

Research Paper

## Birth weight and coronary artery disease. The effect of gender and diabetes

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### Abstract

**Background:** The developmental origin theory of coronary heart disease proposes that undernutrition in utero permanently changes body functions and metabolism leading to an increased risk of coronary artery diseases (CAD) in adult life. Some studies support this theory but others suggest that birth weight (BW) is not a major risk factor for cardiovascular diseases. Gender differences concerning the association between BW and risk factors for CAD have been reported in some studies but not in others.

In this paper we have analyzed the effect of gender and diabetes on the relationship between BW and CAD in the White population of Rome.

**Material and Methods:** 226 subjects admitted to the Hospital for non fatal CAD from the White population of Rome were studied. 395 consecutive newborn infants studied in the same population in the years 1968-1972 were considered for comparison.

**Results:** Among subjects with CAD, reliable information on BW was obtained in 127 subjects. The distribution of BW in CAD depends on gender ( $p=0.009$ ). In females with CAD there is a tendency toward low BW, while in males with CAD there is a tendency toward high BW. These associations are very marked in non-diabetic subjects with CAD ( $p=.001$ ), while no significant association is observed in diabetic subjects ( $p=0.557$ ).

**Conclusion:** Our data confirm the association between BW and CAD and suggest that the association depends on gender and is influenced by diabetes.

Key words: Birth weight, CAD, Gender, Diabetes

### Background

The "Developmental origin of coronary heart diseases" proposes that undernutrition in utero permanently changes body functions and metabolism leading to an increased risk of coronary artery diseases (CAD) in adult life (1). The association between low birth weight (BW) and risk factors for CAD, hypertension and type 2 diabetes reported in various

longitudinal studies (2-5) is in line with the developmental theory. Some studies, however, suggest that birth weight may not be a major risk factor for development of hypertension and cardiovascular disease (6,7).

Gender differences in the association between BW and risk factors for CAD have been reported in

some studies (8-10), but not in others (11). Wilkins and Murphy (12) have suggested that gender-specific genes affecting insulin sensitivity are responsible for the gender difference in birth weight: females would be genetically less responsive to the trophic effect of insulin resulting in a lower birth weight. Insulin resistance would be a risk factor for CAD.

Hormonal differences between sexes influence intrauterine development and may interact with genetic and environmental factors resulting in a different pattern of susceptibility in adult life to coronary artery diseases

In the present study we have considered the effect of gender and diabetes on the relationship between BW and CAD.

## Material and Methods

226 subjects admitted consecutively for treatment of CAD to Valmontone Hospital in Rome, Italy were studied. The sample may be representative of subjects with non fatal CAD living in the area around the Hospital. 395 consecutive newborn infants from the White population of Rome studied between 1968 and 1972 were considered as controls. Among subjects with CAD only 127 were found to have reliable information on birth weight. Informed consent was obtained by the patients to participate in the study that was approved by the Ethical Committee of Valmontone Hospital.

Three way contingency tables were analyzed by a log linear model according to Sokal and Rohlf (13). Given three variables A, B and C by this analysis is possible to study the effect of the categories of a variable (i.e. C) on the association between the other two variables (i.e. A and B). Chi square of independence, T test for difference between means and Logistic Regression were carried out by using the SPSS package (14). Logistic Regression is similar to Discriminant Analysis: it is useful to study the effect of categorical variables to separate classes of a dependent variable.

## Results

Table 1 shows the demographic and clinical parameters in the whole CAD sample.

Table 2 shows the distribution of BW in relation to gender. Among CAD cases the distribution of BW classes was found to depend on gender ( $p=0.009$ ), while in healthy newborns no statistical significant association was observed ( $p=0.541$ ). Three way contingency table analysis shows a statistically significant interaction confirming that the pattern of association BW-gender observed in CAD cases is different from that observed in healthy newborns. In females with CAD there is a tendency toward a low BW, while in

males with CAD there is a tendency toward a high BW.

Table 3 shows the mean birth weight in relation to gender. Among CAD cases BW is higher in males than in females ( $p=0.001$ ) while no statistically significant difference is observed among healthy newborns ( $p=0.688$ ).

In table 4 we examined the effect of diabetes on the association between BW and gender among CAD cases. A highly significant association was observed in non-diabetics ( $p=0.001$ ) while no significant association was observed in diabetic subjects ( $p=0.567$ ). In non-diabetics there is a marked decrease of females with high BW and a marked increase of males with high BW. A three way contingency table analysis shows a highly significant interaction ( $p=0.01$ ) suggesting that the pattern of association BW-gender in non-diabetics is different from that observed in diabetics.

A Logistic Regression analysis with CAD as dependent and birth weight and gender as independent has shown a highly significant effect of birth weight ( $p<0.01$ ) and of the interaction between birth weight and gender ( $p<0.01$ ) (data not shown).

Correlation analysis between birth weight and systolic and diastolic blood pressure is shown in table 5. Among females there is a positive correlation between birth weight and both systolic and diastolic blood pressure, while in males no correlation is observed.

**Table 1.** Clinical data in subjects with coronary artery disease.

Parameter	% Proportion	
Infarction	40.5%	
Major coronary lesions	83.2%	
Bypass	35.2%	
Angioplastic	27.1%	
Gender (Female %)	47.4%	
Hypertension	80.9 %	
Cardiac hypertrophy	54.2 %	
Dilated heart	26.2 %	
Cardiac Arrhythmia	53.9 %	
Diabetes mellitus	36.1 %	
Smoking habit	43.9 %	
Obesity	33.2 %	
High Total Cholesterol	67.3 %	
High LDL	66.8 %	
High Triglycerides	45.2 %	
	Mean	SD
Age (years)	66.7	± 11.6
Body mass index (kg/m <sup>2</sup> )	27.36	± 5.2
Systolic blood pressure (mm Hg)	136.6	± 15.6
Diastolic blood pressure (mm Hg)	84.8	± 9.6
Septum interventricular thickness	11.3	± 1.8
Thickness wall	10.8	± 1.5

**Table 2.** Distribution of birth weight in relation to gender in subjects with coronary artery disease and in healthy newborns from the same population.

	CAD		Newborns	
	females	males	females	males
Birth Weight				
≤ 2500 g	8.3%	1.5%	6.0%	8.0%
>2500 g				
≤3500 g	73.3%	58.2%	63.7%	58.7%
>3500 g	18.3%	40.3%	30.2%	33.3%
Total n°	60	67	182	213
Chi square	χ <sup>2</sup>	9.347	1.228	
test of	df	2	2	
independence	p	0.009	0.541	
Linear Correlation	p	0.002	0.839	
Three way contingency table analysis by a log linear model x=sex ; y=birth weight ; z= sample (CAD vs controls)				
	G	df	p	
xyz interaction	7.348	2	0.028	

**Table 3.** Mean birth weight in relation to gender in subjects with coronary artery disease and in healthy newborns from the same population.

	CAD		Newborns	
	females	males	females	males
Mean BW	3200	3607	3256	3279
S.E.	83	79	43	40
N°	60	67	182	213
t- Student for difference	t	3.565	0.403	
between means	p	0.001	0.688	

**Table 4.** The effect of diabetes on the association between birth weight and gender in subjects with coronary artery disease.

	NON DIABETIC		DIABETIC	
	females	males	females	males
Birth Weight				
≤ 2500 g	9.1%	2.2%	7.1%	0.0%
>2500 g				
≤3500 g	79.5%	52.2%	50.0%	75.0%
>3500 g	11.4%	45.7%	42.9%	25.0%
Total n°	44	46	14	20
Chi square	χ <sup>2</sup>	13.659	3.036	
test of	df	2	2	
independence	p	0.001	0.219	
Linear Correlation	p	0.000	0.557	
Three way contingency table analysis by a log linear model x=sex ; y=birth weight ; z= sample (non diabetics vs diabetics)				
	G	df	p	
xyz interaction	9.350	2	0.01	

**Table 5.** Correlation analysis between BW and systolic and diastolic blood pressure.

	BW-SBP		BW-DBP	
	r	p	r	p
Females	0.24	0.07	0.23	0.08
Males	-0.05	0.71	-0.05	0.69

## Discussion

The negative correlation between BW and risk of CAD present in females might appear in favour of the hypothesis that gender specific genes affecting insulin sensitivity present in females are responsible for low birth weight and risk of CAD in adult life (12). However the fact that the negative relation between BW and risk of CAD is not present in females with diabetes argues against this hypothesis.

Although the present study broadens the field of possible etiological elements of CAD, various limitations are in order.

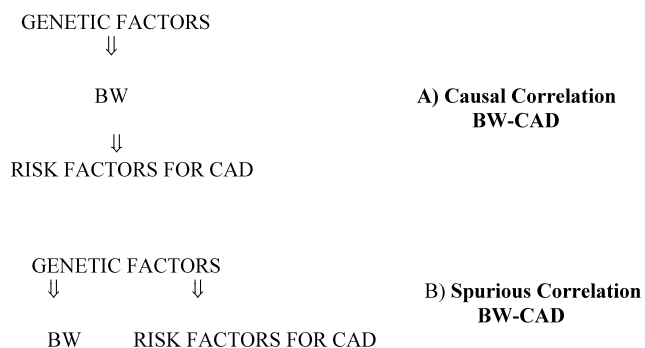
The sample size is relatively modest and the pattern of associations should be re-examined in larger samples.

The differences between males and females observed in our population could be due to differences in clinical severity leading to different rates of mortality between sexes. Indeed our cases include non fatal CAD only and we have no information on fatal cases.

CAD birth weight should be compared with birth weight of adults of the same age without CAD.

Birth weight of newborns refers to the period 1968-1972 while birth weight of CAD patients refers to a period about twenty years before. However no appreciable difference in birth weight has been registered in Italian population during that period.

At present it is unclear which exposure in early life might be responsible for the association between fetal growth and CAD in adult life. Moreover some observations indicate that nourishment before birth is not crucial to adult health (15). The “developmental origin theory” of CAD is generally presented in opposition to the “current orthodoxy” that CAD results from unhealthy life styles with a contribution of genetic factors. The two theories are compatible and many factors may contribute to susceptibility to CAD. Moreover the relationship between BW and CAD could be spurious (fig 1). Section A depicts a true correlation while section B shows that genetic factors influencing BW may independently influence the risk of CAD leading to a spurious correlation between BW and CAD.



**Figure I.** Relationship between BW and CAD

It is becoming increasingly evident that the maternal-fetal relationship has an important role not only in intrauterine survival and development, but also in the well being of offspring during extra uterine life. Additionally, the data presented here suggest that the “developmental origin theory of CAD” deserves increased attention in future investigations.

Several studies point to a significant immune component in the pathogenesis of atherosclerosis that shows many features of a chronic inflammatory disease (16-18). Moreover it has been recently reported that a genetic polymorphism of PTPN22 (19), known to be associated with autoimmunity, is associated with atherosclerosis (20). Maternal and fetal genetic factors interact during intrauterine life in a manner that influences fetal development and the immunological orientation of the fetus. As a result, these interactions could modify the susceptibility of the individual to those diseases having an immunological component.

Recent studies suggest that microchimerism is a common condition mainly due to the fractures of the placental barrier that allow the passage of cells in both directions during pregnancy. Microchimerism could contribute to immune attacks but may be also beneficial in special conditions (21,21). Thus, the “developmental origin hypothesis of CAD” also reflects an immunological facet that was not included in the original formulation.

## Conclusion

Our data confirm the reported association between BW and CAD. However, this association depends on gender: the risk of CAD is correlated negatively to BW in females but positively in males. In the presence of diabetes this pattern of correlation disappears while it is much more evident in subjects without diabetes.

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## Conflict of Interest

The authors have declared that no conflict of interest exists.

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### Author biography

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