarkers of arsenic exposure and childhood BMI [23-29] , and they also differ in measurement methods and in the arsenic fractions analyzed. This heterogeneity makes it

difficult to compare studies and to interpret the observed effect. Moreover, most of the study designs used fail to establish temporality, which limits the ability to adequately assess a causal relationship.

In this context, the objective of the present systematic review is to analyze the available epidemiological evidence on the association between arsenic exposure during the prenatal and early childhood periods and anthropometric outcomes in childhood. This review aims to contribute to closing a gap in the scientific literature and to provide a stronger evidence base to inform public policies focused on preventing and mitigating arsenic exposure during critical stages of human development.

2. Methods

The research question that guided this review was: What is the effect of higher arsenic exposure in early life (prenatal and childhood) on anthropometric outcomes in childhood?

To address this question rigorously, a systematic review was designed following the PRISMA 2020 guidelines (Preferred reporting items for systematic reviews and meta-analyses) [157] and the protocol was registered in the Open Science Framework (https://osf.io/dxc6e). The research question was formulated using the PECO framework (Population, Exposure, Comparator, and Outcome) [156], which is suitable for systematic reviews assessing environmental health risks. The components were defined as follows:

Population (P): Children from birth up to, but not including, 18 years of age.

Exposure (E): Higher exposure to arsenic during early life (prenatal and childhood stages), measured through biomonitoring (e.g., in urine, blood, hair, or nails) or by analyzing arsenic levels in drinking water.

Comparator (C): Children with lower levels of arsenic exposure during the same developmental periods.

Outcome (O): Changes in anthropometric indicators during childhood. For children under 5 years of age, the outcomes considered were: weight-for-age, length-for-age, weight-for-length, and weight-for-height. For children aged 5 years and older, outcomes included: height-for-age, weight-for-age, BMI-for-age, and BMI z-score.

2.1 Search strategy

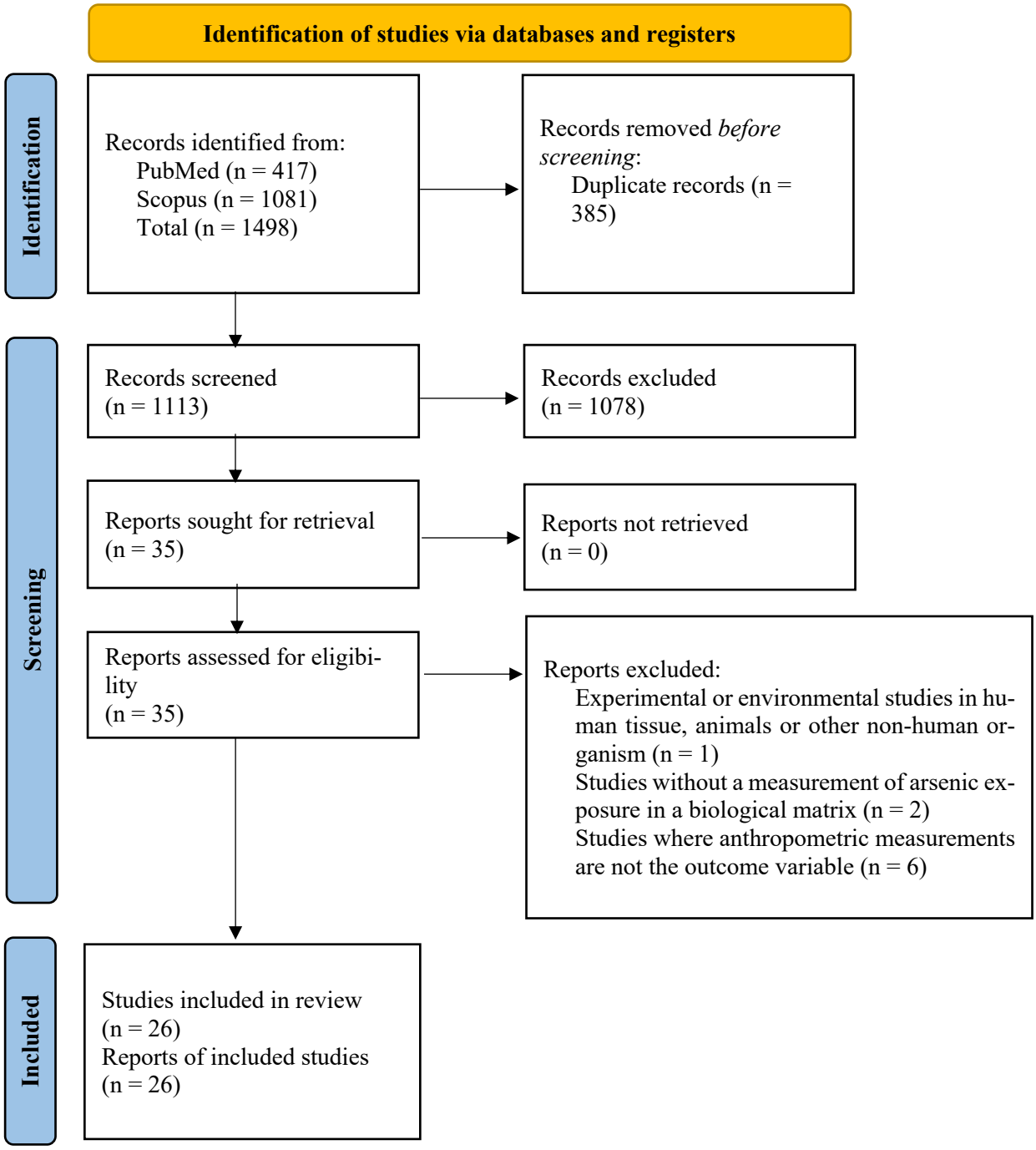
Systematic literature searches were conducted in two main electronic databases: PubMed and Scopus. The search strategy was developed to capture a broad range of relevant studies, using combinations of MeSH (Medical Subject Headings) descriptors, keywords, and Boolean operators specific to each platform. The search was limited to studies published in English between 2009 and 2024, to reflect the evidence from the past 15 years.

Search strategy in PubMed: Terms related to arsenic exposure (e.g., “urinary arsenic,” “arsenic poisoning,” “chronic arsenic exposure”) and anthropometric outcomes (e.g., “body mass index,” “growth,” “height-for-age z-score”) were used. To restrict the results to pediatric populations, age-related terms were included (e.g., “child,” “infant,” “prenatal”). Filters were applied for the English language and publication years between 2009 and 2024. The complete search string is presented in Table 1 of Supplementary 1.

Search strategy in Scopus: An advanced search was conducted using Boolean operators to identify studies containing the selected terms in the title, abstract, or keywords. Terms related to arsenic exposure and descriptors of anthropometric outcomes were combined, along with specific filters for child populations. The results were limited to articles and reviews published in English between 2009 and 2024 (Table 2, Supplementary 1).

The search was conducted independently by two reviewers. The following section summarizes the studies included in the review, in accordance with the PRISMA 2020 guidelines [157]. Figure 1 shows the flow diagram of records throughout each stage of the systematic review process, from initial identification to final inclusion in the qualitative synthesis.

Figure 1. PRISMA 2020 flow diagram of the study selection process



Source: Page MJ, et al. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

2.2 Eligibility criteria

Studies eligibility was determined using predefined inclusion and exclusion criteria based on the PECO (Population, Exposure, Comparator, Outcome) framework (Table 1). Studies were included if they focused on participants aged up to 18 years and evaluated arsenic exposure during the prenatal or childhood periods. Exposure had to be measured through biomonitoring of biological samples such as urine, blood, hair, or nails, or by measuring arsenic concentrations in drinking water.

Studies that compared groups with higher and lower levels of arsenic exposure and reported anthropometric outcomes such as weight-for-age, length or height-for-age, weight-for-length or height, BMI-for-age, and BMI z-score according to the corresponding age group were considered eligible. Only original observational studies (cross-sectional, case-control, or cohort) published in peer-reviewed scientific journals, written in English, and available with full-text were included.

Review articles, meta-analyses, editorials, book chapters, letters to the editor, conference abstracts, and non–peer-reviewed publications were also excluded. Studies conducted in animals, human tissue (cells), or other non-human organisms, as well as environmental risk assessments that did not include outcomes directly measured in human populations, were also excluded. Studies without a comparison group, without a clear measurement of arsenic exposure, or that analyzed mixtures of contaminants without evaluating the effect of arsenic independently were not considered. Likewise, studies that did not report anthropometric outcomes or that only evaluated prenatal growth measures such as birth weight or length were excluded. Articles involving adult populations (>18 years), those not peer-reviewed, or without accessible full text were also excluded.

Table 1. Inclusion and exclusion criteria for article titles and abstracts according to the PECO framework.

	Inclusion	Exclusion
Population	Children from birth up to but not including 18 years of age.	Studies including exclusively adults, or research in human tissue (cells), animals, or other non-human organisms.
Exposure	Exposure to arsenic during the prenatal period and childhood measured through biomonitoring of arsenic concentration in a biological sample (urine, blood, breast milk, nail, or hair) or measurement of arsenic in drinking water samples.	Mixtures of arsenic with other metals without assessing its independent effect. Studies without exposure measurement in a biological matrix or in water were excluded.
Comparator	Children with higher levels of arsenic exposure compared with children with lower levels of arsenic exposure.	Studies without a comparison group (case reports, case series, or descriptive studies). Clinical trials or quasi-experimental designs.
Outcome	Alteration of anthropometric measures reflecting growth deficits or excess in childhood. In children under 5 years: weight-for-age, length-for-age, weight-for-length, and weight-for-height. In children aged 5 years or older: height-for-age, weight-for-age, BMI-for-age, and BMI z-score.	Studies in which anthropometric measures were not the outcome variable were excluded. Likewise, studies that assessed only prenatal growth measures such as birth weight or length were excluded.
Others	Articles written in English.	Letters to the editor, book chapters, conference abstracts, and non–peer-reviewed publications were excluded, as were environmental risk assessments without direct measurement of outcomes in human populations.

2.3 Study selection

The study selection process was carried out in three stages. First, two reviewers independently screened titles and abstracts using the Rayyan platform [175] to identify potentially relevant articles. Second, the full texts of the selected studies were reviewed to verify whether they met the inclusion criteria. Finally, studies that fulfilled all the established criteria were included in the synthesis. Discrepancies between reviewers at any stage were resolved through discussion or, if necessary, by consulting a third reviewer.

2.4 Data extraction

Data extraction from the selected studies was performed using a standardized spreadsheet in Microsoft Excel. The variables extracted included: authors' names, year of publication, and country where the study was conducted; study design; sample characteristics (size and age); exposure assessment method (biological matrix, type of arsenic, concentration); anthropometric outcomes evaluated (e.g., BMI z-scores); and effect estimates (such as odds ratios [OR], regression coefficients [β] along with their 95% confidence intervals).

2.5 Quality assessment of studies

The quality of the included articles was assessed using an adapted version of the risk of bias tool developed by the Office of Health Assessment and Translation (OHAT) of the National Toxicology Program (NTP) [158]. This instrument comprises 10 questions designed to evaluate potential sources of bias, including selection bias, confounding, performance, attrition/exclusion, detection, selective reporting, and threats to internal validity. Each question is designed to be applied to specific types of studies. For this review, only the questions relevant to observational studies, including cohort, case-control, and cross-sectional designs, were considered. The rating criteria were defined based on a previous example of the tool's application in a systematic review on arsenic exposure [176], but were adapted and modified to address the research question of this review. The criteria used are

detailed in Table 3 of Supplementary 1. Although the risk of bias was assessed for all included studies, none were excluded based on their quality score. Instead, the results of this assessment were used to enrich the narrative synthesis and interpret the findings with greater accuracy.

3. Results

A total of 26 studies were included in this systematic review. Most were conducted in Bangladesh (six studies, 23.1%), followed by Spain and the United States (three studies each, 11.5%), and China and Canada (two studies each, 7.7%). Other countries contributed with one study each (3.8%), including Mexico, Congo, Palestine, South Korea, Pakistan, Uganda, Iran, Vietnam, Madagascar, and France.

Regarding study design, 46.2% (12/26) were cohort studies, of which eleven were prospective and one was retrospective. Another 46.2% (12/26) were cross-sectional studies, while the remaining 7.6% (2/26) were case-control studies.

Regarding the populations analyzed, twelve studies focused exclusively on children, mostly within the early childhood and childhood periods (from birth to 12 years), while fourteen studies included mother–child dyads. Sample sizes ranged from small cohorts (n= 60) to national studies with more than 9,000 participants. Most studies (65.4%; 17/26) evaluated arsenic exposure during the postnatal stage, either in infancy or early childhood, whereas 23.1% (6/26) assessed exposure during the prenatal period and 11.5% (3/26) considered both stages. In addition, 38.5% of the studies (10/26) included longitudinal anthropometric follow-up with repeated measurements over time.

Arsenic exposure was mostly assessed through urinary biomarkers (12/26; 46.2%), followed by blood (7/26; 26.9%), hair (4/26; 15.4%), and other matrices such as breast milk, nails, cord blood, or well water (4/26; 15.4%). Exposure was analyzed either as a continuous or categorical variable (by quantiles), and in 23% of the studies (6/26), exposure was measured at least twice prior to the anthropometric assessment. In addition, 84.6% of the studies (22/26) included a comparison group or performed dose–response analyses to compare exposure levels.

Anthropometric outcomes were evaluated in most cases (88.5%) using the World Health Organization (WHO) growth standards. The most frequently reported indicators were weight-for-age z-score (WAZ), present in 57.7% of the studies; height-for-age z-score (HAZ), in 50%; and body mass index-for-age z-score (BMIZ), in 30.8%. All studies used standardized and validated instruments for outcome measurement.

Only seven studies (26.9%) reported statistically significant associations between early-life arsenic exposure and anthropometric outcomes. Of these, four were cohort studies, two were cross-sectional, and one was a case-control study. In contrast, nineteen studies (73.1%) did not find statistically significant associations, including ten cross-sectional, eight cohort, and one case-control study.

Among the studies reporting statistically significant associations between arsenic exposure and anthropometric indicators, four measured exposure during the postnatal stage and three during the prenatal period. Regarding the direction of the effect, most (n= 5) reported negative associations—that is, higher arsenic exposure was associated with lower z-scores in indicators such as weight-for-age (WAZ), height-for-age (HAZ), or weight-for-height (WHZ). Only two studies reported positive associations, both related to length-for-age (LAZ)

in the first year of life, within the context of prenatal exposure. Table 2 summarizes the 26 studies included in this systematic review.

Table 2. Characteristics and main findings of studies assessing the association between early-life arsenic exposure and childhood anthropometry

Reference	Design	Population and country	Exposure	Comparison/control groups	Effect/outcome Assessment Instrument	Results (yes/no association)	Association (measure & direction)
Saha et al., 2012	Prospective birth cohort	2,372 mother-infants. Children followed monthly during the first year and quarterly during the second year of life. Matlab, Bangladesh.	As in maternal urine (iAs + MMA + DMA) at weeks 8 and 30 of gestation (median: 80 µg/L), and in child urine at 18 months (median: 34 µg/L). Adjusted for specific gravity.	Quintile comparison of urinary As levels; primary contrast: Q4 vs. Q1 for maternal and child exposure.	Weight, length, WAZ and LAZ measured monthly during the first year and quarterly during the second year. Underweight was defined as WAZ < –2 and stunting as LAZ < –2, according to WHO standards.	Yes	Girls with higher postnatal As exposure (Q4: 26–46 µg/L vs. Q1: <16 µg/L) had lower weight (–300 g) and shorter length (–0.7 cm) at 18–24 months. Adjusted odds ratios indicated increased risk of underweight (OR = 1.57; 95% CI: 1.02, 2.40) and stunting (OR = 1.58; 95% CI: 1.05, 2.37). No significant associations were observed in boys.
Gardner et al., 2013	Prospective birth cohort	1,505 mother-child pairs (children followed from birth to age 5 years). Matlab, Bangladesh.	Urinary As (iAs + MMA + DMA); specific gravity-adjusted. Prenatal:	Tertile comparison of urinary As levels (<35, 35–<84, ≥84 µg/L) and $\log_2$-transformed continuous exposure.	WAZ and HAZ monthly in year 1, every 3 months in year 2, and at 5-year follow-up (calculated using WHO standards).	No	Prenatal and concurrent urinary As exposure: No significant association with WAZ or HAZ. For concurrent urinary As exposure: WAZ β = –0.02

			maternal urine, 8 weeks (median: 82 µg/L; IQR: 37–210). Concurrent: child urine, 5 years (median: 51 µg/L; IQR: 30–120).				(95% CI: –0.05, 0.01); HAZ β = –0.02 (95% CI: –0.05, 0.02). Crude inverse associations (mid vs. low tertile) lost significance after adjustment.
Agay-Shay et al., 2015	Prospective birth cohort	470 mother–child pairs. Children follow-up at 14 months, 4 years, and 7 years. Sabadell, Spain.	Prenatal urinary As measured in the 1st and 3rd trimesters of pregnancy; mean concentration across both time points: 65.5 ng/g creatinine (95% CI: 57.7–73.3).	Tertile comparison of prenatal urinary As exposure; T1 as reference.	BMIZ and overweight (BMI >85th percentile) at 7 years using WHO growth standards.	No	No significant association with BMIZ or overweight risk in single- or multi-pollutant models. Tertile 2: β = –0.01 (95% CI: –0.29, 0.26); Tertile 3: β = –0.05 (95% CI: –0.34, 0.24).

Choi et al., 2017	Cross-sectional	210 healthy infants aged 8–23 months. Seoul, South Korea.	Blood As levels (median: 1.2 µg/dL; IQR: 0.62–2.26 µg/dL)	Continuous analysis of blood As levels.	Using WHO growth standards, weight gain after birth was calculated as the difference between weight-for-age z-score at assessment and birth weight z-score (WAZ–BWZ).	No	No significant association reported for weight gain (WAZ–BWZ).
Fábelová et al., 2018	Cross-sectional	324 children <6 years old from homeless families. Paris, France.	Hair As (median: 0.05 µg/g; range: 0.01–1.10); log-transformed	Continuous comparison using ln-transformed hair As concentration.	WAZ, HAZ, and BMIZ, calculated using WHO standards.	No	No significant associations with HAZ (β= –0.18; 95% CI: –0.36, 0.00), WAZ (β= –0.09; 95% CI: –0.29, 0.10), or BMIZ (β= 0.01; 95% CI: –0.26, 0.28); findings unchanged after multiple imputation.
Milton et al., 2018	Prospective birth cohort	120 infants followed at 3, 6, and 9 months of age. Bangladesh (arsenic-contaminated sub-district).	Household water As; 33% of children exposed to ≥50 µg/L	Dichotomous comparison of household water As: <50 µg/L vs. ≥50 µg/L.	WAZ, HAZ, WHZ, at 3, 6, and 9 months of age. Using WHO standards.	No	No significant association between water As exposure and WAZ at 3 or 6 months. Underweight prevalence (<–2SD) did not differ significantly by exposure level: 28.8% vs. 17.5% at 3 months (p = 0.18); 12.5% vs. 5.0% at 6 months (p = 0.19).

Ashley-Martin et al., 2019	Cross-sectional	449 mother-child pairs (children aged 2 to 5 years). Vancouver, Toronto, Hamilton, Kingston, Montreal, and Halifax. Canada.	Children's blood As (median: 0.464; IQR: 0.219–0.891 μg/L)	Tertile comparison of blood As levels; T1 (<0.30 μg/L) used as reference.	HAZ, WAZ, and BMIZ, calculated using WHO standards.	No	No significant association with BMIZ (T3 >0.70 vs. T1 <0.30): β = 0.01 (95% CI: –0.22, 0.19); similar null findings for HAZ and WAZ.
Kupsco et al., 2019	Prospective birth cohort	609 mother-child pairs. Children follow-up at 4–6 years of age. Mexico City, Mexico.	Prenatal blood As concentration (2nd trimester); mean ± SD: 0.085 ± 0.058 μg/L	Continuous analysis of prenatal blood As concentration.	BMIZ measured at 4-6 years old. Using WHO standards.	No	No significant association between prenatal blood As and BMIZ at 4–6 years in single-metal (β = 0.04; 95% CI: –0.18, 0.26).

Baraquoni et al., 2020	Prospective birth cohort	69 children and 79 mothers. Children follow-up at 18 months Gaza, Palestine.	Hair As levels. Mother at delivery, median 0.077 ppm (IQR: 0.102); at 18 months, median 0.071 ppm (IQR: 0.111). Infants at birth, median 0.014 ppm (IQR: 0.008); at 18 months, median 0.146 ppm (IQR: 0.140).	Comparison of maternal and infant hair As levels across weight and height categories.	WAZ and HAZ assessed using WHO growth standards at 6 and 18 months (underweight and stunting classification)	Yes	Higher maternal hair As at delivery linked to lower infant WAZ ($p = 0.005$). In contrast, higher neonatal As associated with greater WAZ and HAZ at 6 months ($p < 0.0001$).
Moody et al., 2020	Cross-sectional	97 healthy children (6–59 months) from the Katanga urban settlement in Kampala, Uganda.	Blood As levels (µg/L): median 0.23; IQR: 0.15–0.33	Continuous comparison of blood As concentrations.	HAZ, calculated using CDC/WHO growth standards (1978).	No	No significant association with HAZ ($\beta = -0.052$, $p = 0.846$). In Weighted Quantile Sum (WQS) mixture model, As contributed 33% to the toxic index but was not independently significant.

Muse et al., 2020	Prospective birth cohort	760 mother-infant pairs (children follow-up from birth to 12 months). New Hampshire, USA.	Maternal urinary total As (tAs) and species (iAs, MMA, DMA), measured in the 2nd trimester: median 3.96 µg/L (IQR: 2.02–6.72 µg/L)	Continuous and tertile comparison of maternal urinary As; T1 or lower exposure used as reference.	WAZ, LAZ and WLZ, calculated using WHO standards. At birth and up to 12 months, from medical records.	Yes	Positive associations between maternal tAs and LAZ during first year. Per doubling of tAs: β = 0.05 (95% CI: 0.00, 0.09); at 2 weeks: β = 0.07 (95% CI: 0.01, 0.13). DMA T3 vs. T1 (repeated measures): β = 0.24 (95% CI: 0.09, 0.39); tAs T3 vs. T1 at 2 weeks: β = 0.25 (95% CI: 0.06, 0.45). No associations at later timepoints.
Vigeh et al., 2020	Cross-sectional	207 preschool children (36 to 72 months old). Tehran, Iran.	Concentration of As in children's hair (median: 0.04 µg/g; IQR: 0.00 – 0.91 µg/g)	Continuous comparison of hair As concentration.	Weight-for-age and height-for-age percentiles- Using WHO standards.	No	No association reported between As and anthropometric measures. Only descriptive statistics.

Wai et al., 2019	Prospective birth cohort	108 mother-infant pairs. Children follow-up from birth to 6 months. Faridpur, Chandpur, and Madaripur. Bangladesh.	Prenatal urinary As measured in a single spot urine sample collected from pregnant women in their second or third trimester. Adjusted for specific gravity. The geometric mean was 50.8 µg/L (range: 3.1–339 µg/L).	Continuous model of prenatal urinary As.	Monthly follow-up anthropometry:WAZ, HAZ, and WHZ from birth to 6 months using WHO growth standards.	No	No significant associations with WHZ (β = –0.68; 95% CI: –1.43, 0.06), HAZ (β = 0.20; 95% CI: –0.43, 0.84), or WAZ (β = –0.27; 95% CI: –0.64, 0.09).

Alao et al., 2021	Cross-sectional	465 children (0–59 months old). Matlab, Bangladesh. Cases: severe pneumonia; controls: healthy children.	Children's urinary As measured at enrollment (controls) and 30 days post-discharge (cases). Mean concentration: 45 µg/L. Creatinine-adjusted (included as a covariate in analysis).	Tertile comparison of urinary As in children (0–<8, 8–<31, ≥31 µg/L); T1 as reference.	Stunting (HAZ < –2 SD), underweight (WAZ < –2 SD), and wasting (WHZ < –2 SD), based on WHO growth standards.	Yes	Urinary As was associated with increased odds of wasting in children <24 months (OR = 2.85; 95% CI: 1.18–6.89) and underweight (OR = 2.29; 95% CI: 1.16–4.52); in <24 months, middle (OR = 1.99; 95% CI: 1.01, 3.91) and highest tertiles (OR = 2.50; 95% CI: 1.17, 5.34) also linked to underweight. No association with stunting.
Malin Igra et al., 2021	Prospective birth cohort	1,530 mother-child pairs (children were followed from birth to age 1). Matlab, Bangladesh.	Maternal erythrocyte As (Ery-As) (GW14): median 4.3 µg/kg (p5–p95: 1.1–23); Urinary As (U-As) (10 y): median 57 µg/L (p5–p95: 19–375); total As,	Continuous comparison using log_2-transformed maternal or urinary As concentrations.	HAZ and WAZ at 10 years, calculated using WHO standards. Repeated measures of HAZ/WAZ were also analyzed longitudinally across 19 time points (birth to 10y).	No	No significant associations between urinary As and HAZ (β = 0.027; 95% CI: –0.0056, 0.060) or WAZ (β = 0.013; 95% CI: –0.023, 0.049) at 10y. Ery-As also not associated with HAZ (β = –0.012; 95% CI: –0.042, 0.017) or WAZ (β = 0.0017; 95% CI: –0.027, 0.031). No

			non-speciated				associations observed in sex-stratified or repeated measures models.
García-Villarino et al., 2022	Cross-sectional	328 children (4 to 5 years old) (n = 97 for As analysis). Asturias, Spain.	Urinary As in children, expressed as the sum of iAs, MMA, and DMA (∑As). Median: 4.9 μg/L; IQR: 3.1–7.5 μg/L.	Continuous model; children below the 25th percentile of urinary As used as reference.	Standing height and BMI; measured in absolute values, no reference growth standard was reported.	No	No significant association with BMI (β = 0.36; 95% CI: –0.08, 0.80) or height (β = 0.43; 95% CI: –0.54, 1.41).
Mbunga et al., 2022	Cross-sectional	412 Children aged 6–59 months in urban Kinshasa, Democratic Republic of the Congo (DRC).	Blood levels of As. Median: 1.88 μg/L; IQR: 0.55-5.67 μg/L.	Categorical comparison: <LOD, LOD–LOQ, and ≥LOQ blood As levels.	HAZ, WHZ, WAZ. Using WHO standards.	No	No significant association with HAZ (p = 0.49), WHZ (p = 0.87), or WAZ (p = 0.57).

Zielińska-Dawidziak et al., 2022	Cross-sectional	103 schoolgirls aged 8–15 years from Madagascar, living in urban (UR) area near Antananarivo and rural (RU) Berevo region.	Scalp hair As; < LOD in most samples. Detected in 4 girls: 1.2–18.3 mg/kg.	Comparison across nutritional status groups (underweight, normal, overweight, obese).	As concentration in hair; nutritional status evaluated using Cole's index to classify underweight vs. normal weight.	No	No significant association between As exposure and nutritional status ($p = 0.785$).
Cottrell et al., 2023	Retrospective cohort	60 mother-infant dyads. Infants were followed from birth to 5 years. West Virginia, USA.	Umbilical cord blood As; measured (concentration not reported).	Continuous comparison of cord blood As levels.	Child BMI measured during well-child visits at 4 months, 6 months, 12 months, 2 years, and 5 years. BMI was derived from clinical anthropometric data.	No	No significant association between As exposure and BMI at any age (e.g., $p = 0.33$ at 4 months; $p = 0.50$ at 12 months; $p = 0.75$ at 2 years; $p = 0.39$ at 5 years).
Egwunye et al., 2023	Cross-sectional	658 mother-child pairs (children aged 36 months). Ha Nam Province, Vietnam.	Fingernail As concentration at 36 months. Median: 0.4 μg/g; IQR: 0.3-0.5 μg/g.	Continuous model using fingernail As levels.	HAZ, calculated using WHO standards.	No	No significant association with HAZ (β = –0.00; 95% CI: –0.02, 0.01).

Ma et al., 2023	Cross-sectional	278 children (3 to 6 years old). Jiangsu, China.	Children's urine As measured from pooled first-morning urine samples over three consecutive days. Median: 27.14 μg/g; IQR: 18.81–42.65; creatinine-corrected	Continuous comparison of urinary As levels.	WAZ, HAZ, BMIZ, calculated using WHO standards.	Yes	Urinary As was associated with reduced HAZ in individual (β = –0.22; 95% CI: –0.38, –0.06) and multiple-metal models (β = –0.26; 95% CI: –0.49, –0.04). Negative association with WAZ in single-metal model (β = –0.16; 95% CI: –0.31, –0.01), but not after adjusting for co-exposures.
Smith et al., 2023	Prospective birth cohort	999 mother-child pairs (children followed prospectively from birth to 13 years of age). Massachusetts, USA.	Maternal erythrocyte As concentration in the first trimester of pregnancy. Median: 0.84 ng/g; IQR: 0.43-1.57 ng/g.	Continuous comparison using log_2-transformed maternal erythrocyte As concentrations.	BMIZ at 3y, 8y, and 13y; calculated using WHO standards.	No	No significant association between maternal erythrocyte As and BMIZ at any timepoint: early childhood (β = –0.01; 95% CI: –0.05, 0.04), mid-childhood (β = 0.03; 95% CI: –0.03, 0.08), and early adolescence (β = –0.03; 95% CI: –0.09, 0.03).

Zhang et al., 2023	Prospective birth cohort	919 mother-child pair.Children followed at 1, 3, 6, 8, and 12 months of age. Jiangsu, China.	Prenatal urine As (early and late trimester). Early pregnancy: median 23.05 μg/L (IQR: 15.48–37.71). Late pregnancy: median 19.74 μg/L (IQR: 13.05–29.78).	Continuous analysis of prenatal urinary As.	WAZ, LAZ, WLZ, and BMIZ were assessed at 1, 3, 6, 8, and 12 months of age calculated using WHO standards.	Yes	Prenatal urinary As was positively associated with LAZ from 1 to 12 months (β = 12.61%; 95% CI: 1.02%, 24.20%), significant overall and in boys (β = 12.52%; 95% CI: 1.03%, 24.01%), but not in girls.
Adil et al., 2024	Case–control	62 mother–infant pairs (42 undernourished cases, 20 controls) from Matiari, Sindh, Pakistan.	As in breast milk: Detected only in the case group (not in controls); reported concentration: 0.68 μg/L.	Categorical case–control comparison: undernourished infants vs. controls.	WAZ, WHZ, and HAZ calculated using WHO growth standards.	Yes	Significant negative association between As and WAZ (β = –2.949, $p = 9\times10^{-8}$) and WHZ (β = –2.406, $p = 5\times10^{-7}$); no significant association with HAZ.

Dugandzic et al., 2024	Cross-sectional	9,147 children aged 3–11 years. Canada.	Urinary dimethylarsinic acid (DMA), creatinine-adjusted: median 0.01 µg/L (IQR: 0.00–0.01) across Cycles 2–6 (ages 3-5) and Cycles 1–6 (ages 6-11).	Continuous comparison per unit increase in urinary DMA concentration.	Overweight or obesity, obesity, BMIZ (WHO standards).	No	No significant associations between DMA and overweight/obesity. For Cycles 2–6: OR = 0.94 (95% CI: 0.88–1.00); for obesity: OR = 0.98 (95% CI: 0.92–1.05). Similar null findings for Cycles 1–6.
Salcedo-Bellido et al., 2024	Case-control	143 children (92 controls, 51 overweight/obese), aged 6–12 years. Spain.	Urinary total As: median 25.6 µg/L (IQR: 9.4–53.2) in controls and 12.9 µg/L (IQR: 7.7–53.7) in cases.	Categorical case–control comparison: overweight/obese children vs. normal-weight controls.	BMI calculated as weight/height² and classified according to IOTF criteria; children grouped into cases (overweight/obese) and controls (normal weight).	No	No significant association between urinary As and overweight/obesity. Model 1: OR = 0.94 (95% CI: 0.64, 1.37); Model 2: OR = 1.17 (95% CI: 0.75, 1.82).

Abbreviations: As, arsenic; iAs, inorganic arsenic (arsenite and arsenate); MMA, monomethylarsonic acid; DMA, dimethylarsinic acid; tAs, total arsenic; WAZ, weight-for-age z-score; LAZ, length-for-age z-score; WLZ, weight-for-length z-score; BMIZ, BMI-for-age z-score; HAZ, height-for-age z-score; WHZ, weight-for-height z-score.

Table 3 presents the risk of bias assessment for the 26 included studies, using the OHAT tool [158]. The rationale for the risk of bias classification of each study is provided in Supplementary 2. Ten studies were classified as definitely or probably at low risk of bias across the ten questions corresponding to the seven evaluated domains [14, 21, 22, 24-28, 30, 177]. Of these, six were prospective birth cohort studies and four were analytical cross-sectional studies.

Only two of the ten studies classified as having a low risk of bias reported statistically significant associations between arsenic exposure and anthropometric outcomes. The cross-sectional study by Ma et al. (2023) [21] identified inverse associations, showing that higher concentrations of urinary arsenic in children were associated with lower height-for-age (HAZ) and weight-for-age (WAZ) z-scores, particularly in single-exposure models. In contrast, the prospective cohort study by Zhang et al. (2023) [177] found positive associations, observing that higher prenatal arsenic exposure was associated with greater length-for-age (LAZ) between the first and twelfth months of life among boys.

The domains most frequently classified as having a probably high or definitely high risk of bias were adjustment for other relevant exposures (confounding bias II), adjustment for confounding and modifying variables (confounding bias I), and group comparison (selection bias). In the case of adjustment for other exposures, fifteen studies (57.7%) were rated as having a probably high or definitely high risk of bias. Regarding adjustment for confounding variables, nine studies (34.6%) received negative evaluations, suggesting that the associations reported in these studies could be biased due to uncontrolled factors. Finally, five studies (19.2%) showed a high risk of bias in group comparison, and another five (19.2%) in the handling of attrition or exclusions, indicating potential selection biases both

in the initial formation of groups and during follow-up, which could compromise the internal validity of the findings.

Table 3. Risk of bias assessment of included studies according to the OHAT tool

Author and year/Questions	Selection bias	Confounding bias I	Confounding bias II	Performance bias	Attrition/exclusion bias	Detection bias I	Detection bias II	Detection bias III	Selective reporting bias	Other sources of bias
	Were the comparison groups appropriate?	Did the study design or analysis account for important confounding and modifying variables?	Did researchers adjust or control for other exposures that are anticipated to bias results?	Did researchers adhere to the study protocol?	Were outcome data complete without attrition or exclusion from analysis?	Were confounding variables assessed consistently across groups using valid and reliable measures?	Can we be confident in the exposure characterization?	Can we be confident in the outcome assessment?	Were all measured outcomes reported?	Were there no other potential threats to internal validity (e.g., statistical methods were appropriate)?
Saha et al., 2012	(+)	(++)	(–)	(++)	(+)	(++)	(++)	(++)	(++)	(++)
Gardner et al., 2013	(+)	(++)	(++)	(++)	(+)	(++)	(++)	(++)	(++)	(++)
Agay-Shay et al., 2015	(+)	(++)	(+)	(++)	(+)	(++)	(+)	(++)	(++)	(++)
Choi et al., 2017	(+)	(– –)	(–)	(++)	(++)	(+)	(+)	(++)	(–)	(–)
Fábelová et al., 2018	(+)	(++)	(–)	(++)	(+)	(++)	(+)	(++)	(++)	(+)
Milton et al., 2018	(+)	(–)	(–)	(++)	(+)	(+)	(–)	(+)	(++)	(–)
Ashley-Martin et al., 2019	(+)	(++)	(++)	(++)	(++)	(++)	(+)	(++)	(++)	(++)
Kupsco et al., 2019	(+)	(++)	(++)	(++)	(+)	(++)	(+)	(++)	(++)	(++)
Baraquoni et al., 2020	(–)	(– –)	(–)	(+)	(–)	(+)	(+)	(–)	(–)	(– –)
Moody et al., 2020	(+)	(–)	(–)	(++)	(++)	(++)	(+)	(+)	(++)	(+)

Muse et al., 2020	(+)	(++)	(–)	(++)	(+)	(++)	(++)	(++)	(++)	(++)
Vigeh et al., 2020	(+)	(– –)	(–)	(++)	(–)	(+)	(–)	(++)	(–)	(– –)
Wai et al., 2019	(+)	(++)	(–)	(++)	(–)	(+)	(+)	(++)	(++)	(+)
Alao et al., 2021	(+)	(+)	(–)	(++)	(+)	(+)	(+)	(++)	(++)	(++)
Malin Igra et al., 2021	(+)	(++)	(++)	(++)	(+)	(+)	(+)	(++)	(++)	(++)
García-Villarino et al., 2022	(+)	(+)	(++)	(++)	(+)	(++)	(++)	(+)	(++)	(+)
Mbunga et al., 2022	(–)	(– –)	(–)	(++)	(++)	(+)	(–)	(++)	(++)	(–)
Zielińska-Dawidziak et al., 2022	(– –)	(– –)	(–)	(++)	(–)	(+)	(– –)	(+)	(++)	(–)
Cottrell et al., 2023	(+)	(– –)	(–)	(++)	(–)	(+)	(+)	(+)	(++)	(–)
Egwunye et al., 2023	(+)	(+)	(–)	(++)	(+)	(++)	(+)	(++)	(++)	(+)
Ma et al., 2023	(+)	(++)	(++)	(++)	(++)	(++)	(+)	(++)	(++)	(++)
Smith et al., 2023	(+)	(++)	(++)	(++)	(+)	(++)	(+)	(++)	(++)	(++)
Zhang et al., 2023	(+)	(++)	(+)	(++)	(+)	(++)	(+)	(+)	(++)	(++)
Adil et al., 2024	(–)	(–)	(–)	(++)	(++)	(+)	(+)	(+)	(– –)	(–)
Dugandzic et al., 2024	(+)	(+)	(++)	(++)	(++)	(++)	(++)	(++)	(++)	(++)
Salcedo-Bellido et al., 2024	(–)	(+)	(+)	(++)	(++)	(++)	(+)	(+)	(++)	(++)

Risk of bias was color-coded following [176]: ++ = definitely low risk of bias (green); + = probably low risk of bias (light green);− = probably high risk of bias (light red);– – = definitely high risk of bias (red).

4. Discussion

This systematic review aimed to analyze the available epidemiological evidence on the association between arsenic exposure during the prenatal and childhood periods, and anthropometric outcomes in children. A total of 26 studies meeting the inclusion criteria were identified, of which seven reported significant associations between higher arsenic exposure and alterations in anthropometric indicators such as weight, height, or their corresponding z-scores (WAZ, WHZ, HAZ, or LAZ) [15, 16, 21, 144, 177-179]. In contrast, nineteen studies did not find a statistically significant relationship [14, 22-30, 180-188]. Overall, the findings of this review show inconsistent evidence, consistent with the previous review by Rahman et al., which analyzed the relationship between arsenic exposure and child growth and also found heterogeneous results, mainly based on studies conducted in Bangladesh [13].

Although this review expanded the temporal and geographical coverage compared with the previous review [13], a regional bias persists, with a predominance of studies conducted in South Asia and limited representation from other regions with known arsenic exposure, such as South America. In particular, Chile is among the countries that have reported some of the highest concentrations of arsenic in natural water sources, with levels that, in different historical periods, have exceeded the limits established by the WHO [189]. While in Chile, associations have been documented between arsenic exposure and adverse pregnancy outcomes, such as low birth weight [10] and fetal and neonatal mortality [12], no studies have been reported evaluating its effect on child growth.

This lack of evidence is important, as the exposure conditions and health determinants in Chile differ from those observed in South Asia, where most of the available evidence originates. In Bangladesh, arsenic exposure is higher and primarily results from the

consumption of groundwater in populations with a high prevalence of deficiency-related malnutrition [20, 190]. In contrast, in Chile, exposure occurs mainly through drinking water with naturally occurring arsenic content [191], which, although currently below the 10 µg/L limit in urban areas [192], can still exceed this threshold in rural areas [193]. This exposure tends to be lower than that observed in Bangladesh but is chronic and persistent, affecting populations with a higher prevalence of overweight and obesity. These environmental, nutritional, and ethnic differences could modify the toxicokinetics of arsenic, that is, how the body absorbs, metabolizes, and eliminates this contaminant, and consequently, its effects on anthropometric measures. Therefore, extrapolating results from South Asia to Latin American populations is not appropriate, and it is necessary to generate local evidence that considers these particularities, especially in rural areas with limited access to treated drinking water.

Similarly, participation from Asia-Pacific countries such as Japan, Taiwan, China, and South Korea was limited, despite their extensive research background on arsenic and chronic diseases. It is possible that, in these regions, research has primarily focused on adult populations, particularly regarding cancer and cardiovascular diseases, and that there is lower availability or use of birth cohorts to study child growth [194]. This limited representation hinders the generalization of results and highlights the need to expand research in diverse and currently underrepresented populations.

Of the seven studies included in this review that reported significant associations between arsenic exposure and anthropometric measures, five stood out for their higher methodological quality. These studies used urinary biomarkers of arsenic [15, 16, 21, 144, 177], some conducted repeated measurements of exposure over time [16, 177], and all employed standardized methods to assess growth using weight, length, and height z-scores based

on WHO references. In most of them, the associations indicated weight deficits or a higher likelihood of z-scores below −2 standard deviations. However, in two cohort studies [144, 177] , positive associations were observed with length-for-age during the first months of life, although these were modest and not consistent across all measurement points, which could reflect differences in susceptibility windows, infant sex, or variability in growth patterns.

Beyond the specific findings, the heterogeneity observed among the included studies can be explained by several factors. One of them is the timing of exposure; while some investigations analyzed only prenatal exposure, others focused on childhood, and some covered both periods. Since processes such as organogenesis, cellular differentiation, and epigenetic programming occur within specific developmental windows, it is plausible that arsenic exposure has differential effects depending on the timing of occurrence [195, 196]. Differences in the matrix used to measure exposure also play a role. Drinking water samples provide a less precise general estimate of internal exposure, whereas biological matrices such as urine, blood, hair, or nails offer a more direct approximation, although they are also subject to individual variations related to metabolism and diet [197].

Prenatal exposure to inorganic arsenic can affect child growth through various biological mechanisms. During gestation, it has been associated with oxidative stress, increased proinflammatory cytokines, and elevated placental leptin levels, which could impair placental function and compromise the supply of oxygen and nutrients to the fetus [146-149]. These processes, together with alterations in immune response, have been linked to an increased risk of low birth weight and reduced growth in the first months of life [13, 146, 150]. In turn, low birth weight is a known risk factor for the later development of obesity [31, 34]. On the other hand, experimental studies have shown that arsenic can induce metabolic

alterations such as decreased adiponectin, increased ectopic fat deposits, and reduced adipocyte differentiation capacity, which could contribute to weight gain after birth [31, 130, 151]. Moreover, this exposure has been reported to modify the expression of genes involved in lipid metabolism through epigenetic mechanisms, which could promote accelerated growth trajectories or higher body mass index in childhood [153]. In this context, it is important to consider how the methodological quality of the studies may influence the strength of the findings.

The risk of bias assessment using the OHAT tool [158] allowed for a structured characterization of the methodological quality of the included studies. Prospective designs generally showed a lower risk of bias in participant selection and exposure characterization, as well as more frequent use of urinary biomarkers and adjustment for confounding variables. However, only a small number of studies performed arsenic speciation or measurements across multiple time windows, which limits the precision of exposure assessment. Although the statistical methods used were generally appropriate, approximately one-third of the studies presented limitations, mainly due to the absence of multivariable adjustment or the exclusive use of bivariate tests. Likewise, in some cases, the control of confounding variables was insufficient, which could have contributed to the variability of the results.

Among the strengths of this review are the rigorous application of the PECO framework [156], the inclusion of studies with objective measures of exposure and outcomes, and the use of a broad search strategy in recognized databases. The critical evaluation of studies using the OHAT tool allowed for the identification of key methodological weaknesses, such as the lack of confounding control, the unspecified type of arsenic, and the lack of standardization in anthropometric measurement. Among the limitations of this review are

the exclusion of gray literature and articles published in languages other than English, which could have introduced selection bias. Likewise, methodological heterogeneity in exposure characterization, anthropometric outcomes, and association measures prevented the performance of a quantitative meta-analysis, limiting the ability to synthesize the effects into an overall estimate.

From a public health perspective, it is essential to continue investigating arsenic exposure during early stages of development. The consequences of growth disturbances in childhood are associated with an increased risk of noncommunicable diseases in adulthood, such as obesity, type 2 diabetes, and cardiovascular diseases [198]. Therefore, understanding whether arsenic contributes to altering growth trajectories may have implications for the prevention of chronic diseases [34].

On the other hand, arsenic exposure primarily affects rural and vulnerable communities with limited access to safe drinking water. Therefore, even though the epidemiological evidence on child growth remains inconsistent, it is important to strengthen environmental surveillance in these populations to prevent adverse effects on child health.

Looking ahead, it is necessary to strengthen local capacities to conduct cohort studies in contexts of high exposure. These studies should incorporate repeated exposure measurements, analyses of inorganic arsenic species and methylated metabolites, and standardized protocols for anthropometric data collection. It is also a priority to adequately control for confounding factors, including socioeconomic, environmental, and nutritional variables. Furthermore, the development of international collaborative

platforms that link data from different countries could facilitate cross-context comparisons and enable more robust analyses.

Conclusion

This systematic review did not identify a conclusive association between arsenic exposure during critical developmental stages and anthropometric outcomes in childhood. However, the studies that reported significant associations were generally of higher methodological quality and provided more precise and specific exposure estimates, with most associations observed in a negative direction. These findings suggest that the lack of association in other studies could be related to deficiencies in study design or exposure measurement. Additional longitudinal studies, particularly in underrepresented regions, are needed to clarify this relationship and to guide public health interventions aimed at preventing arsenic exposure in vulnerable populations.

Early-life arsenic exposure and childhood anthropometric measures: a systematic review

Supplementary 1

Table 1. Search keywords to identify articles in PubMed

Search term	Result
(("Arsenate"[Text Word] OR "Arsenic"[Text Word] OR "Arsenic Drinking Water"[Text Word] OR "Arsenic Poisoning"[MeSH Terms] OR "Arsenic Trioxide"[Text Word] OR "Arsenicals"[Text Word] OR "Arsenite"[Text Word] OR "Arsenosis"[Text Word] OR "Blood arsenic"[Text Word] OR "Chronic arsenic exposure"[Text Word] OR "Hair arsenic"[Text Word] OR "Inorganic arsenic exposure"[Text Word] OR "nail arsenic*"[Text Word] OR "toenail arsenic*"[Text Word] OR "Urinary arsenic"[Text Word]) **AND** ("Anthropometry"[MeSH Terms] OR "Body Height"[MeSH Terms] OR "Body Mass Index"[Title/Abstract] OR "Body Size"[MeSH Terms] OR "Body Weight"[MeSH Terms] OR "Body Weights and Measures"[MeSH Terms] OR "Growth"[Title/Abstract] OR "growth trajector*"[Title/Abstract] OR "Height"[Title/Abstract] OR "Nutrition Disorders"[MeSH Terms] OR "Obesity"[Title/Abstract] OR "Overweight"[Title/Abstract] OR "Stunting"[Title/Abstract] OR "Thinness"[Title/Abstract] OR "Underweight"[Title/Abstract] OR "Wasting"[Title/Abstract] OR "Weight"[Title/Abstract] OR "Weight-for-height"[Title/Abstract] OR "height-for-age z-score"[Title/Abstract] OR "BMI-for-age z-score"[Title/Abstract] OR "BMI z-score"[Title/Abstract]) **AND** ("child, preschool"[MeSH Terms] OR "Adolescent"[Title/Abstract] OR "Childhood"[Title/Abstract] OR "Child"[Title/Abstract] OR "Children"[Title/Abstract] OR "infant*"[Title/Abstract] OR "maternal exposure/adverse effects"[MeSH Major Topic] OR "prenatal exposure delayed effects/epidemiology"[MeSH Major Topic] OR "Newborn"[Title/Abstract] OR "Pregnancy"[Title/Abstract] OR "Preschool"[Title/Abstract] OR "Prenatal"[Title/Abstract])) **AND** ((english[Filter]) **AND** (2009:2024[pdat]))	**417**

Table 2. Search keywords to identify articles in PubMed in Scopus

Search term	Result
(TITLE-ABS-KEY (arsenate) OR TITLE-ABS-KEY (arsenic) OR TITLE-ABS-KEY (arsenic AND drinking AND water) OR TITLE-ABS-KEY (arsenic AND poisoning) OR TITLE-ABS-KEY (arsenic AND trioxide) OR TITLE-ABS-KEY (arsenicals) OR TITLE-ABS-KEY (arsenite) OR TITLE-ABS-KEY (arsenosis) OR TITLE-ABS-KEY (blood AND arsenic) OR TITLE-ABS-KEY (chronic AND arsenic AND exposure) OR TITLE-ABS-KEY (hair AND arsenic) OR TITLE-ABS-KEY (inorganic AND arsenic AND exposure) OR TITLE-ABS-KEY (nail AND arsenic) OR TITLE-ABS-KEY (nails AND arsenic) OR TITLE-ABS-KEY (toenail AND arsenic) OR TITLE-ABS-KEY (toenails AND arsenic) OR TITLE-ABS-KEY (urinary AND arsenic)) **AND** (TITLE-ABS-KEY (body AND height) OR TITLE-ABS-KEY (body AND mass AND index) OR TITLE-ABS-KEY (body AND size) OR TITLE-ABS-KEY (body AND weight) OR TITLE-ABS-KEY (body AND weights AND measures) OR TITLE-ABS-KEY (growth) OR TITLE-ABS-KEY (growth AND trajectory) OR TITLE-ABS-KEY (growth AND trajectories) OR TITLE-ABS-KEY (height) OR TITLE-ABS-KEY (nutrition AND disorders) OR TITLE-ABS-KEY (obesity) OR TITLE-ABS-KEY (overweight) OR TITLE-ABS-KEY (stunting) OR TITLE-ABS-KEY (thinness) OR TITLE-ABS-KEY (underweight) OR TITLE-ABS-KEY (wasting) OR TITLE-ABS-KEY (weight) OR TITLE-ABS-KEY (weight-for-height) OR TITLE-ABS-KEY (height-for-age AND z-score) OR TITLE-ABS-KEY (bmi-for-age AND z-score) OR TITLE-ABS-KEY (bmi AND z-score)) **AND** (TITLE-ABS-KEY (child AND preschool) OR TITLE-ABS-KEY (adolescent) OR TITLE-ABS-KEY (childhood) OR TITLE-ABS-KEY (child) OR TITLE-ABS-KEY (children) OR TITLE-ABS-KEY (infant) OR TITLE-ABS-KEY (infants) OR TITLE-ABS-KEY (newborn) OR TITLE-ABS-KEY (pregnancy) OR TITLE-ABS-KEY (preschool) OR TITLE-ABS-KEY (prenatal)) **AND** PUBYEAR > 2008 AND PUBYEAR < 2025 AND (LIMIT-TO (DOCTYPE , "ar") OR LIMIT-TO (DOCTYPE , "re")) **AND** (LIMIT-TO (LANGUAGE , "English"))	**1.081**

Table 3. Risk of bias classification criteria adapted from the OHAT tool

Bias domains and questions	Definitely low risk of bias (++)	Probably low risk of bias (+)	Probably high risk of bias (–)	Definitely high risk of bias (– –)
Selection bias				
Were the comparison groups appropriate?	Groups comparable in age, sex, and relevant sociodemographic characteristics, recruited in the same period and with similar participation rates.	Indirect evidence of comparability; minor differences unlikely to substantially bias the results.	Groups not comparable or recruited in different periods; insufficient information.	Direct evidence of clear differences between groups (e.g., different population base, highly unequal participation rates).
Confusion				
Did the study design or analysis account for important confounding and modifying variables?	Complete and appropriate adjustment for confounders (e.g., maternal BMI, maternal age, maternal education, ethnicity, socioeconomic status).	Partial adjustment; unlikely to substantially change the direction or magnitude of the effect.	Insufficient adjustment or lack of control for important confounders.	No adjustment for variables or inadequate handling leading to biased associations.
Did researchers adjust or control for other exposures that are anticipated to bias results?	Direct evidence that co-exposures were absent or adequately controlled for.	Indirect evidence of adequate adjustment or that co-exposures would not substantially bias the results.	Indirect evidence with insufficient information on co-exposures.	Relevant co-exposures not considered and lack of information compromising validity.
Performance bias				
Did researchers adhere to the study protocol?	No deviations from the design or analysis were reported.	Minor deviations described, without affecting results.	Indirect evidence of major deviations from the protocol.	Direct evidence of important deviations.

Attrition/exclusion bias				
Were outcome data complete without attrition or exclusion from analysis?	Exclusions were documented and justified; balance between groups was not affected.	Exclusions documented, but with uncertain impact.	Insufficient information or exclusions possibly related to the outcome.	Unjustified exclusions or exclusions directly associated with the outcome (imbalance between groups).
Detection bias				
Were confounding variables assessed consistently across groups using valid and reliable measures?	Confounding variables measured in a standardized and validated way across all groups.	Acceptable measurement with minor differences.	Unreliable or inconsistent measurement across groups.	Inadequate or invalid measurement.
Can we be confident in the exposure characterization?	Biomonitoring with validated biomarkers (e.g., speciated urinary arsenic), above LOD, ideally with repeated measures and consideration of multiple sources.	Adequate biomonitoring but with minor limitations (e.g., no complete speciation, single measurement).	Indirect estimates without individual biomonitoring.	Incorrect or non-validated measurements.
Can we be confident in the outcome assessment?	Standardized and validated measurement of anthropometric indicators (e.g., WHO/CDC standards, calibrated scales, stadiometers, calculated z-scores).	Acceptable measurement with minor limitations or non-relevant differences.	Unreliable measurements, no evidence of standardization, or inconsistencies between groups.	Inadequate or unvalidated instruments for anthropometric measurement.
Selective reporting bias				

Were all measured outcomes reported?	All planned outcomes reported in sufficient detail.	Indirect evidence of complete reporting; unplanned analyses clearly identified.	Insufficient information on selective reporting.	Omission of outcomes or reporting of unprespecified outcomes without justification.
Other sources of bias				
Were there no other potential threats to internal validity (e.g., statistical methods were appropriate)?	Appropriate and consistently applied statistical methods.	Generally appropriate methods with minor limitations and no major impact.	Unclear or inappropriate statistical methods.	Inadequate methods that directly compromise the validity of the results.

Supplementary 2 (anexo 3)

7.2 Resultados objetivo 2

Se contó con información de 451 binomios madre-hijo de la cohorte retrospectiva. Las variables concentración de arsénico inorgánico en orina prenatal, el puntaje z del IMC de los niños, el sexo y edad de los niños presentaron datos completos para todos los participantes. Las variables sociodemográficas y de salud materna, como la edad de la madre, el nivel educativo, la fuente de agua durante el embarazo y el IMC al inicio del embarazo, contaron con una completitud sobre 97% (Tabla 4).

Tabla 4. Completitud de las variables sociodemográficas, de exposición y de salud de la cohorte retrospectiva de Arica, Chile

Características	**N=451**	
Características maternas	**N**	**%**
Año ingreso estudio SEREMI	451	100
Edad de la madre, años	450	99,7
Educación de la madre, años	449	99,5
Etnia	446	98,9
Fuente de agua en el embarazo	450	99,7
IMC al inicio del embarazo	449	99,5
Arsénico en orina prenatal	451	100
Creatinina urinaria prenatal	450	99,7
Semana gestacional	443	98,2
Peso de nacimiento, gramos	438	97,1
Características de los niños		
Edad del niño, años	451	100
Sexo	451	100
Z score del IMC	451	100
Realiza actividad física en el colegio	450	99,7
Realiza actividad física fuera del colegio	450	99,7

Se realizó un análisis bivariado que evaluó las categorías de estado nutricional, construidas en base al *z* score del IMC, según variables sociodemográficas, de salud y de exposición al arsénico. Los resultados, presentados en la Tabla 5, mostraron diferencias en la mediana del IMC materno al inicio del embarazo. Este fue más alto en las madres de niños con obesidad severa (mediana= 32,9; IQR= 28,5–35,8) y más bajo en las madres de niños con desnutrición (mediana= 26,5; IQR= 25,8–28,9). Además, se identificaron diferencias en el estado nutricional según el sexo de los niños, observándose una mayor proporción de niños hombres tanto en el grupo con desnutrición (66,7%) como en el grupo con obesidad severa (69,8%).

Por otro lado, no se encontraron diferencias estadísticamente significativas en otras variables analizadas, como la edad materna, los años de escolaridad de la madre, la etnicidad, el arsénico prenatal, la creatinina urinaria prenatal, la edad gestacional, el peso al nacer, o la realización de actividad física en el colegio y fuera de éste.

Tabla 5. Estado nutricional de los niños de acuerdo a características maternas e infantiles

Características	Desnutrición N=9	Riesgo de desnutrición N= 12	Eutrofia N= 177	Sobrepeso N= 103	Obesidad N= 97	Obesidad severa N=53	Valor p
	N (%) or median [IQR]						
Edad de la madre, (años)	28,00 [24,00–30,00]	26,00 [22,50–29,00]	25,00 [21,00–30,00]	28,00 [22,50–32,00]	25,00 [21,00–30,00]	25,00 [22,00–32,00]	0,297
Educación de la madre, (años)	12,00 [12,00–2,00]	12,00 [12,00–14,00]	12,00 [12,00–12,00]	12,00 [12,00–12,00]	12,00 [11,00–12,00]	12,00 [12,00–12,00]	0,148
Etnia de la madre							
No reporta	4 (44,4)	8 (66,7)	116 (65,5)	61 (59,2)	57 (58,8)	32 (60,4)	0,864
Del norte	5 (55,6)	4 (33,3)	55 (31,1)	39 (37,9)	35 (36,1)	18 (34,0)	
Otra	0 (0,0)	0 (0,0)	6 (3,4)	3 (2,9)	5 (5,2)	3 (5,7)	
IMC pre embarazo, (kg/mt^2)	26,50 [25,80–28,90]	28,25 [26,55–29,83]	28,60 [26,00–31,60]	30,25 [26,85–32,88]	30,70 [26,70–33,10]	32,90 [28,50–35,80]	**<0,001**
Arsénico urinario prenatal, (µg/L)	18,00 [14,00–23,00]	18,00 [14,75–21,00]	15,00 [11,00–23,00]	16,00 [10,50–24,50]	16,00 [9,00–25,00]	14,00 [7,00–21,00]	0,346
Creatinina urinaria prenatal, g/L	0,89 [0,82–1,19]	1,03 [0,73–1,49]	0,86 [0,57–1,33]	0,86 [0,57–1,47]	0,95 [0,61–1,38]	0,72 [0,53–1,19]	0,351
Semana gestacional, (semanas)	39,00 [39,00–40,00]	39,50 [38,75–40,00]	39,00 [38,00–40,00]	39,00 [38,00–40,00]	39,00 [38,00–40,00]	39,00 [38,00–40,00]	0,766
Peso al nacer, (g)	3510,00 [3072,50–3642,50]	3390,00 [2920,00–3590,00]	3370,00 [3090,00–3675,00]	3485,00 [3117,50–3772,50]	3535,00 [3220,00–3847,50]	3555,00 [3197,50–3760,00]	0,064
Edad del niño, (años)	8,00 [7,00–8,00]	8,00 [7,00–9,00]	8,00 [7,00–8,00]	8,00 [7,00–8,00]	8,00 [7,00–8,00]	8,00 [7,00–8,00]	0,283
Sexo del niño							
Hombre	6 (66,7)	6 (50,0)	77 (43,5)	45 (43,7)	50 (51,5)	37 (69,8)	**0,016**
Mujer	3 (33,3)	6 (50,0)	100 (56,5)	58 (56,3)	47 (48,5)	16 (30,2)	
Actividad física colegio							
No realiza	0 (0,0)	0 (0,0)	4 (2,3)	1 (1,0)	0 (0,0)	2 (3,8)	0,495
Realiza	9 (100,0)	12 (100,0)	172 (97,7)	102 (99,0)	97 (100,0)	51 (96,2)	
Actividad extra colegio							
No realiza	8 (88,9)	7 (58,3)	98 (55,7)	56 (54,4)	56 (57,7)	30 (56,6)	0,527
Realiza	1 (11,1)	5 (41,7)	78 (44,3)	47 (45,6)	41 (42,3)	23 (43,4)	

7.3 Resultados objetivo 3

Antes de estimar la asociación entre la concentración de arsénico inorgánico prenatal y el z score del IMC, se evaluó si el z score del peso al nacer para la edad gestacional actuaba como un mediador en esta asociación (Tabla 6). Mediante un análisis de mediación causal basado en un marco de resultados potenciales, los efectos se descompusieron en directo e indirecto. Los resultados indican que el ln de la concentración de arsénico en orina prenatal tiene un efecto directo (ED) significativo sobre el z score del IMC (β = -0,199; IC 95%: -0,37 a -0,03), lo que sugiere una asociación negativa directa entre la exposición y el z score del IMC, incluso al controlar por el mediador. En contraste, el efecto indirecto (EI), mediado por el z score del peso al nacer para la edad gestacional, no fue estadísticamente significativo (EI = -0,019; IC 95%: -0,06 a 0,02), indicando que el z score del peso al nacer para la edad gestacional no desempeña un rol relevante como mediador en esta asociación. Por último, el efecto total estimado muestra que un incremento de una unidad en el ln de arsénico inorgánico en orina prenatal se asocia con una disminución promedio de 0,22 unidades en el z score del IMC infantil (IC 95%: -0,39 a -0,05). Este efecto, que incluye tanto las vías directas como indirectas, se mantiene significativo incluso tras ajustar por las variables confusoras. En conjunto, los resultados sugieren que la exposición prenatal al arsénico inorgánico tiene un efecto negativo sobre el z score del IMC infantil, atribuible principalmente al efecto directo, lo que indica que el arsénico afecta el z score del IMC infantil a través de vías distintas del peso al nacer.

Tabla 6. Análisis de mediación del z score del peso al nacer para la edad gestacional en la asociación entre el ln de arsénico en orina prenatal y el z score del IMC

	Z score IMC			
	N= 435	β	$IC\ 95\%$	$Valor\ p$
Efecto indirecto		-0,0190	-0,06; 0,02	0,364
Efecto directo		-0,1974	-0,36; -0,04	0,016
Efecto total		-0,2164	-0,38; -0,05	0,006
% mediada		0,0880	-0,13; 0,44	0,366

Ajustado por variables (edad de la madre, educación de la madre, el IMC de la madre al inicio del embarazo y la etnia)
Simulaciones: 1000

Dado que se descartó el z score del peso al nacer para la edad gestacional como mediador de la asociación entre el ln de la concentración de arsénico inorgánico prenatal y el z score del IMC, esta variable no fue incluida en el modelo de asociación (Tabla 7).

Tabla 7. Asociación entre la concentración de arsénico inorgánico prenatal y el z score del IMC en niños entre 7 y 10 años

	Z score IMC			
	N	β	$IC\ 95\%$	$valor\ p$
Ln arsénico inorgánico µg/L[a]	451	-0,21	-0,38; -0,03	0,022
Ln arsénico inorgánico µg/L[b]	435	-0,20	-0,37; -0,03	0,024
Etnia de la madre				
No reportada		Ref.		
Del norte		0,05	-0,23; 0,33	0,720
Otra		0,54	-0,17; 1,25	0,135
Edad de la madre		-0,02	-0,04; 0,00	0,054
IMC al inicio del embarazo		0,08	0,05; 0,11	<0,001
Educación de la madre		-0,02	-0,08; 0,05	0,565
Z score del peso al nacer		0,19	0,09; 0,29	<0,001

[a] Modelo de regresión lineal simple.

[b] Modelo de regresión lineal ajustado por la etnia de la madre, edad de la madre, el IMC de la madre al inicio del embarazo, la educación de la madre y el z score del peso al nacer para la edad gestacional.

De acuerdo a los resultados de la Tabla 7, se observaron asociaciones negativas entre ln de arsénico inorgánico prenatal en orina y el z score del IMC de los niños de 7 a 10 años. En el modelo crudo, un incremento en el ln de arsénico inorgánico se asoció con una disminución promedio de 0,21 unidades en el z score del IMC (IC 95%: -0,38; -0,03). Esta asociación se mantuvo en el modelo ajustado por edad de la madre, educación materna, IMC de la madre al inicio del embarazo y la etnia de la madre (β = -0,20; IC 95%: -0,37; -0,03). Al ajustar la concentración de ln de arsénico inorgánico en orina por creatinina urinaria utilizando el método de estandarización ajustado por covariables [75], no se encontraron asociaciones estadísticamente significativas (Tabla 8).

Tabla 8. Asociación entre la concentración de arsénico inorgánico prenatal y el z score del IMC en niños entre 7 y 10 años, ajustada por creatinina utilizando el método de estandarización ajustada por covariable

	Z score IMC			
	N	$\boldsymbol{\beta}$	$\boldsymbol{IC\ 95\%}$	$\boldsymbol{p\ valor}$
Ln arsénico inorgánico µg/L [a]	434	-0,20	-0,44; 0,04	0,105
Etnia de la madre				
Ninguna		Ref.		
Del norte		0,06	-0,23; 0,34	0,684
Otra		0,54	-0,17; 1,25	0,137
Edad de la madre		-0,02	-0,04; 0,00	0,050
IMC al inicio del embarazo		0,08	0,05; 0,11	<0,001
Educación de la madre		-0,02	-0,08; 0,05	0,595
Z score del peso al nacer		0,19	0,09; 0,29	<0,001
Creatinina ratio		0,01	-0,26; 0,29	0,917
Ln arsénico/creatinina µg/g [b]	434	-0,17	-0,44 – 0,09	0,201
Etnia de la madre				
Ninguna		Ref.		

Del norte	0,08	-0,20; 0,37	0,560
Otra	0,52	-0,20; 1,24	0,155
Edad de la madre	-0,02	-0,04; 0,00	0,058
IMC al inicio del embarazo	0,08	0,05; 0,10	<0,001
Educación de la madre	-0,02	-0,08; 0,05	0,586
Z score del peso al nacer	0,19	0,10; 0,29	<0,001

[a] Ajustado por etnia de la madre, edad de la madre, el IMC de la madre al inicio del embarazo, la educación de la madre, z score del peso al nacer para la edad gestacional y creatinina ratio.
[b] Estandarización de arsénico con creatinina ajustado por covariables, ajustado por etnia de la madre, edad de la madre, el IMC de la madre al inicio del embarazo, la educación de la madre y z score del peso al nacer para la edad gestacional.

Finalmente, se realizó el diagnóstico del modelo de asociación para verificar los supuestos de la regresión lineal. Para evaluar el supuesto de linealidad entre la concentración de arsénico inorgánico en orina prenatal y el z score del IMC de los niños, se construyó un gráfico de dispersión. Como se muestra en la Figura 5, no se evidencia una relación claramente lineal entre ambas variables. Para abordar esta limitación y mejorar el ajuste del modelo, se aplicó una transformación logarítmica en base 2 (log2) a la variable de concentración de arsénico inorgánico prenatal en orina.

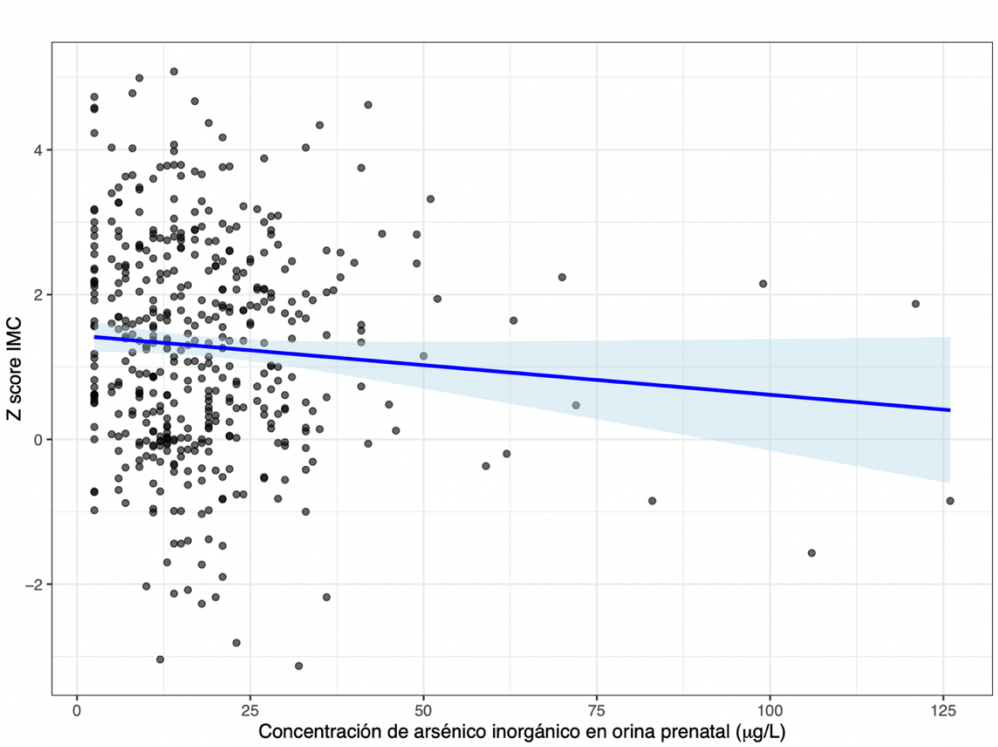


Figura 5. Relación entre la concentración de arsénico inorgánico en orina prenatal y el z score del IMC de los niños.

También, se verificó el supuesto de normalidad de los residuos del modelo ajustado. Esto se evaluó mediante una inspección visual de los residuos utilizando gráficos cuantil-cuantil (Figura 6). En este gráfico, los puntos se distribuyen mayoritariamente a lo largo de la recta normal, con ligeros desvíos en los extremos, lo cual es aceptable. Adicionalmente, se realizó el test de normalidad de Shapiro-Wilk, cuyo p-valor fue 0.522. Dado que este valor es superior a 0.05, no se puede rechazar la hipótesis nula de normalidad. Por tanto, se concluye que los residuos se distribuyen normalmente.

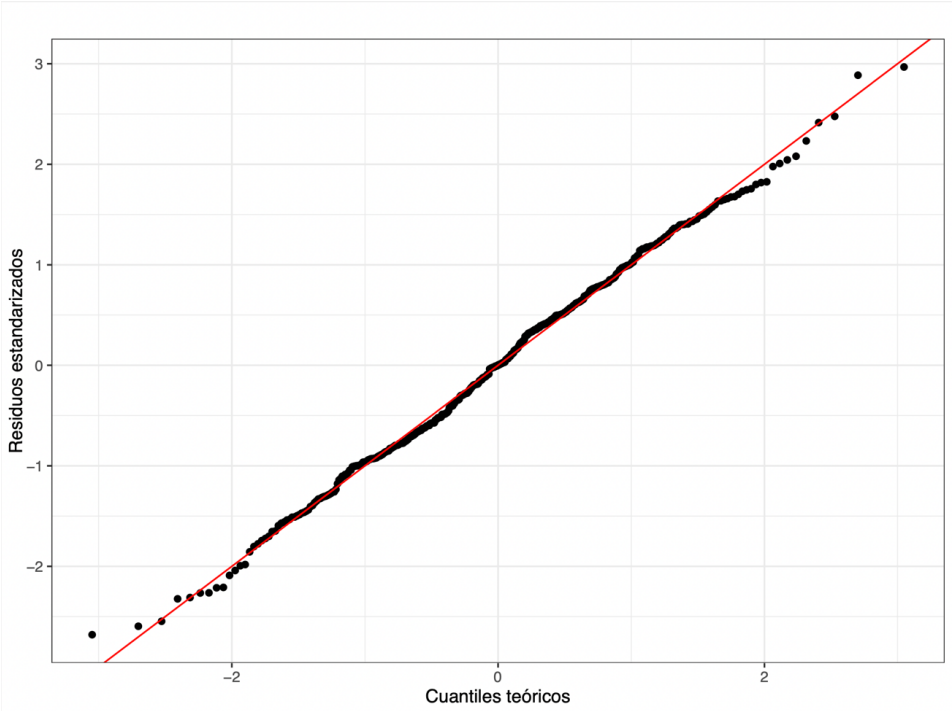


Figura 6. Gráfico de normalidad de los residuos del modelo de asociación entre el ln de la concentración de arsénico inorgánico en orina prenatal y el z score del IMC de los niños.

Para verificar la homogeneidad de la varianza (homocedasticidad), se compararon los residuos estandarizados frente a los valores ajustados mediante un gráfico de dispersión (Figura 7). Este gráfico no muestra un patrón evidente en los residuos alrededor de la línea de referencia (cero), lo que indica que la varianza de los residuos parece ser constante. Además, se realizó el test de Breusch-Pagan, cuyo p-valor fue 0,795. Al ser este valor superior a 0,05, no se puede rechazar la hipótesis nula de homocedasticidad. Por tanto, se concluye que los residuos presentan una varianza constante, cumpliendo con este supuesto.

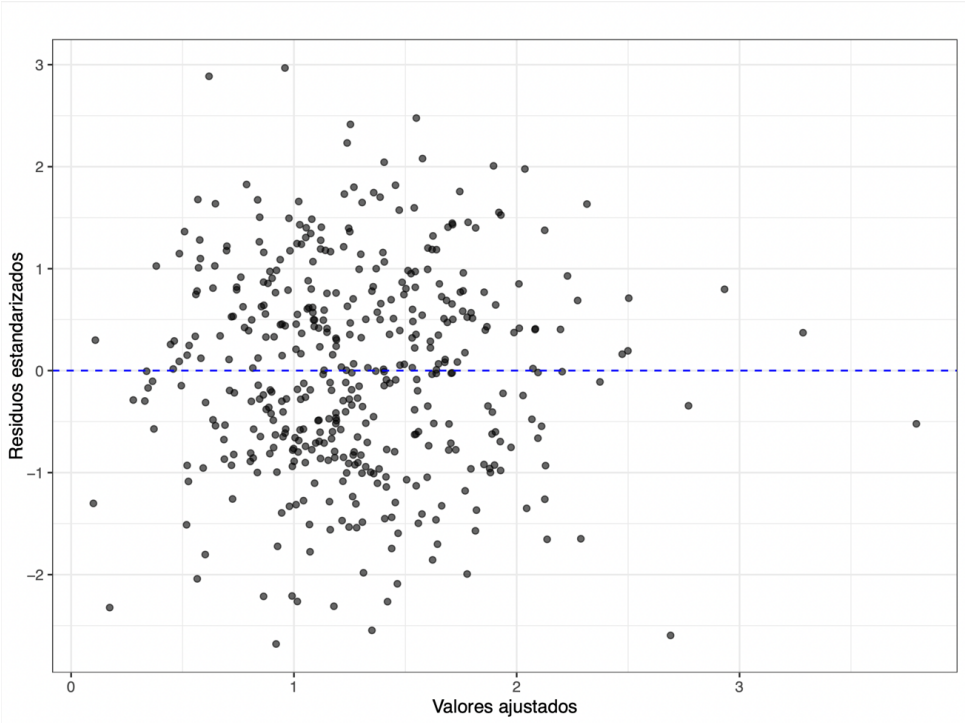


Figura 7. Gráfico de residuos estandarizados versus ajustados.

7.3.1 Manuscrito 2

Prenatal inorganic arsenic exposure and body mass index: a retrospective cohort study in children from Arica, Chile.

Highlights

- Evidence linking prenatal arsenic exposure to higher BMI in children remains limited and mostly null.
- In this retrospective cohort from Arica, Chile, prenatal inorganic arsenic exposure was inversely associated with BMI z score.
- Findings highlight the need for longitudinal studies to clarify the metabolic effects of early-life arsenic exposure.

Abstract

Background: Prenatal exposure to inorganic arsenic has been identified as a potential risk factor for metabolic disorders; however, its relationship with childhood obesity remains unclear. We hypothesized that higher prenatal inorganic arsenic exposure would be associated with a higher body mass index (BMI) z score in children. Therefore, the current study evaluated the association between prenatal exposure to inorganic arsenic and BMI z score in children from Arica, Chile.

Methods: This retrospective cohort study used secondary data from two previous studies. The first included 1,644 pregnant women who delivered at the Regional Hospital of Arica, where information on prenatal inorganic arsenic concentration in urine was collected. The second study involved evaluating 451 children of these women, from whom anthropometric data were obtained. Sociodemographic and health-related covariates

were also obtained and the BMI z score, specific for age and sex, was calculated using the 2007 WHO standard. Linear regression models were applied to analyze the association.

Results: Children had a median age of 8 years (IQR: 7–8) and the median prenatal inorganic arsenic concentration was 16 μg/L (IQR: 10–23). Among the children, 4.7% were undernourished or at risk of undernutrition, while 33.3% were classified as obese. After adjusting for maternal pre-pregnancy BMI, ethnicity, education, and age, a significant inverse association was observed between prenatal urinary arsenic and child BMI z score (β= -0.20; 95% CI: -0.37, -0.03).

Conclusion: Contrary to our expectations, prenatal arsenic exposure was not linked to higher BMI z score. These findings underscore the need for further research into the mechanisms by which arsenic may affect metabolism.

Keywords:

BMI z score, Childhood obesity, Inorganic arsenic, Prenatal exposure, Propensity score

1. Introduction

Arsenic is a contaminant that is naturally distributed in the environment, and its toxicity and high potential for exposure make it a major public health concern [8]. Intrauterine exposure has been associated with higher risks of fetal and infant mortality, preterm birth, reduced birth weight [10-12], and impaired postnatal growth [14-16]. Furthermore, early-life exposure to arsenic is recognized as an endocrine disruptor [143] capable of inducing permanent physiological alterations in lipid metabolism and hormone production, thereby increasing the risk of metabolic disorders later in life [199], such as obesity phenotypes characterized by increased body fat mass and glucose intolerance [33].

Beyond metabolic outcomes, evidence on the relationship between arsenic exposure and childhood obesity remains limited and inconsistent. Most investigations have focused on prenatal or early-life exposure and its association with anthropometric indicators such as weight-for-age (WAZ), height-for-age (HAZ), and body mass index z-score (BMIZ), as well as markers of undernutrition. Findings have been largely null or inverse [14-16, 21, 23], although some studies have reported positive associations with length-for-age in infancy [144, 177]. Only a limited number of studies have specifically examined the association with elevated BMIZ or overweight/obesity, and findings have consistently been null regardless of whether exposure was assessed prenatally [25-27] or postnatally during childhood and adolescence [28, 29].

To address this knowledge gap, the objective of this study is to evaluate the association between prenatal exposure to inorganic arsenic and BMI z-score in children from Arica, Chile, where arsenic exposure primarily occurs through drinking water [39, 40], and affects the general population. To do so, a retrospective cohort was designed based on data from two independent cross-sectional studies. The first was conducted among pregnant women between 2013 and 2016, while the second, carried out in 2023, studied their children. In addition, an alternative approach was used to control for potential confounding by maternal pre-pregnancy BMI, in order to improve understanding of the pathway through which prenatal arsenic exposure may affect children's BMI, especially in the current context of rising childhood obesity.

2. Material and methods

2.1 Design and study population

A retrospective cohort was established based on secondary data from two studies. The first, titled “Prevalence of arsenic in pregnant women and lead in newborns at Dr. Juan Noé Crevani Hospital, Arica 2013–2016,” was conducted by the Regional Health Authority (Secretaría Regional Ministerial, SEREMI) of Arica and Parinacota (n=1,644 pregnant women). The data from this study were provided as part of a collaboration agreement between the SEREMI of Arica and Parinacota and the Faculty of Medicine of the University of Chile, and served as the starting point for cohort follow-up. The second study corresponds to the project titled “Arsenic exposure and its association with proinflammatory cytokines in children born between 2013 and 2016 in the city of Arica,” which included a sample of children from the cohort initiated between 2013 and 2016 (n=451). Data collection for this project took place between June and August 2023 [191]. This research was reviewed and approved by the Research Ethics Committee for Human Subjects of the Faculty of Medicine, University of Chile.

2.2 Measures

2.2.1 Inorganic arsenic concentration

Data for a spot sample of prenatal urinary inorganic arsenic concentration were obtained from the database provided by the SEREMI of Arica and Parinacota. Urine samples were collected at the time of maternal admission to the healthcare facility for delivery. Sample analysis was performed at the Occupational Health Laboratory of the Institute of Public Health, Chile using atomic absorption spectrophotometry, with a detection limit of 5 µg/L. Concentrations below this limit were assigned a value of 2.5 µg/L (detection limit/2). Urinary creatinine concentration (g/L) was also measured in the same samples. For

values below 0.3 g/L, a value of 0.3 g/L was imputed, and for values above 3 g/L, a value of 3 g/L was assigned.

2.2.2 BMI z score

BMI z score, specific for age and sex, was calculated based on anthropometric measurements of weight and height collected from the children between June and August 2023, when they were aged 7 to 10, using the 2007 World Health Organization growth standards as reference [135]. These measurements were carried out by trained personnel, following a standardized research protocol. Weight was measured using a Seca Bella 840 electronic floor scale with an accuracy of 1 g. Height was measured using a Seca Bodymeter 206 wall-mounted stadiometer, with an accuracy of 1 mm, affixed to a smooth, flat wall. Children were measured wearing light clothing and barefoot, in an upright position, with feet together and head aligned so that an imaginary horizontal line between the auditory canal and the lower margin of the orbit was parallel to the floor.

Given that BMI does not fully distinguish between muscle mass and fat mass, and that only a single measurement of weight and height was taken, the validity of this measure was evaluated by examining its correlation with waist circumference. Waist circumference was measured using a Seca 201 ergonomic measuring tape. With the child standing and the abdominal area exposed, the tape was placed horizontally around the waist, passing over the navel and across the iliac crest. The measurement was taken at the end of an exhalation, with the abdomen relaxed. The correlation between BMI z score and waist circumference was rho= 0.85 (p-value < 0.001), indicating a strong positive correlation between the two variables.

2.2.3 Covariates

Sociodemographic and health-related information was collected from both studies. From the first study, data included maternal age, ethnicity, education level, source of drinking water during pregnancy, and pre-pregnancy BMI, as well as infant birth weight and gestational age. Maternal ethnicity was self-report and recategorized into three groups: “No reported” (no ethnicity reported), “Northern” (Aymara n=149, Quechua n=6, Diaguita n=1), and “Other” (Mapuche n=17). From the second study, data were collected on the child’s sex, age, and engagement in physical activity.

Complete data were available for most covariates. Missing values were as follows: pre-pregnancy BMI (n=1), maternal level (n=2), prenatal urinary creatinine (n=1), birth weight (n=13), and gestational age (n=8).

2.3 Data analysis

We considered untransformed prenatal urinary inorganic arsenic concentration log-transformed arsenic, and categorical arsenic (quintiles). To evaluate its association with BMI z score in children aged 7 to 10 years, linear regression models were used. Potential confounders were identified based on the literature and through a directed acyclic graph (DAG). The confounding variables selected for adjustment were maternal age, education level [160, 161], pre-pregnancy BMI, and ethnicity [162, 165] (Supplementary, Figure 1).

Considering that the birth weight z score for gestational age could act as a mediator in the relationship between prenatal arsenic exposure and BMI z score, a causal mediation analysis was conducted within a potential outcomes framework. This analysis allowed the total effect to be decomposed into direct and indirect components. The results

indicated that the indirect effect was not statistically significant, suggesting that the birth weight z score for gestational age does not play a relevant mediating role in this association (Supplementary, Table 1). However, since this variable was associated with BMI z score, it was included as a covariate in the final model assessing the association between prenatal inorganic arsenic concentration and BMI z score. In addition, prenatal urinary creatinine concentration was included as an additional covariate to adjust for prenatal inorganic arsenic concentration in urine (Supplementary, Table 2).

We also evaluated potential interactions between prenatal urinary inorganic arsenic concentration (log-transformed) and maternal age, ethnicity, pre-pregnancy BMI, and birth weight z score for gestational age. For each covariate, an interaction term (log-arsenic × covariate) was added to the fully adjusted linear regression model. Statistical significance was assessed by examining the p-value of the interaction term, with p-values <0.05 considered statistically significant. No statistically significant interactions were observed. Detailed results of these models are presented in Supplementary Table 3.

In addition to standard adjustment for covariates, we also evaluated the association using a propensity score–adjusted model as a sensitivity analysis. We applied the generalized propensity score (GPS) framework for exposures with multiple categories [170, 171], using quintiles of prenatal arsenic exposure as recommended for continuous exposures [200]. First, we estimated the propensity scores by fitting a multinomial logistic regression model [172], which provided the probability of being in each exposure quintile given a set of covariates (ethnicity, maternal age, pre-pregnancy BMI, education level, and birth weight z score for gestational age).

Covariate balance was assessed by comparing standardized mean differences (SMDs) before and after weighting for each quintile (one-vs-rest contrast), using inverse probability weights defined as $w_i = 1/p_j(X_i)$ if the subject i was in quintile j and $w_i = 1/[1 - p_j(X_i)]$ otherwise, and the pooled standard deviation, with a threshold of 0.1 as the criterion to determine adequate covariate balance [201]. These diagnostic weights were used exclusively to evaluate balance and visualize results with love plots. After confirming adequate balance, quintile-specific inverse probability weights estimated from the multinomial logistic model were applied to weighted linear regressions of child BMI z score on log-transformed arsenic. The resulting quintile-specific regression coefficients were combined using inverse-variance weighting to obtain an overall regression coefficient and its 95% confidence interval. All statistical analyses were performed using R software version 4.5.0 .

3. Results

Table 1 shows the characteristics of mothers and their children included in this retrospective cohort analysis. A total of 59.4% of mothers enrolled in the study between 2015 and 2016. The median age of the participants was 26 years) (IQR 21–31), with a median of 12 years of education (IQR 12–12), and 34.6% identified as belonging to a northern ethnic group. During pregnancy, most mothers (58.2%) reported using bottled water. Regarding maternal health characteristics, the median pre-pregnancy BMI was 29.7 kg/m² (IQR: 26.4–32.9), while the median prenatal urinary arsenic concentration was 16 µg/L (IQR: 10–23).

Regarding children, the median age at the time of study participation was 8 years (IQR: 7–8), and 51% were female. In terms of nutritional diagnosis, 39.2% of the children had

normal weight, 22.8% were overweight, 21.5% had obesity, and 11.8% had severe obesity. A smaller proportion were at risk of (2.7%) or had undernutrition (2.0%).

Table 1. Maternal and child characteristics in the Arica cohort, Chile.

Characteristics	**N=451**
Maternal	N (%) or median [IQR]
Year of enrollment in SEREMI study	
2013 to 2014	183 (40.6)
2015 to 2016	268 (59.4)
Age (years)	26.0 [21.0; 31.0]
Education (years)	12.0 [12.0; 12.0]
Ethnicity	
No reported	278 (61.6)
Northern origin	156 (34.6)
Other	17 (3.8)
Source of water during pregnancy	
Tap water	176 (39.1)
Bottled water	262 (58.2)
Rural system, well, river, cistern	12 (2.7)
Pre-pregnancy BMI (kg/m²)	29.7 [26.4; 32.9]
Prenatal urinary arsenic (µg/L)	16.0 [10.0; 23.0]
Prenatal urinary creatinine (g/L)	0.9 [0.6; 1.4]
Child	
Gestational age (weeks)	39.0 [38.0; 40.0]
Birth weight (g)	3470.0 [3130.0; 3740.0]
Child's age (years)	8.0 [7.0; 8.0]
Sex, female	230 (51.0)
Nutritional status	
Undernutrition	9 (2.0)
Risk of undernutrition	12 (2.7)
Normal weight	177 (39.2)
Overweight	103 (22.8)
Obesity	97 (21.5)
Severe obesity	53 (11.8)
Engages in physical activity at school	443 (98.4)
Engages in physical activity outside school	195 (43.3)

We observed negative associations between both untransformed and natural log–transformed prenatal urinary inorganic arsenic concentration and child BMI z score in the regression models (statistically significant only for the log-transformed exposure). The log-transformed exposure fit better (R-square: 0.007 vs 0.012) and is presented in Table 2 below. In the crude model, the natural log of inorganic arsenic was significantly associated with a decrease in BMI z score (β= -0.21; 95% CI: -0.38, -0.03). This association remained in the model adjusted for maternal ethnicity, age, pre-pregnancy BMI, education, and birth weight z score (β= -0.20; 95% CI: -0.37, -0.03). Similarly, when prenatal arsenic exposure was modeled in quintiles, we observed negative associations across all exposure categories (R-square: 0.122). However, the relationship was not linear, with the strongest associations observed in the second and third quintiles (Table 2).

Table 2. Association between prenatal inorganic arsenic concentration and BMI z score in children aged 7 to 10 years.

	BMI z score				
	N	***β***	***95% CI***	***p-value***	***R-square***
Unadjusted model					
Inorganic arsenic (µg/L)[a]	451	-0.01	-0.02, 0.00	0.084	0.007
Ln inorganic arsenic (µg/L)[a]	451	-0.21	-0.38, -0.03	0.022	0.012
Arsenic quintiles (µg/L)[a]	451				
Q1: 2.5-9		Ref.			
Q2: 10-13		-0.80	-1.23, -0.37	<0.001	0.033
Q3: 14-19		-0.55	-0.94, -0.15	0.008	
Q4: 20-27		-0.39	-0.81, 0.03	0.066	
Q5: 28-126		-0.51	-0.93, -0.09	0.019	
Adjusted model					
Ln inorganic arsenic (µg/L)[b]	435	-0.20	-0.37, -0.03	0.024	0.111
Maternal ethnicity					
No reported		Ref.			
Northern origin		0.05	-0.23, 0.33	0.720	
Other		0.54	-0.17, 1.25	0.135	

Maternal age (years)		-0.02	-0.04, 0.00	0.054	
Pre-pregnancy BMI (kg/m²)		0.08	0.05, 0.11	<0.001	
Maternal education (years)		-0.02	-0.08, 0.05	0.565	
Birth weight z score		0.19	0.09, 0.29	<0.001	
Arsenic quintiles (µg/L)[b]	435				
Q1: 2.5-9		Ref.			
Q2: 10-13		-0.61	-1.03, -0.19	0.005	0.122
Q3: 14-19		-0.48	-0.86, -0.09	0.016	
Q4: 20-27		-0.33	-0.74, 0.08	0.113	
Q5: 28-126		-0.48	-0.89, -0.06	0.023	
Maternal ethnicity					
No reported		Ref.			
Northern origin		0.04	-0.24, 0.32	0.770	
Other		0.50	-0.21, 1.22	0.168	
Maternal age (years)		-0.02	-0.04, 0.00	0.106	
Pre-pregnancy BMI (kg/m²)		0.07	0.05, 0.10	<0.001	
Maternal education (years)		-0.02	-0.08, 0.04	0.555	
Birth weight z score		0.18	0.09, 0.28	<0.001	

[a] Simple linear regression model.
[b] Linear regression model adjusted for maternal ethnicity, age, pre-pregnancy BMI, education, and birth weight z score for gestational age.

Regarding propensity score, in general, the covariates showed reasonably good balance across quintiles in the unweighted sample. However, imbalances (SMD > 0.1) were observed in certain specific comparisons Using the propensity score approach, the balance of baseline covariates across quintiles of prenatal arsenic exposure was improved (Supplementary, Figure 2).

Table 3 shows the IPTW-adjusted associations from the linear regression models for each exposure quintile, using log-transformed exposure. In general, the weighted average of the β estimates from the IPTW-weighted models for each quintile (β= -0.18; 95% CI: -0.26, -0.09) is similar to the effect observed in the linear regression model (Table 2), reinforcing the evidence of a negative association between prenatal arsenic exposure and child growth.

Table 3. IPTW-weighted regression models for the association between prenatal inorganic arsenic concentration and BMI z score in children aged 7 to 10 years.

		BMI z score		
Arsenic quintiles (µg/L)	**N= 448**	***β***	***95% CI***	***p-value***
Q1: 2.5-9		-0.20	-0.36, -0.04	0.014
Q2: 10-13		-0.14	-0.35, 0.08	0.213
Q3: 14-19		-0.21	-0.44, 0.02	0.078
Q4: 20-27		-0.14	-0.34, 0.07	0.195
Q5: 28-126		-0.18	-0.35, -0.01	0.038

4. Discussion

This retrospective cohort study found an inverse association between prenatal inorganic arsenic exposure and child BMI z score, a finding that contrast with our initial hypothesis. Specifically, linear regression models showed that higher concentrations of natural log–transformed prenatal urinary inorganic arsenic were associated with lower BMI z scores among children measured between 7 and 10 years of age. Findings using standard covariate adjustment were confirmed when using propensity scores to adjust for covariates.

Our hypothesis, that arsenic would be associated with higher BMI, was based on previous evidence, in both animal and human models, suggesting that arsenic may contribute to the development of obesity through various biological mechanisms [31]. In animal models, arsenic exposure has been shown to reduce the expression of perilipin protein in adipose tissue, promote fat deposition in skeletal muscle, limit the ability of preadipocytes to differentiate into mature adipocytes, and decrease the expression of the glucose transporter protein GLUT4. In addition, arsenic exposure during pregnancy

has been associated with lower adiponectin levels and increased body weight after birth [31, 130, 151]. Other proposed mechanisms include epigenetic modifications, such as DNA methylation and histone modification, which may influence the development of long-term metabolic disorders [32]. For example, DNA methylation marks associated with maternal lineage arsenic exposure have been identified, which are linked to an increased risk of metabolic diseases in offspring [152]. Early arsenic exposure has also been associated with reduced expression of the gene encoding peroxisome proliferator-activated receptor gamma (PPARγ), a key regulator of adipocyte differentiation. Low expression of this gene may disrupt lipid balance and metabolism, promoting obesity and other metabolic problems later in life [153].

Beyond the available information on potential mechanisms of action, the epidemiological evidence regarding the relationship between urinary arsenic exposure and childhood obesity is limited and the results are inconclusive for both prenatal and postnatal exposure. Regarding prenatal exposure, a cohort study of Spanish children exposed to low levels of urinary arsenic found no evidence of an association with anthropometric measurements at age 7 years (β= -0.01; 95% CI: -0.29, 0.26 for the second tertile and β= -0.05; 95% CI: -0.34, 0.24 for the third tertile) [25]. As for postnatal exposure, a cross-sectional study of Canadian children found no association between urinary arsenic (measured as DMA) and obesity in either the 3–5 year age group (OR= 0.98; 95% CI: 0.92, 1.05) or the 6–11 year age group (OR= 1.01; 95% CI: 0.96, 1.06) [28]. Similarly, a case-control study of Spanish children aged 6 to 12 years also reported no significant association between urinary arsenic and overweight/obesity (OR= 1.17; 95% CI: 0.75, 1.82) [29].

With respect to studies using other biomarkers of arsenic exposure, such as arsenic in blood, findings have also been inconclusive. In a cohort of Mexican children, no significant association was observed between prenatal blood arsenic and BMIZ at ages 4–6 years (β= 0.04; 95% CI: -0.18, 0.26) [26]. Likewise, in a U.S. cohort, no association was found between maternal erythrocyte arsenic and BMIZ at different follow-up points: at age 3 years (β= -0.01; 95% CI: -0.05, 0.04), 8 years (β= 0.03; 95% CI: -0.03, 0.08), and 13 years (β= -0.03; 95% CI: -0.09, 0.03) [27]. Similarly, in a cross-sectional study of Canadian children aged 2–5 years, no significant differences were observed in BMI z-score across tertiles of concurrent arsenic exposure measured in blood (tertile 2: β = -0.071; 95% CI: -0.27, 0.13; tertile 3: β = -0.01; 95% CI: -0.22, 0.19) [24].

In our study, we did not find evidence of an association between prenatal inorganic arsenic exposure and an increase in BMI z score. However, our analysis relied on a single prenatal arsenic measurement and did not include postnatal exposure data. Although we had a cross-sectional measurement of arsenic at the time BMI was assessed, this variable was not included in the analysis because it is not possible to confirm whether arsenic exposure preceded the development of obesity. This is particularly relevant given that BMI has been identified as a predictor of arsenic methylation capacity, showing a positive relationship with the percentage of dimethylarsinic acid (DMA) and a negative relationship with the percentage of monomethylarsonic acid (MMA) in adults [202-204] and children [205]. Nevertheless, a higher proportion of DMA may be influenced by greater dietary intake in children with higher BMI. For example, a study in Uruguayan children found that those with higher BMI consumed more rice than non-obese children [205]. In this context, a positive association between urinary arsenic concentration and BMI might represent reverse causality rather than a causal effect of arsenic exposure on obesity.

One strength of this study was the measurement of inorganic arsenic exposure during the prenatal period, a critical window of susceptibility, using specifically the inorganic fraction of urinary arsenic, which is the most toxic form of arsenic. In addition, the use of prenatal urinary arsenic concentration allowed us to establish temporality between exposure and outcome. However, our study has several limitations. First, the fact that the data for this retrospective cohort were drawn from two previous studies that were not specifically designed for the objectives of this analysis, limited the availability of some variables of interest, such as methylated arsenic metabolites. Second, the outcome variable (BMI z score) was based on a single measurement of weight and height, which may introduce random variability in BMI estimation due to the lack of repeated measurements; nevertheless, a strong correlation was observed between BMI z score and waist circumference, supporting the validity of the anthropometric measurement used. Third, the absence of longitudinal measurements of weight and height after birth, which restricted the analysis to a single time point in childhood and prevented the identification of BMI trajectories over time. Finally, the lack of postnatal arsenic measurements limited evaluation of cumulative exposure, which could have affected BMI.

These findings highlight the need to continue monitoring and controlling arsenic exposure during pregnancy, a critical period of susceptibility in child development. Although we found an inverse association between prenatal inorganic arsenic exposure and child BMI z score, these results should be interpreted with caution, given that the existing evidence is limited and sometimes inconsistent. Understanding the effects of prenatal arsenic is essential not only from a scientific perspective, to clarify the underlying mechanisms through which arsenic affects metabolic health and growth, but also from a public health

perspective, as it provides evidence to support the prevention and mitigation of exposure in vulnerable populations, such as pregnant women and children.

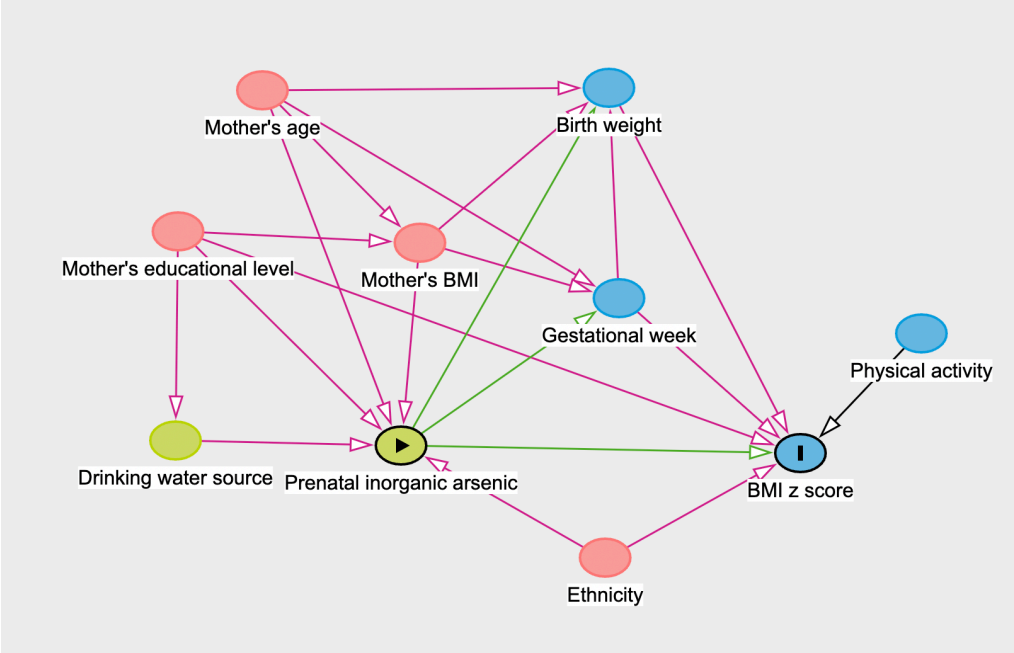
Conclusions

Contrary to the initial hypothesis, prenatal inorganic arsenic exposure was not associated with an increase in child BMI z score, but instead showed a modest inverse association in children aged 7 to 10 years in Arica, Chile. While these results add to the limited and inconsistent evidence on arsenic and childhood growth, they should be interpreted with caution given the study's limitations. These findings underscore the need for future longitudinal studies incorporating repeated exposure measurements and assessment of trajectories over time to better understand the mechanisms through which arsenic may influence metabolism and child growth.

Prenatal inorganic arsenic exposure and body mass index: a retrospective cohort study in children from Arica, Chile.

Supplementary

Figure 1. Directed acyclic graph (DAG) of variables involved in the relationship between prenatal arsenic exposure and the BMI z score



The DAG was used to identify the minimally sufficient adjustment set for estimating the association between prenatal arsenic exposure and BMI z score. The covariates selected for adjustment were: maternal ethnicity, maternal BMI at the beginning of pregnancy, maternal age, and maternal education level. These covariates were included in the adjusted model to control for confounding.

We evaluated whether the birthweight-for-gestational-age z score acts as a mediator in this association (Table 1). A causal mediation analysis based on the potential outcomes framework was conducted to decompose the effects into direct and indirect components. The results indicate that the natural logarithm of prenatal urinary arsenic concentration

has a significant direct effect (DE) on the BMI z score (β= -0.19; 95% CI: -0.36, -0.04), suggesting a negative direct association between the exposure and BMI z score, even when controlling for the mediator. However, the indirect effect (IE), mediated by the birthweight-for-gestational-age z score, was not statistically significant (IE = -0.019; 95% CI: -0.06, 0.02), indicating that birthweight-for-gestational-age z score does not act as a mediator in this association. Lastly, the estimated total effect shows that a one-unit increase in the natural log of prenatal inorganic arsenic concentration is associated with an average decrease of 0.21 units in the child's BMI z score (95% CI: -0.38, -0.05).

Table 1. Mediation analysis of birthweight-for-gestational-age z score in the association between the natural log of prenatal urinary arsenic and BMI z score.

		BMI z score		
	N= 435	***β***	***95% CI***	***p-value***
Indirect effect		-0.0190	-0.06, 0.02	0.364
Direct effect		-0.1974	-0.36, -0.04	0.016
Total effect		-0.2164	-0.38, -0.05	0.006
% Mediated		0.0880	-0.13, 0.44	0.366

Adjusted for: Maternal ethnicity, age, education, and pre-pregnancy BMI.
Simulations: 1,000

Table 2 presents the results of the regression models using the natural log of prenatal inorganic arsenic concentration in urine, adjusted for urinary creatinine.

Table 2. Association between prenatal inorganic arsenic concentration and BMI z score in children, adjusted for urinary creatinine.

	BMI z score				
	N	***β***	***CI 95%***	***p-value***	***R-square***
Ln inorganic arsenic (µg/L)[a]	434	-0.22	-0.47, 0.02	0.069	0.110
Maternal ethnicity					
No reported		Ref.			

Northern origin		0.07	-0.22, 0.35	0.652	
Other		0.53	-0.18, 1.24	0.141	
Maternal age (years)		-0.02	-0.04, 0.00	0.055	
Pre-pregnancy BMI (kg/m²)		0.08	0.05, 0.11	<0.001	
Matrnal education (years)		-0.02	-0.08, 0.05	0.589	
Birth weight z score		0.19	0.09, 0.29	<0.001	
Prenatal urinary creatinine (g/L)		0.07	-0.26, 0.40	0.684	
Ln arsenic/creatinine (µg/g)[b]	434	-0.21	-0.47, 0.06	0.130	0.105
Maternal ethnicity					
No reported		Ref.			
Northern origin		0.09	-0.20, 0.38	0.538	
Other		0.52	-0.20, 1.23	0.154	
Maternal age (years)		-0.02	-0.04, 0.00	0.062	
Pre-pregnancy BMI (kg/m²)		0.08	0.05, 0.10	<0.001	
Maternal education (years)		-0.02	-0.08, 0.05	0.578	
Birth weight z score		0.19	0.10, 0.29	<0.001	

[a] Adjusted for maternal ethnicity, age, pre-pregnancy BMI, education, birth weight z score for gestational age, and prenatal urinary creatinine.
[b] Model for ln arsenic/creatinine (µg/g), adjusted for maternal ethnicity, age, pre-pregnancy BMI, education, and birth weight z score for gestational age.

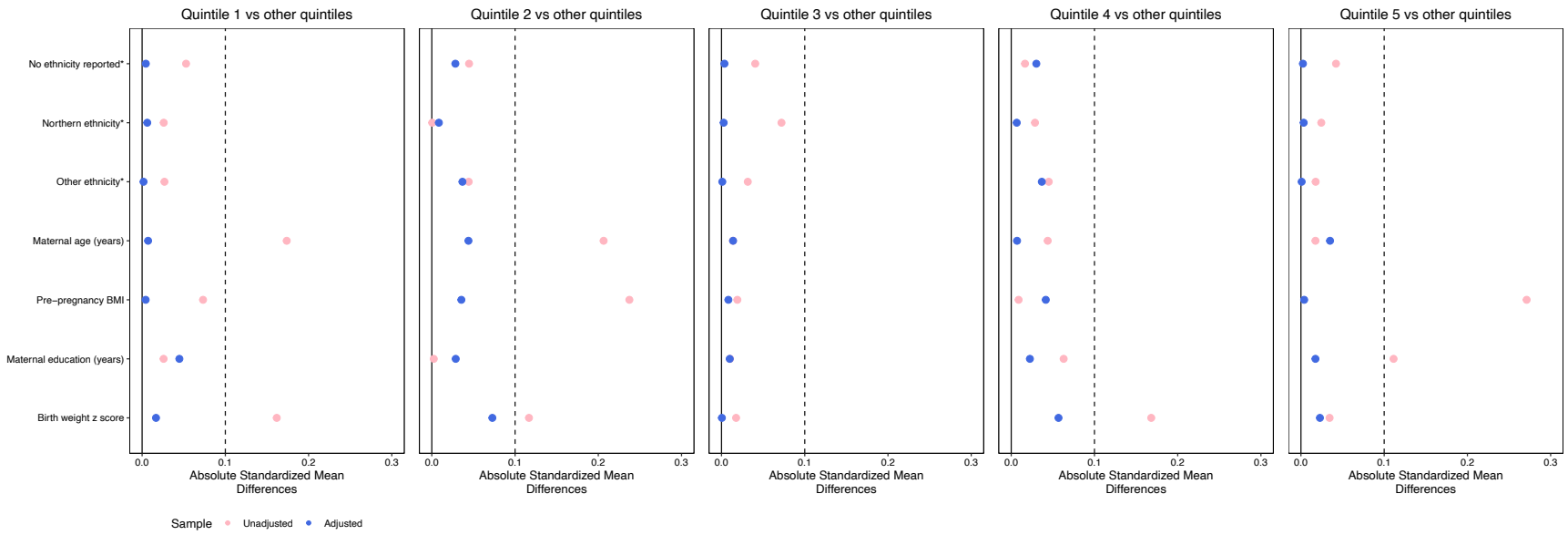
Table 3 presents interaction models between prenatal urinary inorganic arsenic concentration (log-transformed) and selected maternal and child characteristics, adjusted for all covariates in the model. No statistically significant interactions were observed.

Table 3. Interaction models between prenatal urinary inorganic arsenic concentration (log-transformed) and maternal/child characteristics.

Interaction term	*N*	*β*	*95% CI*	*p-value*
Ln inorganic arsenic (µg/L) × ethnicity (Del norte)	434	0.02	-0.34, 0.38	0.912
Ln inorganic arsenic (µg/L) × ethnicity (Otra)	434	-0.25	-1.13, 0.62	0.572
Ln inorganic arsenic (µg/L) × maternal age	434	-0.00	-0.03, 0.03	0.944
Ln inorganic arsenic (µg/L) × pre-pregnancy BMI	434	-0.01	-0.05, 0.03	0.577
Ln inorganic arsenic (µg/L) × birth weight z score	434	0.07	-0.03, 0.18	0.180

All models were adjusted for maternal ethnicity, age, pre-pregnancy BMI, education, birth weight z score for gestational age, and prenatal urinary creatinine.

Figure 1. Standardized mean differences before and after propensity score adjustment for each quintile of prenatal inorganic arsenic exposure.



Each plot shows the standardized mean differences of covariates between a specific exposure quintile and the remaining quintiles. Pink dots represent unweighted differences (original sample), while blue dots show the differences after adjustment using the IPTW. The vertical dashed line at 0.1 indicates the threshold for good balance; mean differences below this value suggest adequate covariate balance between the groups being compared.

Note: The categories of the variable maternal ethnicity are labeled in the figure as “No ethnicity reported,” “Northern ethnicity,” and “Other ethnicity.”

8. Discusión

La exposición al arsénico inorgánico continúa siendo un problema de salud pública a nivel mundial, particularmente en regiones donde las concentraciones naturales en aguas subterráneas superan los niveles establecidos por la OMS [206]. La evidencia epidemiológica ha documentado de manera consistente los efectos de la exposición crónica al arsénico en la salud, incluyendo cáncer [113], enfermedades cardiovasculares [116], alteraciones del neurodesarrollo [207] y resultados adversos en el embarazo [118]. No obstante, la relación entre la exposición temprana al arsénico y el crecimiento infantil [13], así como su influencia en el desarrollo de obesidad [25-29], sigue siendo poco clara y los resultados disponibles son inconsistentes. En este contexto, la presente tesis tuvo como objetivo evaluar la asociación entre la exposición prenatal al arsénico inorgánico y el z score del IMC en los niños, combinando la síntesis de evidencia mediante una revisión sistemática de la literatura y el análisis de datos de una cohorte retrospectiva de niños y niñas de Arica, Chile.

La revisión sistemática incluyó 26 estudios observacionales publicados entre 2009 y 2024 que evaluaron la asociación entre la exposición prenatal o postnatal al arsénico y desenlaces antropométricos en la infancia y adolescencia. En conjunto, los resultados de los estudios incluidos no respaldan una asociación concluyente, ya que solo siete estudios reportaron asociaciones estadísticamente significativas, la mayoría de ellas en dirección negativa, es decir, asociando mayores concentraciones de arsénico con menor peso o talla para la edad, mientras que la mayoría no encontró asociación. Entre las principales limitaciones identificadas destacan el uso de mediciones únicas de exposición al arsénico, la ausencia de especiación de arsénico (iAs, MMA y DMA), necesaria para diferenciar la fracción tóxica y el control insuficiente de variables de

confusión. Además, se observó una concentración geográfica de estudios en el sur de Asia, particularmente Bangladesh (23%), lo que restringe la generalización de los resultados a otras poblaciones. Estos resultados coinciden con los reportados por la revisión previa de Rahman et al., que tampoco encontró evidencia concluyente sobre el efecto de la exposición al arsénico en el crecimiento infantil y que se basó principalmente en estudios realizados en Bangladesh [152].

En el estudio de cohorte retrospectiva realizado en esta tesis se evaluó la asociación entre la concentración de arsénico inorgánico en orina materna, medida al momento del parto, y el z score del IMC en 451 niños de 7 a 10 años de edad. Contrario a la hipótesis inicial, que planteaba que una mayor exposición prenatal al arsénico inorgánico se asocia con mayor z score del IMC, los resultados mostraron una asociación inversa; concentraciones más altas de arsénico inorgánico prenatal se relacionaron con un menor z score del IMC. Esta asociación se mantuvo tras ajustar por covariables basales como la edad y la educación materna, el IMC al inicio del embarazo y z score del peso al nacer, y se confirmó mediante análisis con IPTW. Tampoco se observaron interacciones estadísticamente significativas con edad materna, etnia, IMC al inicio del embarazo ni z score peso al nacer, confirmando que la exposición prenatal al arsénico se asocia negativamente con el IMC en los niños, principalmente a través de efectos directos.

La integración de los hallazgos de la revisión sistemática y del estudio de cohorte proporciona una visión más amplia sobre el posible rol del arsénico en las medidas antropométricas en la infancia y adolescencia. Mientras que la evidencia epidemiológica disponible no permite concluir que exista una asociación positiva entre la exposición temprana al arsénico y un mayor IMC en la infancia, los resultados de esta tesis sugieren

una relación inversa. Esta coincidencia con los estudios que han reportado efectos negativos en las medidas antropométricas refuerza la plausibilidad de una asociación inversa entre la exposición al arsénico y el IMC. Aunque los mecanismos no están completamente dilucidados, se postula que la exposición prenatal al arsénico podría afectar la función placentaria al inducir estrés oxidativo, incrementar la producción de citoquinas proinflamatorias y elevar los niveles de leptina placentaria, lo que en conjunto podría comprometer el transporte de oxígeno y nutrientes hacia el feto [146, 147]. Estos procesos podrían dar lugar a bajo peso al nacer y alteraciones inmunológicas tempranas, que a su vez podrían afectar el crecimiento durante los primeros meses de vida y manifestarse en una reducción de las medidas antropométricas [13, 146, 150].

Asimismo, los mismos mecanismos biológicos implicados en el deterioro del crecimiento podrían también contribuir, en etapas posteriores, al desarrollo de obesidad y trastornos metabólicos, dado que tanto el bajo peso al nacer como el retraso en el crecimiento se reconocen como factores de riesgo [31, 34]. Además, el arsénico puede influir en la fisiopatología de la obesidad mediante modificaciones epigenéticas como la metilación del ADN y la modificación de histonas [32], la alteración en la diferenciación de adipocitos y la disminución en la expresión de reguladores en el metabolismo lipídico [153]. Estas vías de acción refuerzan la hipótesis de que la exposición temprana al arsénico puede ejercer un efecto al restringir el crecimiento en etapas iniciales y, al mismo tiempo, predisponer a un mayor riesgo de obesidad y alteraciones metabólicas a lo largo del curso de vida.

Al interpretar los resultados de esta tesis es necesario considerar no solo las limitaciones propias del estudio de cohorte retrospectiva, sino también aquellas identificadas en la revisión sistemática. En el caso de la revisión, la evidencia disponible sobre la asociación entre exposición temprana al arsénico y crecimiento infantil es heterogénea e

inconsistente, en parte debido a la variabilidad en los diseños de estudio, las pocas investigaciones con mediciones repetidas de exposición y la ausencia de especiación de arsénico que permita diferenciar las fracciones inorgánicas y sus metabolitos (iAs, MMA, DMA). A ello se suma el control insuficiente de variables de confusión en un número importante de estudios y la marcada concentración geográfica de la evidencia en el sur de Asia, particularmente en Bangladesh. Esta concentración de estudios en un solo contexto limita la validez externa de los hallazgos y restringe su generalización a otras poblaciones, incluyendo aquellas de América Latina, donde existe exposición natural al arsénico [48, 49]. Además, la revisión incluyó únicamente artículos en inglés, lo que podría haber excluido investigaciones en otros idiomas y generado un sesgo de selección de la evidencia.

En este sentido, los resultados de la cohorte retrospectiva de Arica complementan la evidencia epidemiológica publicada hasta el momento, al aportar datos desde un contexto latinoamericano naturalmente expuesto a niveles de arsénico en el agua. Una fortaleza importante de este estudio es la medición de arsénico en orina materna durante el período prenatal, una ventana crítica de susceptibilidad, así como el uso de la fracción inorgánica, que representa la forma más tóxica de arsénico. Sin embargo, este análisis presenta varias limitaciones que deben considerarse al interpretar los resultados. En primer lugar, el diseño retrospectivo se basó en datos de dos estudios previos que no fueron originalmente diseñados para responder la pregunta de investigación de esta tesis, lo que restringió la disponibilidad de variables, como los metabolitos metilados de arsénico y el ajuste por otras exposiciones ambientales que podrían actuar como factores de confusión. En segundo lugar, la exposición prenatal se evaluó mediante una única medición en el momento del parto, lo que podría no reflejar la exposición acumulada a lo largo de todo el embarazo, y no se contó con datos de exposición

postnatal. Esta ausencia impide diferenciar el efecto de la exposición prenatal del posible efecto de exposiciones posteriores, que también podrían influir en las medidas antropométricas. En tercer lugar, el z score del IMC se calculó a partir de una única medición de peso y talla en la niñez, lo que puede introducir variabilidad aleatoria y limita la capacidad de analizar trayectorias de crecimiento a lo largo del tiempo. La incorporación de mediciones repetidas permitiría modelar trayectorias de crecimiento y evaluar si la exposición prenatal al arsénico se asocia con patrones de aceleración o desaceleración en distintas etapas de la infancia, lo que entregaría una mejor evidencia sobre la direccionalidad y temporalidad del efecto.

Por lo anterior, aunque los resultados de este estudio muestran una asociación inversa entre la exposición prenatal al arsénico y el IMC infantil, las limitaciones mencionadas impiden establecer una relación causal. Más bien, los resultados deben interpretarse con cautela, lo que justifica la realización de estudios prospectivos con mediciones repetidas de exposición y seguimiento longitudinal de las medidas antropométricas. No obstante, el análisis de potencia a posteriori mostró que el estudio tuvo suficiente poder estadístico para detectar la magnitud del efecto estimado, lo que indica que la ausencia de una asociación positiva no se debe a falta de potencia, sino que podría reflejar un efecto real en dirección inversa a la hipótesis inicial.

Los resultados de esta tesis tienen implicancias para la salud pública, especialmente en la vigilancia de la exposición a arsénico y en el monitoreo del crecimiento infantil en poblaciones potencialmente expuestas. La identificación de una asociación inversa entre exposición prenatal y z score del IMC sugiere que el arsénico podría influir en el crecimiento infantil a través de mecanismos que aún no se comprenden completamente. Si bien en Arica el agua distribuida por las redes urbanas cumple actualmente con la

normativa nacional y con las recomendaciones de la OMS [192], estos resultados refuerzan la importancia de mantener y fortalecer los programas de vigilancia ambiental y sanitaria existentes, asegurando la continuidad de la monitorización de arsénico en agua potable tanto en zonas urbanas como en localidades rurales, particularmente aquellas que no están bajo la supervisión de la Superintendencia de Servicios Sanitarios y que podrían depender de sistemas de agua no tratada adecuadamente.

Asimismo, los programas de control de salud de niños y niñas en atención primaria cumplen un rol fundamental para detectar desviaciones en las trayectorias de crecimiento. Integrar de manera coordinada los datos antropométricos recolectados rutinariamente en el control de niño sano con sistemas de vigilancia ambiental podría facilitar la identificación de posibles impactos de la exposición ambiental en el crecimiento. Este enfoque permitiría una detección temprana de patrones atípicos de crecimiento en poblaciones vulnerables y apoyaría la toma de decisiones basadas en evidencia.

Desde una perspectiva de investigación, este estudio subraya la necesidad de avanzar hacia diseños longitudinales que incluyan mediciones repetidas de exposición y de desenlaces antropométricos, así como la especiación de arsénico inorgánico y la determinación de metabolitos metilados. La integración de datos socioeconómicos y ambientales permitirá un mejor control de factores de confusión y una caracterización más precisa de la relación entre exposición temprana al arsénico y crecimiento. Además, generar evidencia en contextos latinoamericanos es importante para complementar el conocimiento disponible, hoy concentrado principalmente en el sur de Asia, y para apoyar decisiones de política pública en la región.

Conclusión

Esta tesis aporta nueva evidencia al demostrar que la exposición prenatal al arsénico inorgánico en una población chilena se asocia inversamente con el z score del IMC en la niñez, aportando evidencia novedosa en un contexto latinoamericano, donde la literatura sigue siendo escasa. Los resultados, en conjunto con la revisión sistemática, muestran que la relación entre arsénico y las medidas antropométricas es compleja y aún no está claramente establecida. Estos hallazgos subrayan la necesidad de estudios longitudinales que permitan comprender los efectos metabólicos de la exposición temprana al arsénico y diseñar intervenciones oportunas para proteger la salud infantil en zonas con riesgo de exposición.

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Anexo 1

Instrumento de riesgo de sesgo OHAT [158]

Dominios de sesgos y preguntas	Definitivamente bajo riesgo de sesgo (++)	Probablemente bajo riesgo de sesgo (+)	Probablemente alto riesgo de sesgo (-)	Definitivamente alto riesgo de sesgo (--)
Sesgo de selección				
¿Fueron apropiados los grupos de comparación?				
Confusión				
¿El diseño o análisis del estudio tuvo en cuenta importantes variables de confusión y modificación?				
¿Los investigadores ajustaron o controlaron otras exposiciones que se prevé que sesguen los resultados?				
Sesgo de desempeño				
¿Se adhirieron los investigadores al protocolo del estudio?				
Sesgo de desgaste/exclusión				
¿Los datos de resultados estaban completos sin desgaste o				

exclusión del análisis?				
Sesgo de detección				
¿Se evaluaron las variables de confusión de manera consistente entre los grupos utilizando medidas válidas y confiables?				
¿Se puede confiar en la caracterización de la exposición?				
¿Se puede tener confianza en la evaluación de resultados?				
Sesgo de información selectiva				
¿Se informaron todos los resultados medidos?				
Otros				
¿No hubo otras amenazas potenciales a la validez interna (por ejemplo, los métodos estadísticos eran apropiados)?				

Anexo 2

Comparación de las características maternas y de los niños entre quienes participaron en el estudio 2 (FONIS) y aquellos que no participaron.

Características	No participa en estudio 2 N=1223	Participan en estudio 2 N=451
	N (%) or median [IQR]	
Edad de la madre, (años)	26.00 [22.00, 31.00]	26.00 [21.00, 31.00]
Educación de la madre, (años)	12.00 [12.00, 12.00]	12.00 [12.00, 12.00]
Etnia de la madre		
No reporta	792 (64.8)	278 (61.6)
Del norte	387 (31.6)	156 (34.6)
Otra	44 (3.6)	17 (3.8)
IMC pre embarazo, (kg/mt^2)	29.13 [26.21, 33.14]	29.70 [26.40, 32.90]
Arsénico urinario prenatal, (µg/L)	15.00 [9.00, 23.00]	16.00 [10.00, 23.00]
Creatinina urinaria prenatal, g/L	0.84 [0.51, 1.24]	0.88 [0.58, 1.37]
Semana gestacional, (semanas)	39.00 [38.00, 40.00]	39.00 [38.00, 40.00]
Peso al nacer, (g)	3420.00 [3090.00, 3730.00]	3470.00 [3130.00, 3740.00]

Análisis de mediación:

El análisis de mediación se llevó a cabo para evaluar el efecto de la exposición prenatal al arsénico sobre el z score del IMC y determinar si el peso al nacer actúa como mediador en esta relación. Se utilizó un enfoque de mediación causal basado en un marco de resultados potenciales, que permite descomponer el efecto total en un efecto directo natural (ED) y un efecto indirecto natural (EI) [208].

Para estimar estos efectos, se asumieron los supuestos de control de la confusión descrito por VanderWeele T. [209]: i) no existe confusión no medida entre la exposición y el resultado; ii) no hay confusión no medida entre el mediador y el resultado; iii) no hay confusión no medida entre la exposición y el mediador; y iv) no debe existir un confusor en la relación entre el mediador y el resultado que pueda ser explicado por la exposición.

A partir de un análisis teórico, se identificaron las posibles variables de confusión para las relaciones entre a) exposición prenatal al arsénico y z score del IMC: edad y nivel educacional de la madre [160, 161]; b) z score peso al nacer y z score del IMC: IMC materno [4, 210], sexo [64] nivel educacional de la madre [161, 210] y etnia [162, 210]; y por último, c) z score del peso al nacer y z del IMC: sexo y nivel educacional de la madre[160, 210].

Se procedió a estimar el ED y el EI mediante el ajuste de dos modelos de regresión lineal. En primer lugar, se ajustó un modelo para la variable de resultado (z score del IMC) que incluyó el logaritmo de la concentración prenatal al arsénico, el mediador (z score del peso al nacer) y las covariables identificadas. Este modelo se describe mediante la siguiente ecuación:

$$\mathbb{E}[Y|t,m,c] = \theta_0 + \theta_{1t} + \theta_{2m} + \theta_{3c}$$

Donde Y es el z score del IMC (variable de resultado), t es el logaritmo natural de la concentración prenatal al arsénico (variable de exposición), m es el z score del peso al nacer (mediador), y c las covariables (edad materna, nivel educacional de la madre, IMC materno antes del embarazo, sexo y etnia). θ_0 es el intercepto que representa el valor esperado del z score del IMC cuando las variables t, m, c son = 0. θ_{1t} expresa el efecto directo del logaritmo natural de la concentración prenatal al arsénico sobre el z score del IMC, controlando por el mediador y las covariables. θ_{2m} es el efecto del mediador (z score del peso al nacer) sobre el z score del IMC, controlando por la exposición y las covariables, y θ_{3c} expresa los efectos de las variables confusoras.

En segundo lugar, se ajustó un modelo de regresión lineal para el mediador (z score del peso al nacer):

$$\mathbb{E}[M|t,c] = \delta_0 + \delta_1 t + \delta_2 c$$

Donde M es el z score del peso al nacer (mediador), t es el logaritmo de la concentración prenatal al arsénico, y c las covariables (edad materna, nivel educacional de la madre, IMC previo al embarazo, sexo del niño y la etnia). δ_0 es el intercepto, representa el valor

esperado del z score del peso al nacer cuando la exposición y las covariables son cero. $\delta_1 t$ expresa el coeficiente de la exposición, el logaritmo de la concentración prenatal al arsénico sobre el mediador (z score del peso al nacer), y $\delta_2 c$ representa los efectos de las covariables sobre el z score del peso al nacer.

Así, los efectos directos e indirectos se derivaron de las siguientes ecuaciones empíricas simplificadas:

Efecto directo natural (ED) [208]:

$$ED = \mathbb{E}[Y_{tMt*} - Y_{t*Mt*}|c] = \theta_1(t - t*)$$

El coeficiente θ_1 representa el cambio en el z score del IMC asociado a un cambio en la exposición (*t* a *t**), manteniendo el mediador constante.

Mientras que el efecto indirecto natural (EI) para un cambio en la exposición prenatal al arsénico del nivel t al nivel t* estaría dado por [208]:

$$EI = \mathbb{E}[Y_{tMt*} - Y_{tMt*}|c] = (\theta_2\delta_1)(t - t*)$$

Este efecto combina el efecto de la exposición sobre el mediador ($\boldsymbol{\delta_1}$) y el efecto del mediador sobre el resultado ($\boldsymbol{\theta_2}$).

Efecto total (TE):

$$TE = ED + EI$$

Representa la asociación global entre la exposición prenatal al arsénico y el z score del IMC.

Para evaluar la incertidumbre en las estimaciones del ED, EI y TE, se calcularon intervalos de confianza al 95% mediante el método de bootstrapping no paramétrico con 1000 repeticiones.

Anexo 3

Early-life arsenic exposure and childhood anthropometric measures: a systematic review

Supplementary 2

OHAT risk of bias classification for each study

Reference	**Selection bias** Were the comparison groups appropriate?	**Confounding bias I** Did the study design or analysis account for important confounding and modifying variables?	**Confounding bias II** Did researchers adjust or control for other exposures that are anticipated to bias results?	**Performance bias** Did researchers adhere to the study protocol?	**Attrition/exclusion bias** Were outcome data complete without attrition or exclusion from analysis?	**Detection bias I** Were confounding variables assessed consistently across groups using valid and reliable measures?	**Detection bias II** Can we be confident in the exposure characterization?	**Detection bias III** Can we be confident in the outcome assessment?	**Selective reporting bias** Were all measured outcomes reported?	**Other sources of bias** Were there no other potential threats to internal validity (e.g., statistical methods were appropriate)?

Saha et al., 2012	Probably low risk of bias (+). All participants came from the same cohort, and there were no baseline differences between those with and without data. Comparisons were made by quintiles of urinary arsenic within the same population. However, participation rates by exposure quintile were not reported, which prevents ensuring complete comparability.	Definitely low risk of bias (++). Models were adjusted for child's sex, maternal BMI, and socioeconomic status (wealth index); sensitivity analyses included birth weight/length and maternal arsenic.	Probably high risk of bias (–). Other metals or contaminants were not considered.	Definitely low risk of bias (++). No deviations from the study design or analysis were reported.	Probably low risk of bias (+). There were initial losses, but they were analyzed and found to be nondifferential; coverage improved during follow-up.	Definitely low risk of bias (++). Confounders were measured objectively and in a standardized manner.	Definitely low risk of bias (++). Urinary biomonitoring with arsenic speciation, repeated measurements, and quality control.	Definitely low risk of bias (++). Anthropometric measures followed WHO/CDC standards, using calibrated instruments and trained personnel.	Definitely low risk of bias (++). Reported main outcomes (WAZ, LAZ, underweight, stunting) and stratifications (sex, SES).	Definitely low risk of bias (++). Statistical methods were appropriate for the study design.

Gardner et al., 2013	Probably low risk of bias (+). Same cohort and period; comparison by exposure levels. The supplementary material indicates that included and excluded participants were similar, but participation rates by exposure level were not reported.	Definitely low risk of bias (++). Adjusted for multiple covariates: age, sex, socioeconomic status, maternal BMI, passive smoking, parity, and other factors influencing child growth.	Definitely low risk of bias (++). Measured and adjusted for other metals, including cadmium and lead (models with all three metals and models including both prenatal and concurrent exposure).	Definitely low risk of bias (++). No deviations from the study design or analysis were reported.	Probably low risk of bias (+). Included 1,505 of 2,853 mother–child pairs with complete data; included and excluded participants were similar, though the exclusion rate was high.	Definitely low risk of bias (++). Confounders measured using standardized methods (SES based on assets and education, maternal anthropometry), applied consistently.	Definitely low risk of bias (++). Urinary biomonitoring with arsenic speciation (iAs, MMA, DMA), prenatal and postnatal measurements (at 1.5 and 5 years), adjusted for specific gravity; laboratory with quality control procedures.	Definitely low risk of bias (++). Anthropometry conducted at 19 time points using standardized WHO methods, calibrated equipment, and trained personnel.	Definitely low risk of bias (++). Reported multiple outcomes (weight, height, z-scores, growth velocities) and null/attenuated results after adjustment; no indication of selective reporting.	Definitely low risk of bias (++). Models were appropriate (nonlinearity, $\log_2$ transformations, mixed models with random slopes, stratification by sex/SES, prenatal vs. concurrent comparison, robust standard errors).
Agay-Shay et al., 2015	Probably low risk of bias (+). Single cohort (INMA-Sabadell), same period and criteria; comparisons by urinary	Definitely low risk of bias (++). Adjusted for multiple confounders (child's sex, gestational age, birth weight,	Probably low risk of bias (+). The main study was multicontaminant; however, single-contaminant	Definitely low risk of bias (++). The INMA protocol was	Probably low risk of bias (+). Of 657 pregnant women, 470 children were followed up at 7	Definitely low risk of bias (++). Sociodemographic, anthropometric, and behavioral variables were	Probably low risk of bias (+). Arsenic exposure was measured in two urine samples (without	Definitely low risk of bias (++). Weight and height at 7 years were measured by trained personnel following	Definitely low risk of bias (++). All prespecified outcomes (zBMI and overweight at 7 years) were	Definitely low risk of bias (++). Linear and robust Poisson models, linearity tests, multiple

	arsenic levels within the same population. However, there is no direct evidence of baseline comparability across arsenic tertiles defined from pregnancy.	maternal age, pregestational BMI, weight gain, smoking, socioeconomic status, breastfeeding, and age at measurement).	analyses for arsenic were adjusted for confounders. No clear evidence of specific adjustment for other metals (Pb, Cd) in arsenic models, but the multicontaminant design suggests indirect consideration of co-exposures.	previously described; no deviations from the design or analysis were reported.	years (28% loss). Although comparisons between followed and non-followed participants were not reported, losses were clearly documented and missing exposure data (including arsenic) were handled statistically through multiple imputation (m = 100) under the MAR assumption, reducing potential bias.	measured using standardized questionnaires and records.	speciation) during pregnancy, adjusted for creatinine, and analyzed using validated analytical methods (LC/MS-MS).	standardized protocols; z-scores were calculated using WHO standards.	reported, with no evidence of selective reporting.	imputation with 100 datasets, and PCA with simultaneous adjustment were appropriately applied.

Choi et al., 2017	Probably low risk of bias (+). Healthy children aged 8–23 months from the same hospital and period; however, no comparison of characteristics between high and low arsenic groups was reported.	Definitely high risk of bias (– –). No adjusted models were presented for arsenic and WAZ/HAZ/WHZ.	Probably high risk of bias (–). Models for arsenic were not adjusted for other metals, despite significant correlations.	Definitely low risk of bias (++). No deviations from the study design or analysis were reported.	Definitely low risk of bias (++). 210 children were evaluated; missing data occurred for some covariates but not for the main outcomes.	Probably low risk of bias (+). Validated questionnaires were used; however, some variables were available only for a subsample.	Probably low risk of bias (+). Direct and valid biomonitoring (ICP-MS in blood), but only a single measurement without speciation.	Definitely low risk of bias (++). Weight and height were measured in a standardized manner, and WHO z-scores were used.	Probably high risk of bias (–). Arsenic results with HCAZ were reported, but results for WAZ/BWZ shown for lead were omitted.	Probably high risk of bias (–). Statistical methods were generally appropriate, but no multivariable models were applied to assess the association between arsenic and WAZ/HAZ/WHZ.
Fábelová et al., 2018	Probably low risk of bias (+). Defined population (<6 years, homeless children), random multistage sampling; comparability between high/low arsenic groups not	Definitely low risk of bias (++). Multivariable models adjusted for multiple maternal, socioeconomic, and child confounders; sensitivity analyses included birth weight.	Probably high risk of bias (–). Analyzed As, Cd, Hg, Pb, and Se, but arsenic models did not simultaneously adjust for other metals despite observed correlations (As–Pb).	Definitely low risk of bias (++). No deviations from the study design or analysis were reported.	Probably low risk of bias (+). Complete results for 324 children; exclusions were documented and compared, though some maternal differences	Definitely low risk of bias (++). Variables measured using standardized questionnaires administered by trained bilingual interviewers; moderate missing	Probably low risk of bias (+). Hair arsenic measured by ICP-MS with quality control; only one measurement, without speciation.	Definitely low risk of bias (++). Weight and height measured by nurses using calibrated scales; WHO z-scores calculated.	Definitely low risk of bias (++). All planned anthropometric outcomes (WAZ, HAZ, BMIZ) were reported, with no evidence of selective omission.	Probably low risk of bias (+). Multivariable linear regressions with appropriate multiple imputation; backward elimination may have introduced

	specifically reported.				could have introduced minor bias.	data handled with imputation.				minor bias.
Milton et al., 2018	Probably low risk of bias (+). Cohort of 120 newborns from a subdistrict, prospectively recruited; groups defined by arsenic levels in water (<50 vs. ≥50 µg/L and quartiles). Baseline comparability between high and low arsenic groups was not reported.	Probably high risk of bias (–). Only socioeconomic and dietary characteristics were described; no multivariable models adjusting for relevant confounders were used.	Probably high risk of bias (–). Other metals or contaminants were neither measured nor adjusted for, despite the risk of co-exposure in the area.	Definitely low risk of bias (++). No deviations from the study design or analysis were reported.	Probably low risk of bias (+). Follow-up was completed up to 9 months; no differential losses were detailed, although the sample size was small.	Probably low risk of bias (+). Socioeconomic and dietary information was collected through a structured questionnaire; measurement quality was acceptable.	Probably high risk of bias (–). Indirect estimation of exposure (a single household water sample) instead of biomonitoring, although the laboratory method was validated.	Probably low risk of bias (+). Weight and length were measured with basic instruments but following standardized protocols; outcomes were calculated as z-scores using WHO Anthro 2006.	Definitely low risk of bias (++). All planned outcomes (WAZ, HAZ, WHZ) were reported at all three time points, in detailed tables.	Probably high risk of bias (–). Analyses were limited to prevalence and exposure category comparisons without multivariable models, reducing internal validity.

Ashley-Martin et al., 2019	Probably low risk of bias (+). Cross-sectional analysis from a multi-site cohort (six sites); comparisons by arsenic tertiles. Baseline characteristics by exposure not reported, but global descriptive data support indirect comparability.	Definitely low risk of bias (++). Models adjusted for maternal education, country of birth, age, maternal postnatal BMI, prenatal smoking, and paternal BMI; also models considering maternal prenatal exposure.	Definitely low risk of bias (++). Concurrent adjustment for other metals/elements (Hg, Zn, Mo, Se) using Bayesian Model Averaging (BMA), appropriately addressing confounding by mixtures.	Definitely low risk of bias (++). No deviations from the design or analysis reported.	Definitely low risk of bias (++). 449/480 participants had complete data; one predefined outlier excluded; multiple imputation used for missing covariates.	Definitely low risk of bias (++). Covariates collected via standardized, validated MIREC questionnaires; no quality differences between groups; imputation for missing data applied.	Probably low risk of bias (+). Arsenic measured in child blood samples via ICP-MS at INSPQ; single measurement, no speciation; 19% <LOD, imputed by laboratory.	Definitely low risk of bias (++). Weight and height measured with calibrated scales and stadiometers, in duplicate/triplicate; WHO growth z-scores calculated for ages 2–5 years.	Definitely low risk of bias (++). Reported BMI, height, and weight z-scores for arsenic in three models (M1–M3), stratified by sex; no evidence of selective reporting.	Definitely low risk of bias (++). Appropriate analytical methods (log2 transformation, tertiles to assess non-linearity, splines, BMA, sex-stratified GAM models, and multiple imputation).
Kupsco et al., 2019	Probably low risk of bias (+). Subcohort of the PROGRESS cohort, with children followed up at 4–6 years. Comparisons made by maternal blood arsenic levels (second trimester).	Definitely low risk of bias (++). Models adjusted for key confounders: child sex, age, birth weight, gestational age, maternal pre-pregnancy BMI, maternal	Definitely low risk of bias (++). Explicitly adjusted for other metals (multi-metal models) and used advanced methods (BKMR) to analyze mixtures and	Definitely low risk of bias (++). No deviations from the design or analysis reported.	Probably low risk of bias (+). Of 948 women, 609 children (64%) were followed, and 548 had complete data for analysis. Baseline	Definitely low risk of bias (++). Covariates were collected through validated questionnaires in the PROGRESS cohort and standardized	Probably low risk of bias (+). Prenatal exposure measured in maternal blood (ICP-QQQ, validated method, with quality control). However, only one	Definitely low risk of bias (++). Weight and height were measured with calibrated instruments (Seca balance and stadiometer), and WHO standards were	Definitely low risk of bias (++). BMI z-score was a prespecified outcome in the protocol and was fully reported, with no evidence of	Definitely low risk of bias (++). Appropriate analytical methods: multivariable linear models, BKMR for mixtures, adjustment for non-

	Baseline comparability tables by arsenic level were not presented, but the cohort was similar in age, sex, and recruitment period. Indirect evidence of comparability.	education, socioeconomic status, and exposure to tobacco smoke. Also used splines for visit date to control for temporal trends.	interactions. Direct evidence of co-exposure control.		characteristics did not differ between included and excluded participants. Although attrition was considerable, it was well-documented and not clearly associated with outcomes.	measurements, with no evidence of between-group differences.	measurement was taken during the 2nd trimester and arsenic speciation was not performed.	used for z-score calculations. Procedures were consistent and reliable.	selective omission.	linearity and co-exposures, sensitivity analyses, and minimal imputation.
Baraquoni et al., 2020	Probably high risk of bias (–). Comparisons were made between categories of outcomes (weight/height according to WHO) and arsenic load; groups were not defined a priori by exposure level,	Definitely high risk of bias (– –). Associations were evaluated with non-parametric tests across categories without adjusted models; maternal BMI, education, SES, and other	Probably high risk of bias (–). Multiple metals in hair were measured, but no adjustments were made for mixtures or correlated metals, resulting in a high probability	Probably low risk of bias (+). Standardized protocols and questionnaires were used across	Probably high risk of bias (–). At 6 months: 22% attrition; at 18 months: 38–39% total loss. Although some comparisons between completers and non-completers	Probably low risk of bias (+). Comprehensive questionnaire (adapted EU-ROCAT) and systematic collection of socio-demographic	Probably low risk of bias (+). Hair biomonitoring by ICP-MS in an ISO 17025-accredited laboratory, with low LODs and quality control. However, exposure	Probably high risk of bias (–). At 6 months, weight and height were parent-reported; at 18 months, measurements were taken by pediatricians using WHO standards. Main	Probably high risk of bias (–). Multiple metals and comparisons were reported, but some results were mentioned as “not shown.” No preregistered	Definitely high risk of bias (– –). Predominant use of Kruskal–Wallis and sign tests without multivariable adjustment; no modeling of non-linear

	and no baseline comparability between groups was reported. Insufficient information to ensure similarity.	confounders were not controlled.	of confounding by co-exposure.	measurement periods; minor variations were mentioned, and staff were trained.	were described, the magnitude of attrition could be related to outcomes.	variables; no evidence of differential measurement between groups.	was measured in a single matrix without urinary speciation.	associations at 6 months rely on non-objective measures.	protocol was available to ensure complete outcome reporting.	relationships or interactions, compromising internal validity.
Moody et al., 2020	Probably low risk of bias (+). Children were recruited under uniform inclusion criteria (age, residence, caregiver availability) within the same community. No direct baseline comparisons by arsenic levels were reported, so comparability evidence is indirect.	Probably high risk of bias (–). The model adjusted only for maternal education and child hospitalization history. Important confounders such as maternal BMI, age, and detailed nutritional status were not considered, resulting in limited confounding control.	Probably high risk of bias (–). Mixtures of Pb, As, Cd, Se, and Zn were analyzed, but the independent effect of As was not evaluated in models adjusted for other metals. Confounding by co-exposure cannot be ruled out.	Definitely low risk of bias (++). No deviations from the design or analysis were reported.	Definitely low risk of bias (++). Of 100 recruited children, 97 were included (3 excluded for missing data). Attrition was minimal, well-documented, and unlikely to generate bias.	Definitely low risk of bias (++). Confounding variables (maternal education, hospitalization) were collected via standardized and consistently applied questionnaires.	Probably low risk of bias (+). Arsenic measured in blood using ICP-MS/MS, above LOD for all participants, but based on a single total blood measurement without urinary speciation.	Probably low risk of bias (+). Height measured during physical examination; HAZ calculated using CDC/WHO 1978 reference. Although valid, not using WHO 2006 standards represents a minor limitation.	Definitely low risk of bias (++). All planned outcomes (HAZ, stunting) were fully reported, along with complete model results.	Probably low risk of bias (+). Multivariable regression and WQS models were appropriate for mixture analysis, but the small sample size (n=97) could reduce statistical power.

Muse et al., 2020	Probably low risk of bias (+). Same clinics and study period, common population base, and comparison across quantiles of maternal urinary arsenic. No baseline comparability table by As levels presented; evidence of comparability is indirect.	Definitely low risk of bias (++). Models adjusted for major confounders (maternal BMI, weight gain, education, parity, smoking, sex, and gestational age). Multiple sensitivity analyses conducted (e.g., excluding rice or fish consumers, adjusting for creatinine, gestational diabetes, exclusive breastfeeding).	Probably high risk of bias (–). Other metals or contaminants were not considered.	Definitely low risk of bias (++). No deviations from the design or analysis were reported.	Probably low risk of bias (+). From 1,758 to 760 participants with both urinary As and anthropometry data. Missing data handled through indicators/means and mixed models (MAR). Some differences from the full cohort, but no evidence of differential loss by exposure.	Definitely low risk of bias (++). Confounders obtained through standardized questionnaires and clinical records, applied uniformly.	Definitely low risk of bias (++). Prenatal biomonitoring (2nd trimester) via HPLC-ICP-MS with arsenic speciation (iAs, MMA, DMA); reported LODs; adjusted for dilution (creatinine in subsample) and for arsenobetaine/seafood intake. Limitation: single measurement.	Definitely low risk of bias (++). Weight and height obtained from clinical records; WHO z-scores used; multiple time points (2 weeks–12 months) with consistent measurement methods.	Definitely low risk of bias (++). All prespecified anthropometric results reported (cross-sectional and longitudinal), including species-specific arsenic analyses and multiple sensitivity analyses.	Definitely low risk of bias (++). Applied linear, mixed, and segmented (piecewise) models; verified linearity; assessed interactions (sex, maternal BMI) with likelihood ratio tests; performed quantile and sensitivity analyses.

Vigeh et al., 2020	Probably low risk of bias (+). Recruitment occurred in the same context (growth/vaccination controls, Tehran 2013–2016) under uniform criteria for children aged 36–72 months. 22% non-response; no documentation of baseline comparability by arsenic strata.	Definitely high risk of bias (– –). No model evaluating the association between As and anthropometry; key confounders (maternal BMI, diet, smoking) were missing.	Probably high risk of bias (–). Although multiple metals were measured, no adjustment was made for co-exposures (e.g., lead or cadmium) in analyses of arsenic effects.	Definitely low risk of bias (++). No deviations from design or analysis were reported.	Probably high risk of bias (–). 31 of 207 samples (15%) lacked As data due to non-detects or technical issues, introducing possible bias.	Probably low risk of bias (+). Maternal education and income were collected through questionnaires; though no validation was reported, they were applied uniformly.	Probably high risk of bias (–). Arsenic measured in hair using ICP-MS without speciation and with a high proportion of non-detects; less reliable biomarker than urine.	Definitely low risk of bias (++). Weight and height measured using standardized scales and stadiometers; WHO z-scores calculated.	Probably high risk of bias (–). No statistical analyses examining associations between arsenic and anthropometry were reported; only descriptive statistics were presented.	Definitely high risk of bias (– –). No specific statistical analysis conducted for arsenic–anthropometry associations.
Wai et al., 2019	Probably low risk of bias (+). Single prospective cohort with uniform eligibility criteria across three districts; comparisons made by urinary arsenic levels within the same	Definitely low risk of bias (++). Adjusted for multiple confounders including child sex, gestational age, maternal weight, nutritional status, and	Probably high risk of bias (–). Did not measure or adjust for exposure to other environmental contaminants.	Definitely low risk of bias (++). No deviations from design or analysis reported.	Probably high risk of bias (–). Of 152 participants, 108 had complete data (29% attrition); characteristics of those lost versus retained were not	Probably low risk of bias (+). Standardized questionnaires administered by local staff to assess SES, gestational week, and	Probably low risk of bias (+). Prenatal arsenic measured via ICP-MS, adjusted for specific gravity and with quality control; however,	Definitely low risk of bias (++). Monthly anthropometric measurements conducted by trained staff; WHO Anthro used to compute z-scores.	Definitely low risk of bias (++). All prespecified anthropometric outcomes (WAZ, HAZ, WHZ, HCZ, and percentile analyses)	Probably low risk of bias (+). Used linear mixed models for repeated measures and regression analyses.

	population. Sample restricted to births in health centers, which may affect representativeness.	socioeconomic level.			compared, and non-differentiality was not tested.	breastfeeding; formal validation not reported.	no speciation and only a single measurement.		were reported, including null findings, with no evidence of omission or publication bias.	
Alao et al., 2021	Probably low risk of bias (+). Analysis used data from a case–control study of pneumonia, so inclusion depended on hospitalization for pneumonia rather than nutritional status. Although case/control status was statistically controlled and stratified analyses were performed, it is possible that child growth	Probably low risk of bias (+). The model included confounders (age, creatinine, paternal education, breastfeeding, crowding, and case status). However, maternal variables such as age, education, or BMI were not included. Adjustment was partial, though unlikely to change the	Probably high risk of bias (–). Only arsenic exposure was evaluated, without considering potential co-exposures to other heavy metals or environmental contaminants.	Definitely low risk of bias (++). No deviations from the study design or analysis were reported.	Probably low risk of bias (+). Excluded 46 of 511 participants for lack of urine samples (91% included). Exclusions were documented, but their impact on exposure group balance is uncertain.	Probably low risk of bias (+). Confounding variables were measured consistently across participants using study questionnaires, although validation of the instruments was not documented.	Probably low risk of bias (+). Total urinary arsenic measured via GF-AAS (LOD 2 µg/L) with creatinine adjustment; however, speciation was not conducted. For cases, samples were collected at the convalescent stage to avoid distortion	Definitely low risk of bias (++). Weight and height were measured using WHO z-scores; for cases, measurements were taken at convalescence to avoid acute illness effects. Standardized and appropriate procedures were used.	Definitely low risk of bias (++). All three prespecified outcomes (stunting, wasting, underweight) and sensitivity analyses were fully reported.	Definitely low risk of bias (++). Logistic regression models, stratified sensitivity analyses (by age, case status, sex), and p-trend tests for dose–response relationships were appropriately applied.

	influenced pneumonia risk and thus selection, which cannot be fully ruled out.	direction of the association.					from acute illness, introducing timing differences relative to controls.			
Malin Igra et al., 2021	Probably low risk of bias (+). Single cohort (MINIMat) recruited from the same area and period, with uniform follow-up procedures and high retention at 10 years. Minor differences were described between included and non-included participants, documented, and with no indication of dependence on anthropometric status.	Definitely low risk of bias (++). Models adjusted for child's sex and age, maternal education, parity, SES, maternal height (for HAZ), and maternal weight at gestational week 8 (for WAZ), as well as season of conception in prenatal analyses.	Definitely low risk of bias (++). Sensitivity analyses included simultaneous adjustment for Cd and Pb (Model 3), showing no substantive changes in associations with As; adjustment for nutritional supplementation groups was also tested (Model 4), reducing potential bias due to mixtures.	Definitely low risk of bias (++). No deviations from study design or analysis were reported.	Probably low risk of bias (+). Approximately 1,530 children were included with a high follow-up rate; the few non-participants mainly corresponded to families that migrated out of the study area or declined participation. For gestational exposure, some missing data were	Probably low risk of bias (+). Confounders were collected consistently using study instruments (maternal education, parity, SES, etc.); no specific validation of all questionnaires was detailed, but their application was uniform.	Probably low risk of bias (+). Arsenic was measured as total As in urine and erythrocytes using ICP-MS, with quality control and dilution adjustment (specific gravity). Previous studies within the same cohort showed high correlation between total and speciated As,	Definitely low risk of bias (++). HAZ/WAZ were calculated using WHO references; weight and height were measured by trained personnel with calibrated equipment at multiple time points up to age 10.	Definitely low risk of bias (++). HAZ and WAZ were systematically reported in cross-sectional, prenatal, and longitudinal analyses, with stratification by sex and sensitivity analyses.	Definitely low risk of bias (++). Linear regressions with $\log_2$ transformations, adjusted and stratified models were applied. For growth trajectories, longitudinal models with robust clustered variances by individual and time modeled using 5-knot splines

					noted, with minor documented differences.		supporting its use despite incomplete speciation.			were used.
García-Villarino et al., 2022	Probably low risk of bias (+). The cohort (INMA-Asturias) derives from a single population-based study with follow-up from pregnancy and high participation (93.4%). However, arsenic measurement was conducted in a subsample (n = 97) of the 328 children with complete data. Supplementary material (Table S1) shows that this subsample was similar in	Probably low risk of bias (+). Models included maternal factors (age, social class, education, smoking, passive exposure) and child characteristics (age, sex, diet, physical activity) based on a DAG. Important covariates such as maternal BMI were omitted, suggesting partial but reasonably adequate adjustment.	Definitely low risk of bias (++). Multiple metals were included in multi-exposure models and analyzed with BKMR, reducing the likelihood of confounding by co-occurring environmental exposures.	Definitely low risk of bias (++). No deviations from study design or analysis were reported.	Probably low risk of bias (+). Of the 453 children, 328 had complete data and only 97 had arsenic measurements. The authors indicated that the characteristics of excluded participants did not differ from those included.	Definitely low risk of bias (++). Confounders were measured using standardized questionnaires and validated procedures applied uniformly across groups.	Definitely low risk of bias (++). Arsenic species and methylated metabolites (iAs, MMA, DMA, AsB) were measured by ion chromatography coupled to ICP-MS, with quality control using repeated and blank samples. Dilution was adjusted by specific gravity, and the LOD was very low.	Probably low risk of bias (+). Anthropometric measurements were standardized and taken by trained personnel (height measured twice with a stadiometer, digital scale for weight) and BMI was calculated; however, WHO z-scores were not used.	Definitely low risk of bias (++). The study focused its analysis on ΣAs as a proxy for inorganic arsenic, without presenting separate results for individual species (iAs, MMA, DMA). This reflects an analytical choice rather than selective outcome reporting.	Probably low risk of bias (+). Statistical methods were appropriate (adjusted regressions, BKMR, multi-metal models). The main limitation was the small sample size for arsenic analyses.

	sociodemographic and anthropometric characteristics to the full cohort.									
Mbunga et al., 2022	Probably high risk of bias (–). Arsenic exposure was defined post hoc (<LOD, LOD–LOQ, ≥LOQ), and no baseline comparisons between exposure categories were reported. Although all children were from the same population, there was no evidence of comparability between exposure groups.	Definitely high risk of bias (– –). The association between arsenic and anthropometric measures was evaluated using non-parametric tests by arsenic categories, without multivariable adjustment for confounders.	Probably high risk of bias (–). Cd, Pb, and Hg were measured but not simultaneously adjusted for when analyzing anthropometric outcomes; only medians by metal level were compared.	Definitely low risk of bias (++). No deviations from study design or analysis were reported.	Definitely low risk of bias (++). N = 412 participants were included; no differential loss or exclusions were described for anthropometric or exposure variables.	Probably low risk of bias (+). Potential confounders were measured using standardized questionnaires and procedures applied to all participants. However, no formal validation details were provided for some instruments.	Probably high risk of bias (–). Arsenic was measured in blood by ICP-MS, with more than 40% of values below the LOQ and without speciation.	Definitely low risk of bias (++). Weight, height, and z-scores (WAZ/HAZ/WHZ) were calculated using WHO Anthro; measurements were conducted by trained personnel following standard protocols.	Definitely low risk of bias (++). All results for HAZ, WAZ, and WHZ were reported by arsenic levels.	Probably high risk of bias (–). The distribution of serum arsenic was limited by detection (>40% below LOQ); analyses were performed only with non-parametric summaries (Kruskal–Wallis), with no possibility of confounder adjustment.

Zielińska-Dawidziak et al., 2022	Definitely high risk of bias (– –). No comparisons were made by arsenic levels: As in hair was <LOD in almost all participants (only 4 detections). Comparisons were instead between rural versus urban areas and by nutritional status, with clear differences in socioeconomic conditions, diet, water access, and basic services.	Definitely high risk of bias (– –). No association between As and anthropometry was modeled; there were no multivariable models simultaneously adjusting for age, caregiver education, or socioeconomic level. Only t-tests, ANOVA, and simple correlations were used.	Probably high risk of bias (–). Multiple metals (Al, Cd, Cr, Hg, Pb, Ni, Sb, Sn) were measured, but associations with anthropometry were not adjusted for these co-exposures.	Definitely low risk of bias (++). No deviations from study design or analysis were reported.	Probably high risk of bias (–). Of 298 recruited participants, only 103 girls remained; large exclusions occurred due to lack of hair samples and by design (girls only).	Probably low risk of bias (+). Socioeconomic and environmental variables were collected; however, the instruments were neither standardized nor formally validated.	Definitely high risk of bias (– –). Hair biomarker without speciation, with >95% of samples below LOD; individual exposure could not be classified, and reliability for As assessment was very low.	Probably low risk of bias (+). Nutritional status was measured using standardized weight and height, but the Cole Index was used instead of WHO z-scores.	Definitely low risk of bias (++). All results were reported, including both detected and undetected values (below LOD). There was no omission of outcomes or selective reporting bias.	Probably high risk of bias (–). Analyses were mainly bivariate (t-test/ANOVA/Spearman), with no models controlling for confounding or co-exposures; for As, no association analysis with anthropometry was performed due to non-detectable levels.

Cottrell et al., 2023	Probably low risk of bias (+). Retrospective cohort from a single hospital and time period, with uniform inclusion criteria. No baseline comparisons by arsenic levels were presented. Indirect evidence of comparability.	Definitely high risk of bias (– –). No adjustment for confounders in the analyses assessing the association between arsenic and BMI. Only p-values were reported.	Probably high risk of bias (–). Although other metals (Pb, Cd, Hg, etc.) were measured, they were not simultaneously controlled for in the arsenic analysis.	Definitely low risk of bias (++). No deviations from study design or analysis were reported.	Probably high risk of bias (–). Of the hospital population, only 60 children met the criteria of having cord blood available and follow-up to 5 years. It was not described whether included children differed from those not included, nor the percentage of losses, which could introduce selection bias.	Probably low risk of bias (+). Sociodemographic variables were extracted from electronic medical records. However, the methods did not specify which confounders were measured, nor were the procedures or validations described.	Probably low risk of bias (+). Cord blood was analyzed by ICP-MS in a clinical laboratory with established protocol, but LOD/LOQ were not specified. Only one measurement was performed and no speciation was conducted.	Probably low risk of bias (+). BMI data came from routine pediatric check-ups; weights and heights were obtained with clinical scales/stadiometers, and standard calculations suggest acceptable and consistent measurements, although z-scores were not reported and it was not specified whether WHO or CDC standards were used.	Definitely low risk of bias (++). Results for arsenic and BMI were presented for all available ages, with no indication of selective reporting.	Probably high risk of bias (–). Small sample size (n = 60). Analyses were univariate (ANOVA), without confounder adjustment or multivariable modeling, limiting the validity of associations.

Egwunye et al., 2023	Probably low risk of bias (+). Comparisons were made by arsenic levels within the same cohort, age, and period. Although no table of baseline characteristics by exposure strata was presented, the population-based sampling and adjustment for RCT arm and covariates provide indirect evidence of comparability.	Probably low risk of bias (+). Models were adjusted for child's sex, maternal education, RCT arm, exclusive breastfeeding, and wealth index. Some potential confounders (e.g., maternal age/BMI) were not included, indicating partial control.	Probably high risk of bias (–). As, Pb, and Hg were modeled separately; there was no simultaneous multi-metal adjustment or explicit control for other co-exposures that could bias the association between As and HAZ.	Definitely low risk of bias (++). No deviations from study design or analysis were reported.	Probably low risk of bias (+). Documented exclusions (n = 361) with comparison between included and excluded participants showed no differences in variables or HAZ. There was no evidence of differential loss by exposure or outcome.	Definitely low risk of bias (++). Covariates were collected (RCT) using standardized instruments applied uniformly.	Probably low risk of bias (+). Arsenic in toenails was measured by ICP-MS in an accredited laboratory with quality control; reflects 3–6 months prior exposure, but without speciation and with possible semiquantification for samples <10 mg.	Definitely low risk of bias (++). Height was measured in triplicate using ShorrBoard ® by trained personnel; HAZ was calculated using WHO Anthro (v3.2.2).	Definitely low risk of bias (++). HAZ was reported with estimates and confidence intervals for As; null results were included, with no indication of selective omission.	Probably low risk of bias (+). Linear regressions with log-transformed exposure, Se interaction, and sensitivity with robust regression; absence of multi-metal models is a limitation already captured under the co-exposure domain.

Ma et al., 2023	Probably low risk of bias (+). Comparisons by arsenic levels were made within the same school population recruited during the same period. A stratified random sampling approach was used to select kindergartens and classes in two cities. Although no baseline comparability tables by exposure were shown, the design supports indirect evidence of comparability.	Definitely low risk of bias (++). Models were adjusted (DAG-based) for sex, age, site, birth weight, physical activity, sleep duration, screen time, parental education and employment, and household income, with FDR correction and sensitivity analyses.	Definitely low risk of bias (++). Multi-metal models included nine additional metals and mixture analysis methods (BKMR, WQS, Quantile G-Computation), assessing joint effects, nonlinearity, and interactions.	Definitely low risk of bias (++). No deviations from study design or analysis were reported.	Definitely low risk of bias (++). Cross-sectional study with n = 278 participants; arsenic detectable in 100% of samples (<LOD replaced by LOD/√2); no follow-up losses or differential exclusions.	Definitely low risk of bias (++) Confounding variables were assessed through structured questionnaires applied uniformly.	Probably low risk of bias (+). Urinary As measured in three first-morning urine samples (pooled) using ICP-MS with QA/QC and creatinine adjustment; no speciation.	Definitely low risk of bias (++). Weight and height were measured in triplicate by trained technicians using calibrated equipment; WAZ/HAZ/BAZ z-scores were calculated using WHO growth standards.	Definitely low risk of bias (++). All three prespecified anthropometric outcomes (BAZ, HAZ, WAZ), arsenic, and mixture results were reported, including sensitivity analyses.	Definitely low risk of bias (++). Multiple statistical approaches were used (BKMR, WQS, G-computation), all appropriate for mixture analysis.
Smith et al., 2023	Probably low risk of bias (+). Comparisons by	Definitely low risk of bias (++). Models were	Definitely low risk of bias (++). Co-	Definitely low risk of bias	Probably low risk of bias (+). Exclusions	Definitely low risk of bias (++). Maternal	Probably low risk of bias (+). Arsenic	Definitely low risk of bias (++). Height and	Definitely low risk of bias (++). Fully	Definitely low risk of bias (++).

	exposure levels were made within the same cohort recruited during the same period and from the same centers. The analytical sample (n = 999) consisted of participants with prenatal metals and at least one size/adiposity measure. Although there was some reduction from initial recruitment, there were no indications of systematic differences that would compromise comparability.	adjusted for maternal age and pre-pregnancy BMI, education, income, race/ethnicity, smoking, parity, and child sex (based on DAG).	exposures were controlled using quantile g-computation: As was included in a mixture of non-essential metals (As, Ba, Cd, Cs, Pb, Hg) with simultaneous adjustment for essential metals (Mg, Mn, Se, Zn, log_2) and confounders. Although an individual As model adjusted for other metals was not presented, the mixture approach adequately controls for confounding by co-exposures.	(++). No deviations from study design or analysis were reported.	were documented; the distributions of erythrocyte metals were very similar between the analytical sample (N = 999) and complete-case subset (N = 348) (As medians identical or nearly identical).	and socio-demographic covariates were obtained from standardized interviews/questionnaires and study records.	measured in maternal erythrocytes (~10 weeks) by ICP-MS-QQQ with quality control (blanks, verification, acceptable intra/inter-day CVs); single prenatal measurement, no speciation.	weight measured by trained personnel using calibrated equipment; BMI-for-age z-scores calculated using WHO reference standards.	reported all pre-specified anthropometric outcomes (BMI-z) across all age points, including 95% CIs and sensitivity analyses; no indication of selective omission.	Appropriate and consistent methods (multivariable regressions, quantile g-computation for mixtures, sex interaction analyses, and complete-case analyses).

Zhang et al., 2023	Probably low risk of bias (+). Single cohort recruited from the same hospital and period (10–12 weeks). Comparisons by exposure levels (urinary As quartiles) were conducted within the same population. Baseline tables by As strata were not presented, so comparability is indirect.	Definitely low risk of bias (++). Adjusted for maternal age and pre-pregnancy BMI, parity, infant sex, passive smoking, and socioeconomic variables (education; income with imputation for missing data) based on a DAG. Infant age was included in the GEE models.	Probably low risk of bias (+). Models for As did not simultaneously adjust for other metals despite high correlations; however, the study addressed metal mixtures using GWQS (grouped elements), partially mitigating confounding by co-exposures.	Definitely low risk of bias (++). No deviations from study design or analysis were reported.	Probably low risk of bias (+). Of 1,715 pregnant women, 919 mother–child pairs were included in analyses. Exclusions were documented (e.g., no urine, no follow-up, extreme WHO z-scores). Comparisons between included and excluded participants showed no significant differences except for education. Missing data (e.g., income 17.8%)	Definitely low risk of bias (++). Confounders were obtained through standardized interviews and clinical records, applied uniformly; the missing-data imputation strategy was documented.	Probably low risk of bias (+). Urinary As was measured by ICP-MS at two time windows (early ~12 weeks, late ~32 weeks), adjusted for creatinine, with LODs and quality control; no speciation.	Probably low risk of bias (+). Weight and length were measured by trained personnel using standardized equipment, in triplicate; WAZ, LAZ, WLZ/BMIZ were calculated with WHO standards at 1, 3, 6, 8, and 12 months.	Definitely low risk of bias (++). Reported WAZ, LAZ, BMIZ, and HCAZ over time, with longitudinal GEE models, LAZ trajectories, and mixture models. Included non-significant estimates and q-values with BH correction; no signs of omission.	Definitely low risk of bias (++). Appropriate methods for longitudinal and multi-exposure data: GLM over time, GEE (1–12 months), GBTM for growth trajectories, GWQS for mixtures, RCS for dose–response, and BH correction for multiple testing.

					were handled using random forest imputation.					
Adil et al., 2024	Probably high risk of bias (–). Cases and controls differed in baseline variables (age at sampling, birth weight, and gestational age); comparability was limited despite being from the same area and period.	Probably high risk of bias (–). Adjustment was limited to birth weight, gestational age, and age at sampling; no control for maternal education/SES, maternal BMI, or other confounders.	Probably high risk of bias (–). Models relating As to HAZ/WAZ/WHZ did not adjust simultaneously for other metals.	Definitely low risk of bias (++). No deviations from study design or analysis were reported.	Definitely low risk of bias (++). No differential losses or exclusions were reported during analysis.	Probably low risk of bias (+). Confounders were measured consistently. However, the methods section did not specify which confounders were included or provide details on measurement procedures or validation.	Probably low risk of bias (+). Breast milk biomonitoring performed using ICP-MS with calibration curves and blanks; single measurement and no speciation.	Probably low risk of bias (+). HAZ/WAZ/WHZ were reported, and the use of WHO standards was mentioned (in the abstract); however, the Methods section did not specify the standard, calibration, or measurement procedures.	Definitely high risk of bias (– –). The article states that only “significant” elements ($p < 0.05$) and filtered models were presented in the tables.	Probably high risk of bias (–). Regression analyses assessing associations with HAZ/WAZ/WHZ were single-pollutant models for As, selected by significance, with incomplete confounder adjustment and no control for co-exposure to other metals (Pb, Mn, Ba) in a multi-

										exposure context.
Dugandzic et al., 2024	Probably low risk of bias (+). National probabilistic sample (CHMS) with standardized protocols; comparisons were made by exposure levels within the same population. Overall response rate was ~51%, and subsampling by cycle prevents full comparability across exposure cycles.	Probably low risk of bias (+). Adjusted for a minimal set based on DAG (age, sex, diet, breastfeeding, maternal age, education, income, ETS/cotinine, physical activity, built environment/PM2.5/LAN). Maternal BMI was not included.	Definitely low risk of bias (++). Effects were estimated using quantile g-computation for contaminant mixtures, with component-specific weights and survey/bootstrapped weights.	Definitely low risk of bias (++) No deviations from study design or analysis were reported.	Definitely low risk of bias (++). Cross-sectional study without follow-up; analysis included only participants with ≥70% detectable exposure data per cycle.	Definitely low risk of bias (++). Covariates were measured with validated/standardized instruments and applied uniformly across groups.	Probably low risk of bias (+). Urinary biomonitoring of arsenic (DMA only) conducted using standardized procedures and adjusted for creatinine.	Definitely low risk of bias (++). Anthropometric measurements followed standardized CHMS protocols and WHO classification (BMI z-scores).	Definitely low risk of bias (++). All prespecified outcomes were reported in the methods, including both adjusted and unadjusted models, null and significant results, as well as secondary and sensitivity analyses in appendices.	Definitely low risk of bias (++). Appropriate analytical methods (quantile g-computation accounting for survey design).

Salcedo-Bellido et al., 2024	Probably high risk of bias (–). Cases and controls were recruited from mixed sources (schools/health centers) with relevant baseline differences (higher child age in cases; markedly different maternal education distribution). Comparability between groups was not ensured.	Probably low risk of bias (+). Models were adjusted for creatinine, age, sex, physical activity, energy intake, and additionally for maternal education, fish and rice consumption. However, important confounders such as maternal BMI were not included.	Probably low risk of bias (+). For As, individual models did not adjust simultaneously for other metals; although WQS mixture models were applied (with As contributing positively to the index), this approach does not isolate the independent effect of As in primary models.	Definitely low risk of bias (++). No deviations from study design or analysis were reported.	Definitely low risk of bias (++). Case–control study without follow-up; included vs. excluded participants (without metal data) were compared (Table S2) and showed no significant differences.	Definitely low risk of bias (++). Covariates were obtained using a structured questionnaire.	Probably low risk of bias (+). First morning urine analyzed by ICP-MS-QQQ; LOD = 0.07 µg/L, 100% detection, adjusted for creatinine (as covariate). However, only one measurement was taken and no speciation was performed.	Probably low risk of bias (+). Weight and height measured by trained personnel using a Tanita scale and Seca stadiometer; overweight/obesity classified by IOTF criteria (not WHO z-scores).	Definitely low risk of bias (++). Reported results for all metals and mixture models (WQS), both adjusted and unadjusted, including sex-stratified and sensitivity analyses.	Definitely low risk of bias (++). Statistical methods were appropriate for the study design.