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The serum copper/zinc ratio in childhood and educational attainment: a population-based study

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ABSTRACT

Background Micronutrients are potentially important determinants of adult outcomes such as educational attainment. Copper and zinc have known effects on several medical conditions and cognitive development. Elevated copper and depressed zinc is a common trace metal imbalance.

Methods We estimate the correlation between the copper/zinc ratio (Cu/Zn) in childhood (year 1980) and educational attainment in adulthood (year 2010). We use the Young Finns Study (YFS) combined with the Finnish Linked Employer-Employee Data (FLEED). The regression models account for confounders such as other biomarkers and parental observables.

Results We report a sizeable, negative correlation between Cu/Zn and educational attainment as measured by education in years, grades as well as the likelihood of completing university education. For example, a one standard deviation increase in Cu/Zn decreases the probability of university education by ~4%.

Conclusions The findings are consistent with a Cu/Zn effect influencing cognitive functioning early in life. Future research should explore more deeply the precise mechanisms by which Cu/Zn affects educational attainment.

Keywords copper–zinc ratio, educational attainment, grade point average score

Introduction

Childhood conditions are important for health outcomes in adulthood. Cognitive, non-cognitive and health endowments developed by the age of 10 are significant determinants of health differences at age 30, and parental background partly determines subsequent education and lifestyle choices.[1–4]

The contribution of micronutrients to the determination of adult outcomes is under-researched. Two essential trace metals, zinc and copper, provide an interesting case for multiple reasons.

First, zinc activates several hundred different enzymatic reactions that are important to life and biological activity.[5] Zinc is involved in the nervous system and brain function. The need for zinc is higher in stages of rapid growth such as infancy, adolescence and pregnancy.[6] Copper is essential for

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maintaining the strength of the skin, blood vessels, epithelial and connective tissue throughout the body.[7,8] Elevated copper is known to induce toxic effects. Although zinc toxicity is also possible, it is far more common to have zinc deficiency and copper toxicity.

Second, elevated copper and depressed zinc is one of the most common trace metal imbalances. The normal copper/zinc (Cu/Zn) ratio, in children and adults, is close to 1:1.[9,10] Imbalances may occur for many reasons. A key determinant of both copper and zinc intake is diet. Organ meats, nuts and seeds, chocolate and shellfish have the highest copper content. The richest food sources of zinc include oysters and meat (e.g. beef, veal, pork and lamb).[11] The prevalence for zinc deficiency worldwide is estimated to be higher than 20%.[12] Zinc supplementation may be useful in some specific situations.[13] Every doubling of Zn intake increases Zn serum concentration only by 6%.[14] Copper and zinc concentrations are also influenced significantly by physiological conditions such as age and gender as well as malabsorption, inflammatory condition and genetics.[10,15–18]

Third, copper and zinc are vital in humans' cellular metabolism but, according to a review of the medical literature, 'the ratio of copper to zinc is clinically more important than the concentration of either trace metal'.[8] The ratio of copper to zinc, rather than the absolute amount of copper or zinc in the body alone, makes it possible for enzymes to function properly.[8] Elevated copper levels, especially when zinc levels are also low, may also contribute to medical conditions such as schizophrenia, hypertension, autism, fatigue, muscle and joint pain, headaches, childhood hyperactivity, depression, insomnia, senility and premenstrual syndrome.[10] The Cu/Zn ratio has also been related to childhood neurological disorders.[9] Furthermore, elevated Cu/Zn ratios have been found among assaultive individuals.[19]

Fourth, there is no prior literature linking copper and zinc to economic outcomes such as education although micronutrients may affect educational outcomes via their effects on cognitive function. In particular, zinc has been linked to synaptic plasticity and is thus important for learning.[20–22] Zinc deficiency may also have an influence on cognitive development by alterations in attention, activity, neuropsychological behavior and motor development.[23] The long-term effects of zinc supplementation on overall cognitive development have not been proven to be significant but specific aspects of cognitive functioning may be positively affected.[24] Serum samples from patients with Alzheimer and mild cognitive impairment suggest that aluminium and labile forms of copper were increased in demented patients, while zinc was reduced.[25] Clinical evidence points to the use of copper chelators as protective factors against Alzheimer disease.[26]

Methods

Data sources and the sample

We use longitudinal research design based on linked data. The data on biomarkers, GPA (Grade Point Average) scores and family background are drawn from the Cardiovascular Young Finns Study (YFS). (The YFS is described at http://youngfinnsstudy.utu.fi/studydesign.html.) The YFS began in 1980 when 4320 participants in six age cohorts (aged 3, 6, 9, 12, 15 and 18) were randomly chosen from five Finnish university regions using the national population register.[27] A total of 3596 persons participated in the study in 1980 and 7 follow-up studies have been conducted, most recently in 2011–2012. Because the participants were chosen randomly, the data may contain children with specific conditions such as autism and ADHD.

To obtain register information on educational attainment we linked the YFS to the Finnish Longitudinal Employer-Employee Data (FLEED) of Statistics Finland (SF) using unique personal identifiers. This is exact matching and there are no misreported ID codes. FLEED includes information on individuals' educational attainment taken directly from comprehensive administrative registers that are maintained by SF.

Measures

The serum Cu/Zn ratios in YFS were obtained in 1980 when the participants were 3 to 18 year old. Serum copper and zinc concentrations on 3142 children were determined based on fasting samples taken between 9 and 11 a.m. The samples were collected by venipuncture in acid-washed test tubes, and after clot separation the serum was frozen and stored at −18°C. The copper and zinc concentrations were determined by using the flame technique of atomic absorption spectrophotometry and the single dilution method.[28] The Cu/Zn ratios were also obtained in 1983 for a subsample of males (cohorts 2–4, $n = 592$). The seven other biomarkers (height, body fat, pulse, diastolic blood pressure, logarithm of triglyceride, insulin and logarithm of urine creatinine) were obtained in 1980 based on physical measurements and blood tests. These biomarkers are available for the total sample.

We use three outcome variables for educational achievement. We use two register-based measures, namely the years of completed education and an indicator for those who have completed tertiary education (i.e. polytechnic or university degree), based on the highest obtained degree from FLEED in 2010. The years of education are obtained by transforming the degrees into the years of education, using official estimates of SF for completing a specific degree. The third measure, GPA is based on self-reported information.[29] It was obtained from the YFS for the youngest cohorts 1–4 in 1989, 1986,

1983 and 1980, respectively, when the participants were 12 years old. The GPAs are the means of grades (4 = failed, 10 = excellent) in several subjects in annual school reports including theoretical subjects, physical education and arts. We are not able to examine the heterogeneity by the type of subject for the GPA.

To account for parental background, we link the YFS to the Longitudinal Population Census (LPC) of SF from the year 1980. As family background variables we use indicators for parents' university-level education and the family's total annual income in 1980. Household total income is related to the composition of food intake that is an important determinant of the Cu/Zn ratio.

Statistical methods

There are two elements in our analyses. First, we run educational attainment models for the three outcomes noted above. The baseline models for the years of education are estimated using ordinary least squares (OLS). For completing polytechnic or university education, we estimate a linear probability model using OLS. In these models we control for gender, birth cohort and birth month—all clearly predetermined variables. Second, we run robustness tests that account for potential confounders.

We measure Cu/Zn in 1980 and register-based educational achievement in 2010. An advantage of this temporal ordering of our key measures is that it lessens reverse causality concerns. There remain potential concerns related to omitted-variable bias and measurement error in Cu/Zn.

Omitted-variable bias is caused by a variable that is correlated with the dependent and the explanatory variable of interest, but is unobservable to the analyst, so it cannot be included in the regression. In our longitudinal research setting it is possible that Cu/Zn at least partly reflects parental background while having no independent effect on subsequent education attainment, raising concerns about the causal interpretation of the baseline OLS estimates. We therefore link the YFS data to the LPC of SF containing comprehensive retrospective information on parents' education and income level. We use this information to account for intergenerational correlation in the choice variables. Parental background is predetermined for offspring.

Instrumental variable estimation is able to correct the measurement error bias if measurement error is classical. Measurement error in an independent variable would result in conservative (OLS) estimates for the effect of Cu/Zn on subsequent educational attainment. In our context measurement error may arise due to the fact that Cu/Zn measured at a single point in time is not an exhaustive measure of the ratio from a lifetime perspective. Thus, the attenuation bias caused by random measurement error in Cu/Zn would bias the estimate towards zero. For these reasons, we have also used Cu/Zn measured in 1980 as an instrument for Cu/Zn in 1983. Our IV approach does not mitigate omitted-variable bias unless the omitted variable is correlated only with the 1983 measure. Thus, we do not use IV to establish causal inference but only to tackle potential measurement error in Cu/Zn.

Results

Table 1 reports the average Cu/Zn ratios, the average years of education, the share of individuals who have completed tertiary education and the average GPA at the age of 12. Women, on average, have higher Cu/Zn ratios and higher educational achievements relative to men. The null hypothesis of equal group means was rejected at the 5% level.

Next we turn to the relationships between childhood copper and zinc and educational achievement later in adulthood. There is a substantial variation in the Cu/Zn ratio between individuals (Fig. 1, Panels C–D). We find statistically significant unconditional raw correlations between education years with copper and Cu/Zn (Fig. 1A and C). To establish the conditional correlations, estimation of a full-fledged regression model is required to account for variations related to factors such as gender and cohort that are well-known determinants of the amount of copper and zinc in the body, according to the medical literature.[15]

We first estimated models in which copper and zinc levels were entered separately in the same specification. The association between copper and education years is negative and the relationship between zinc and education years is positive.

Table 1 Mean values and standard deviations of the key variables.

	Total sample (n = 3142)	*Females (n = 1563)*	*Males (n = 1579)*
Copper/zinc ratio (1980)	1.26 (0.31)	1.27 (0.31)	1.24 (0.31)
Years of education (2010)	13.41 (2.85)	13.91 (2.70)	12.92 (2.91)
University education indicator (2010)	0.28 (0.45)	0.32 (0.47)	0.24 (0.43)
GPA at the age of 12	7.84 (0.74)	8.06 (0.69)	7.62 (0.74)

Standard deviations are reported in parentheses. The copper/zinc ratio was obtained in 1980 when the participants were 3, 6, 9, 12, 15 and 18 years old. Register-based education is measured in 2010.
GPA, grade point average.

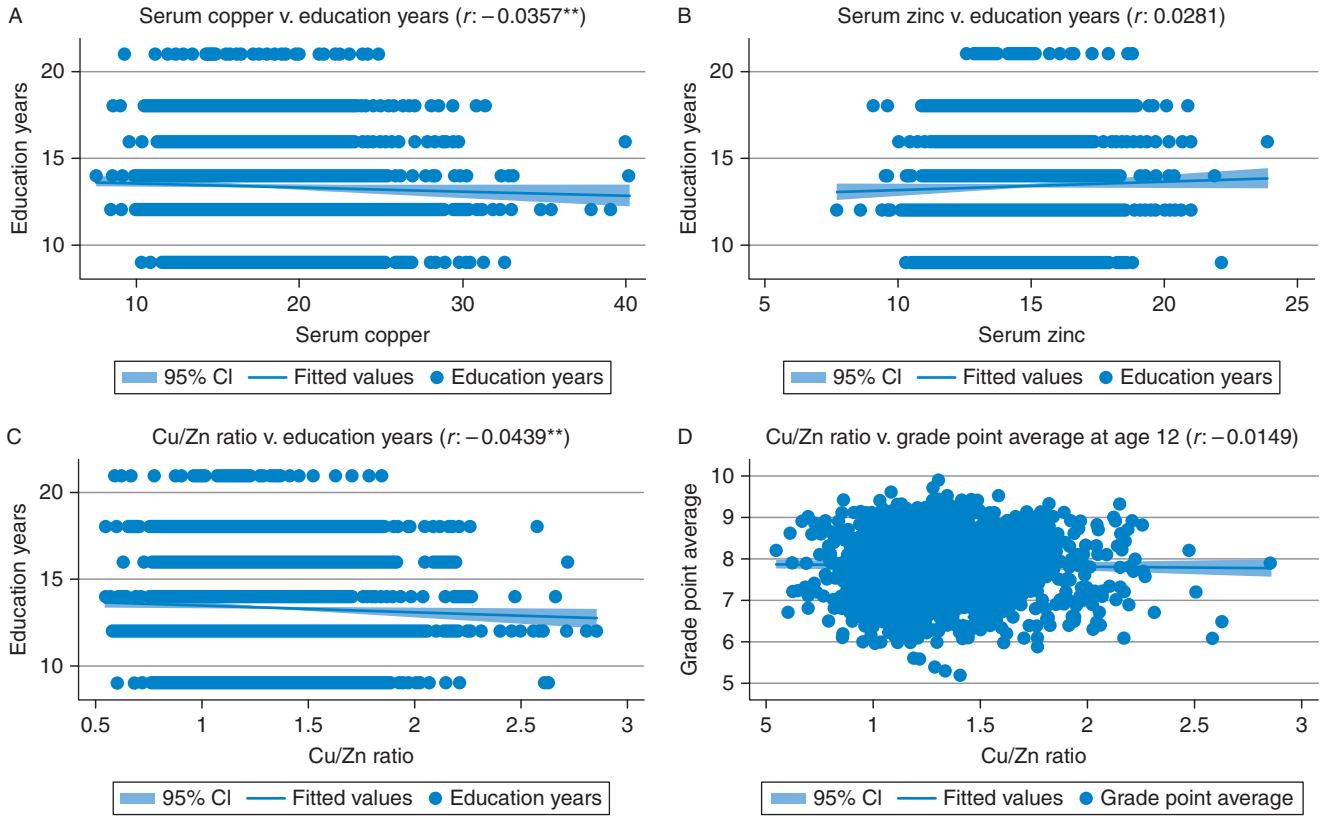

Fig. 1 The unconditional raw correlations between copper and zinc and educational outcomes. Notes: The 95% confidence level is shaded. The correlation coefficients are reported in parentheses. Significant at **5% level. Copper and zinc are measured in 1980. Education years are measured in 2010.

Both of these associations are statistically significant (Table 2, Column 1). The coefficients for gender, cohort and birth month indicators cannot be constrained to zero, according to the *F*-test.

Because the medical literature has stressed the role of Cu/Zn ratio,[8] we focus on the effects of Cu/Zn on educational achievement in adulthood from Column 2 onwards. The data do not reject the Cu/Zn ratio restriction: *F*-test (1, 3122) = 0.29. Thus, we can use the Cu/Zn ratio as the explanatory variable and exclude the level effects for copper and zinc. We use the Cu/Zn ratio as a continuous variable in the models, because there are no commonly accepted thresholds for the Cu/Zn ratio.

We find that the Cu/Zn ratio is negatively related to educational attainment (Table 2, Column 2). The relationship is statistically significant at the 1% level (a two-sided test). The quantitative magnitude of the effect of the Cu/Zn ratio is substantial, relative to the average years of education in the population (Table 1). The point estimate implies that one standard deviation increase in the Cu/Zn ratio is associated with a ∼0.30 decrease in the years of completed education.

Given the potential for biomarker effects to differ by gender we ran estimates separately by sex. The point estimates are almost identical for men and women (Table 2, Columns 3–4). We also confirm that the negative relationship between the Cu/Zn ratio and educational achievement is robust to controlling for other biomarkers (Table 2, Column 5).

We test the sensitivity of the baseline result using alternative measures for education. Reassuringly, the negative effect of Cu/Zn ratio on educational outcomes remains intact (Table 2, Columns 6–7). The point estimate implies that one standard deviation increase in Cu/Zn decreases the probability of completing university education by ∼4% (Table 2, Column 6). Again this is a sizeable effect. Likewise, a one standard deviation increase in the Cu/Zn ratio is associated with a statistically significant 0.05 point decrease in the GPA at age 12 (Table 2, Column 7). Because for the 4th age cohort GPA and the Cu/Zn ratio are measured simultaneously, we have also estimated the model without including it. The point estimate changes only slightly (−0.222***).

The negative association remains also intact in the models that control for parental background using information from the LPC (Table 3, Columns 1–2). Thus, the social environment of the child does not seem to be particularly important for the correlation. The point estimates are only slightly lower than without controlling for parental background. We have

Table 2 The baseline estimation results.

	(1) Education years (OLS)	*(2) Education years (OLS)*	*(3) Education years (OLS)*	*(4) Education years (OLS)*	*(5) Education years (OLS)*	*(6) University education (OLS)*	*(7) GPA at the age of 12 (OLS)*
Copper	−0.072*** (0.014)						
	[−0.099, −0.045]						
Zinc	0.085*** (0.029)						
	[0.028, 0.142]						
Copper/zinc ratio		−0.971*** (0.172)	−0.962*** (0.219)	−0.955*** (0.285)	−0.779*** (0.176)	−0.137*** (0.027)	−0.182*** (0.063)
		[−1.309, −0.634]	[−1.392, −0.532]	[−1.515, −0.396]	[−1.125, −0.433]	[−0.190, −0.083]	[−0.305, −0.059]
Sample							
Women	x	x	x		x	x	x
Men	x	x		x	x	x	x
Controls							
Gender	x	x			x	x	x
Cohort	x	x	x	x	x	x	x
Birth month	x	x	x	x	x	x	x
Other biomarkers					x		
R^2	0.0576	0.0569	0.0303	0.0292	0.0713	0.0484	0.1319
N	3142	3142	1563	1579	3142	3142	1849

The dependent variable is the years of education except in Columns 6 and 7. Statistically significant at ***1% level. Heteroskedasticity-robust standard errors are reported in parentheses. The 95% CIs for the parameter estimates are reported in square brackets. The other biomarkers used in Column 5 are height, body fat, pulse, diastolic blood pressure, logarithm of triglyceride, insulin and logarithm of urine creatinine all measured in 1980.

OLS, ordinary least squares.

Table 3 Additional estimation results.

	(1) *Education years (OLS)*	*(2)* *Education years (OLS)*	*(3)* *Education years (OLS)*	*(4)* *Education years (IV)*
Copper/zinc ratio	−0.824*** (0.167) [−1.151, −0.496]	−0.877*** (0.174) [−1.218, −0.537]	−1.041** (0.505) [−2.032, −0.049]	−2.461** (1.212) [−4.836, −0.085]
Controls				
Parents' education	x			
Family income		x		
Gender	x	x	x	x
Cohort	x	x	x	x
Birth month	x	x	x	x
R^2	0.1232	0.1092	0.0328	
N	3142	2947	538	538

The dependent variable is the years of education. Significant at **5%, and ***1% level. Heteroskedasticity-robust standard errors are reported in parentheses. The 95% CIs for the parameter estimates are reported in square brackets. In Columns 1–2 parental years of education and family income are obtained from the LPC of SF (the year 1980). In Column 3 the copper/zinc ratio is measured in 1983. In Column 4, the Cu/Zn ratio in 1983 is instrumented with the Cu/Zn ratio obtained in 1980.

estimated the models using self-reported information from the YFS data on parental background as well. The results remain intact.

Instrumental variable estimation (Table 3, Column 4) is based on the correlation of the Cu/Zn ratios in 1980 and 1983. The Cu/Zn ratios are strongly positively correlated across the years. The correlation coefficient between Cu/Zn in 1980 and 1983 for males is 0.441***. The first-stage *F*-statistics of a regression of instrumented variable on instrument is 18.38. The *F*-test statistics are therefore well above 10, the commonly accepted threshold proposed for a weak instrument.[30] The validity of instrument is based on the classical measurement error assumption of non-correlated measurement errors in different years.

Reassuringly, the negative relationship between Cu/Zn and educational achievement remains intact in a much smaller sample using IV estimation. The IV point estimate is larger than the corresponding baseline OLS estimate (Table 3, Column 4). But the IV estimate has a much larger 95% confidence interval from −4.836 to −0.085 such that the OLS point estimate is included in the 95% confidence interval of the IV estimate.

It is important to understand the mechanism behind the correlation more deeply. To this end, we estimated a set of additional models using the specification in Column 2 of Table 2 in which we added controls for potential confounders (depression measured using Beck Depression Inventory in 1992, cognitive development using Cambridge Neuropsychological Test Automated Battery in 2001–12, BMI in 1980 and C-reactive protein as a biomarker for inflammation and infection in 1980) that may be related to the correlation. The correlation between Cu/Zn in childhood and educational attainment in adulthood remains intact in all these specifications despite the fact that some of these measures are only available for subsamples of the original YFS data. For example, the estimate for Cu/Zn is −0.927*** and −0.840*** while controlling for the Beck Depression Inventory (1992) and the amount of C-reactive protein (1980), respectively.

Discussion

Main finding of the study

Using longitudinal research design in which the Young Finns Study (YFS) is combined with the Finnish Linked Employer-Employee Data (FLEED) we show that the Cu/Zn ratio in childhood is negatively associated with education attainment in adulthood. Those with higher Cu/Zn ratio have lower grade point average scores at age 12, fewer years of schooling, and a lower likelihood of university education. The effects are sizeable. For example, a one standard deviation increase in the Cu/Zn ratio decreases the probability of completing polytechnic or university education by ∼4%. 14.6% of children were above one standard deviation away from the mean in the Cu/Zn ratio in 1980.

What is already known for this topic

Childhood conditions are important for health in adulthood. The role of micronutrients in the determination of adult outcomes is under-researched.

What this study adds

Our paper is the first population-based study examining the links between the Cu/Zn ratio in childhood and educational outcomes in adulthood. Although it is unclear from our study why Cu/Zn imbalance should affect educational attainment early in life, we can discount a number of mechanisms since proxies for them do not affect the significance or the size of the Cu/Zn effect. These include parental background and other biometric markers that are often unobservable to the analyst.

Limitations of this study

We were not able to identify the precise mechanism by which the Cu/Zn ratio affects educational attainment in childhood. However, the findings are consistent with a Cu/Zn effect influencing cognitive functioning early in life.

We were not able to examine the heterogeneity by the type of subject for the GPA. It is possible that the Cu/Zn ratio is particularly strongly correlated with some specific component of GPA.

Cu/Zn imbalance needs to prevail for a long period of time before having a large effect in adulthood. A transient zinc deficiency or Cu/Zn imbalance may be present, especially after infections or a period of low dietary intake.

An important limitation of our study is that the YFS data contain only two measurements for Cu/Zn (1980 and 1983). The fact that we are still able to identify a statistically significant correlation strengthens our conclusion, because classical measurement error leads to conservative estimates.

There are some conditions known to be linked to Cu/Zn imbalance which are age-dependent and for which we have no proxies. For instance, low levels of zinc in childhood are associated with a range of behavioural disorders such as attention deficit disorder, as well as lethargy and apathy, many of which will not reach into adulthood.

Future research could fruitfully explore whether these are the mechanisms by which Cu/Zn affects educational attainment in adulthood. This is particularly important since it is possible to over/underdose both Cu and Zn. Thus, deeper knowledge of mechanisms is needed in order to draw policy conclusions and public health guidelines to determine Cu/Zn that is not in an optimal range.

Ethical approval

All participants of the Y.F.S. provided written informed consent, and the study was approved by local institutional review boards (ethics committees of the participating universities). Parents or guardians provided written informed consent on behalf of the under-aged children enrolled in the study. The use of linked YFS/FLEED data has been approved by Statistics Finland. The population-based data are analysed in an anonymous form using the remote access of Statistics Finland.

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Conflict of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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