**Table S4. Pleiotropic links between coronary artery disease (CAD) and earlylife fitness-related traits due to shared genetic loci.** The table below provides extensive support (143 studies) that antagonistic pleiotropy is likely to be present for CAD genes due to their consistent connections with fitness-related traits expressed early in life. See Fig. 5 for discussion and conceptual overview of these potential effects. Fitness-related traits include fertility potential, reproductive outcomes, pregnancy outcomes, fetal growth and survival, i.e. affecting the ability of an organism to reproduce and transfer genes to the next generation. The first 3 columns give CAD gene rank (no.; based on rank of 40 genes from Fig. 1B), name and full name. Columns 4-8 provide key details of each study where CAD genes also contribute to traits that influence fitness, including what <u>species</u> that was demonstrated in, what biological process or <u>fitness effects</u> that gene is impacting, what <u>fitness class</u> that effect is likely to impact (e.g. dysfunctional spermatogenesis or embryogenesis will affect male and female fertility, ability to conceive), what the <u>observed genetic effect or mechanism</u> that gene was associated with.

no.	CAD gene	full name	species	fitness effects	fitness class*	observed genetic effect or mechanism	ref
1	BCAS3	Breast Carcinoma Amplified Sequence 3	human/ mouse	embryogenesis	fertility	<i>BCAS3</i> highly expressed in developing oocytes	[1]
	BCAS3		mouse	embryogenesis	female potential fertility	<i>BCAS3</i> significantly up- regulated in developmentally incompetent mouse oocytes	[2]
2	CNNM2	Cyclin And CBS Domain Divalent Metal Cation Transport Mediator 2	human	pregnancy-related blood pressure	pregnancy outcomes	<i>CNNM2</i> significantly differentially expressed	[3]
	CNNM2		mouse	pregnancy complications, hypoxia	pregnancy outcomes	<i>CNNM2</i> significantly down- regulated (-2.5 fold change) during pregnancy	[4]
3	TEX41	Testis Expressed 41 (Non- Protein Coding)	human	fetal IUGR, developmental delays	pregnancy outcomes	triplication involving <i>TEX41</i> causes IUGR	[5]
4	SMG6	Nonsense Mediated MRNA Decay Factor	mouse	altered embryogenesis	female potential fertility	<i>SMG6</i> essential for normal embryogenesis based on gene knock-down study	[6]
5	PHACTR1	Phosphatase And Actin Regulator 1	human	reproductive timing	reproductive outcomes	PHACTR1 genetic variation	[7]
	PHACTR1		human	oocyte function	female potential fertility	<i>PHACTR1</i> highly significantly expressed	[8]
	PHACTR1		human	placental inflammatory responses	pregnancy outcomes	PHACTR1 significantly down-regulated	[9]
	PHACTR1		human	endometrium implantation receptivity	female potential fertility	<i>PHACTR1</i> 8-fold significantly up-regulated	[10]
	PHACTR1		mouse	uterus functioning	female potential fertility	<i>PHACTR1</i> significant 1.4-1.9 fold change	[11]
	PHACTR1		rat	lactation	reproductive outcomes	PHACTR1 significantly expressed (4.7 fold change) in mammary tissues	[12]

6	<i>COG5</i>	Component of Oligomeric Golgi Complex 5	Drosophi la	spermatogenesis	male potential fertility	<i>COG5</i> expression required for normal spermatogenesis	[13]
	<i>COG5</i>		human	intrauterine growth	pregnancy outcomes	<i>COG5</i> expression required for normal fetal growth	[14]
7	ABCG8	ATP-Binding Cassette, Sub-Family G, Member 8		infertility		Knockout mice deficient <i>Abcg8</i> are infertile	[15]
	ABCG8		human	fetal distress, asphyxial events, intrauterine death	pregnancy outcomes	ABCG8 involved in intrahepatic cholestasis of pregnancy (ICP), enterohepatic circulation, specifically for exportation of cholesterol	[16]
8	RAI1	Retinoic Acid Induced 1	human/ mouse	growth retardation, embryonic-postnatal development		knock-out mouse model for Smith-Magenis syndrome shows involvement of <i>RAI1</i>	[17]
	RAI1		mouse	growth retardation, impaired motor and sensory coordination, smaller litter size (direct reproductive fitness)	outcomes	Transgenic mice over- expressing <i>RAI1</i> have developmentally impaired offspring	[18]
9	NT5C2	Nucleotidase, Cytosolic II	human	female reproduction	female potential fertility	<i>NT5C2</i> is over-expressed in fallopian tube, uterine endometrium, endocervix, ectocervix	[19]
	NT5C2		human	fetal growth, birthweight, postnatal growth & metabolism	pregnancy outcomes	<i>NT5C2</i> genetic variation affects birthweight	[20]
10	LDLR	Low Density Lipoprotein Receptor	human/ mouse	IUGR in offspring of <i>LDLR-/-</i> mice. Childhood obesity.	pregnancy outcomes	<i>LDLR</i> involved in fetal/offspring growth	[21]
	LDLR		human	Placental regulation of cholesterol	pregnancy outcomes	Maternal lipid profile affecting placental protein expression of <i>LDLR</i>	[22]
	LDLR		mouse	Placental regulation of cholesterol	pregnancy outcomes	LDLR involved in maternal- fetal transfer of lipids	[23]
	LDLR		rat	Pregnancy loss	fetal/offspring mortality	LDLR rat model for diabetes	[24]
11	KCNK5	Potassium Channel, Two Pore Domain Subfamily K, Member 5	human	Fertility - sperm volume	male potential fertility	<i>KCNK5</i> involved in protein and mRNA levels in sperm	[25]
	KCNK5		human	Male infertility	male potential fertility	<i>KCNK5</i> involvement in sperm inability to fertilize egg	[26]
	KCNK5		mouse	Male infertility	male potential fertility	<i>KCNK5</i> involved in sperm volume	[27]
	KCNK5		primate	Male fertility	male potential fertility	<i>KCNK5</i> involved in sperm function	[28]
	KCNK5		mouse	Female fertility		<i>KCNK5</i> involved in oocyte survival/viability	[29]
	KCNK5		cattle	Lactation	reproductive	KCNK5 expression	[30]

					outcomes		
12	ABO	ABO Blood Group (Transferase A, Alpha 1-3-N- Acetylgalactosaminylt ransferase; Transferase B, Alpha 1-3- Galactosyltransferase)	human	Birth weight, maternal age at child-bearing	pregnancy outcomes	<i>ABO</i> variation effects	[31]
	ABO	Galactosyftransierasej	human	Fetal growth restriction	pregnancy outcomes	ABO variation effects	[32]
	ABO		human	fetal hypoxia, pregnancy complications, hemolytic disease of fetus/newborn, fetal death	pregnancy outcomes	<i>ABO</i> incompatibility effects	[33]
	ABO		human	protection against malaria	pregnancy outcomes	ABO variation effects	[34]
	ABO		human	Age at menarche	reproductive outcomes	ABO blood group phenotypes	[35]
	ABO		human	male infertility	male potential fertility	ABO involved in sperm concentration/function	[36]
	ABO		human	pregnancy complications	pregnancy outcomes	ABO involved in preeclampsia	[37]
	ABO		human	female fertility, embryo implantation		ABO variation effects	[38]
13	SWAP70	SWAP Switching B- Cell Complex 70kDa Subunit	monkey	female fertility, implantation, placentation	female potential fertility	<i>SWAP-70</i> expression effects	[39]
	SWAP70		human	fetal growth restriction	pregnancy outcomes	<i>SWAP70</i> involved in preeclampsia	[40]
14	SH2B3	SH2B Adaptor Protein 3	human	intrauterine/postnat al growth	pregnancy outcomes	SH2B3 variation effects	[41]
	SH2B3		human	male testicular function	male potential fertility	SH2B3 variation effects	[42]
15	PEMT	Phosphatidylethanola mine N- Methyltransferase	human	fetal growth, placental function	pregnancy outcomes	Choline metabolism/ <i>PEMT</i> expression effects	[43]
	PEMT		human	premature birth	pregnancy outcomes	<i>PEMT</i> variation [744CC genotype] effects	[44]
	PEMT		human	sperm quality	male potential fertility	<i>PEMT</i> variation [27774G.C] effects	[45]
	PEMT		human	fetal growth, placental function	pregnancy outcomes	mRNA levels of <i>PEMT</i> involved in fetal/placental function	[46]
	PEMT		mouse	embryo survival/viability during pre- implantation	female potential fertility	<i>PEMT</i> expression effects	[47]
	PEMT		human	fetal development	pregnancy outcomes	PEMT expression effects	[48]
16	MRAS	Muscle RAS Oncogene Homolog	mouse	male testicular function	fertility	MRAS expression effects	[49]
	MRAS			embryo implantation	female potential	MRAS regulation by androgen	[50]

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	MRAS		moure	ombruo nluvinotor	fertility	and progesterone receptors <i>MRAS</i> expression effects	[51]
			mouse		fertility	-	[51]
	MRAS	Muscle RAS Oncogene Homolog	human	breastfeeding capacity	reproductive outcomes	MRAS expression effects	[52]
17	KIAA1462	KIAA1462	bird	offspring number	reproductive outcomes	<i>KIAA1462</i> expression effects	[53]
	KIAA1462		human	birth-related myometrial gene expression	pregnancy outcomes	<i>KIAA1462</i> expression effects	[54]
	<i>KIAA1462</i>		mouse	female reproduction	female potential fertility	<i>KIAA1462</i> highly expressed in oocytes & ovaries	[55]
	<i>KIAA1462</i>		pig	fetal growth	pregnancy outcomes	<i>KIAA1462</i> expression effects	[56]
	<i>KIAA1462</i>		human	embryo implantation		<i>KIAA1462</i> significantly differentially expression	[57]
18	GUCY1A3	Guanylate Cyclase 1, Soluble, Alpha 3	cattle	embryo implantation	female potential fertility	GUCY1A3 expression effects	[58]
	GUCY1A3				fertility	GUCY1A3 expression effects	[59]
	GUCY1A3		human	placental functioning	pregnancy outcomes	<i>GUCY1A3</i> expression effects	[60]
	GUCY1A3		human	birth weight	pregnancy outcomes	<i>GUCY1A3</i> expression effects	[61]
	GUCY1A3		human	fetal growth, birthweight, postnatal growth & metabolism	pregnancy outcomes	<i>GUCY1A3</i> fetal genotype involved in fetal development	[62]
19	CDKN2B- AS1	CDKN2B Antisense RNA 1	human	fertility	<b>^</b>	CDKN2B-AS1 linked endometriosis	[63]
	CDKN2B- AS1		human	fetal growth restriction	pregnancy outcomes	CDKN2B-AS1 variation	[64]
20	ANKS1A	Ankyrin Repeat And Sterile Alpha Motif Domain Containing 1A	cattle	fertility	female potential fertility	<i>ANKS1A</i> significant expression in endometrium and corpus luteum	[65]
	ANKS1A		cattle	fertility	•	<i>ANKS1A</i> 6.7-fold significantly up-regulated in blastocysts	[66]
	ANKS1A		human/ mouse	male fertility	male potential fertility	ANKS1A expression	[67]
21	PDGFD	Platelet Derived Growth Factor D	human	female fertility	female potential fertility	<i>PDGFD</i> involved in ovarian hyperstimulation	[68]
	PDGFD		human	female reproduction	fertility	expressed in oocytes	[69]
	PDGFD		mouse	male/female reproduction	female potential fertility	PDGFD significantly expression	[70]
	PDGFD			female reproductive function	female potential fertility	<i>PDGFD</i> significantly down-regulated in endometrium	[71]
	PDGFD		rat	female reproductive function		•	[72]
	PDGFD		human	pregnancy complication, preeclampsia		<i>PDGFD</i> significantly down- regulated in placenta	[73]
22	KSR2	Kinase Suppressor Of Ras 2	mouse	male fertility	fertility	<i>KSR2 -/-</i> knockout mouse model for spermatogenesis	[74]
	KSR2		cattle	female reproductive		KSR2 significantly up-	[75]

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	WORG			function	fertility	regulated in epithelial cells	[8.4]
	KSR2		mouse	offspring growth	fetal/offspring mortality	<i>KSR2 -/-</i> knockout mouse model	[76]
23	FLT1	Fms-Related Tyrosine Kinase 1	human	fetal development	pregnancy outcomes	<i>FLT1</i> expression effects	[77]
	FLT1		mouse	offspring viability, fetal growth	pregnancy outcomes	FLT1 knockdown effects	[78]
	FLT1		human	pregnancy loss	fetal/offspring mortality	FLT1 involved in immune responses to placental malaria	[79]
	FLT1			female reproduction	female potential fertility	<i>FLT1</i> significantly expression in oocytes	[80]
	FLT1		human	intrauterine growth restriction		<i>FLT1</i> significantly up-regulated	[81]
	FLT1		human	fetal growth	pregnancy outcomes	<i>FLT1</i> significantly expressed in placenta	[82]
	FLT1		human	female reproduction	female potential fertility	<i>FLT1</i> significantly expressed in oocytes	[83]
	FLT1		human	female reproduction, implantation		<i>FLT1</i> significantly expressed in uterus	[84]
	FLT1		human	female reproduction	pregnancy outcomes	<i>FLT1</i> significantly expressed in placenta, fetal tissues	[85]
	FLT1		human	intrauterine growth restriction	pregnancy outcomes	<i>FLT1</i> significantly expressed during pregnancy	[86]
24	ABCG5	ATP-Binding Cassette, Sub-Family G, Member 5		intrauterine growth restriction	pregnancy outcomes	rat model of IUGR	[87]
	ABCG5			trophoblast, blastocyst development	female potential fertility	<i>ABCG5</i> gene expression effects	[88]
25	ZC3HC1	Zinc Finger, C3HC- Type Containing 1		male fertility	male potential fertility	meiosis disruptors	[89]
	ZC3HC1		mouse	pregnancy establishment, maintenance, conceptus survival	female potential fertility	<i>ZC3HC1</i> expression, 1.57-fold significantly changed	[90]
26	SMAD3	SMAD Family Member 3		folliculogenesis	female potential fertility	SMAD3 expression effects	[91]
	SMAD3		mouse/r at	oocyte function	female potential fertility	SMAD3 expression effects	[92]
	SMAD3			estrogen receptor interactions	female potential fertility	SMAD3 expression effects	[93]
	SMAD3		rat	testis function	male potential fertility	SMAD3 expression effects	[94]
	SMAD3		human	age at natural menopause	reproductive outcomes	SMAD3 interaction effects	[95]
	SMAD3		human	twinning capacity	reproductive outcomes	<i>SMAD3</i> genotype (rs17293443-C) effects	[96]
	SMAD3		human	female fertility and fecundity	fertility	SMAD3 promotes proliferation and steroidogenesis of human ovarian lutenized granulosa cells	[97]
	SMAD3		mouse	embryo viability	female potential fertility	SMAD3 signalling effects	[98]

	SMAD3		human	spermatogenesis,	-	SMAD3 expression effects	[99]
27	SLC22A3	Solute carrier family 22, extra neuronal monoamine transporter	human	male reproduction placental functioning	fertility pregnancy outcomes	<i>SLC22A3</i> expression effects	[100]
	SLC22A3		human	fetal development, fetal-placental resource provisioning	pregnancy outcomes	<i>SLC22A3</i> expression effects	[101]
	SLC22A3		human	fetal-placental functioning	pregnancy outcomes	<i>SLC22A3</i> expression changes during pregnancy	[102]
	SLC22A3		human	fetal-placental functioning	pregnancy outcomes	<i>SLC22A3</i> significantly expressed by trimester	[102]
28	REST	RE1-Silencing Transcription Factor	mouse	embryo functioning	fertility	<i>REST</i> regulatory network effects	[103]
29	PPAP2B	Phospholipid Phosphatase 3	human	endometriosis, female fertility	fertility	PPAP2B -1.69-fold significantly changed	[104]
	PPAP2B		human/r odent	gametogenesis	fertility	<i>PPAP2B</i> expression effects	[105]
	PPAP2B		sheep	breeding capacity	reproductive outcomes	<i>PPAP2B</i> association effects	[106]
	PPAP2B		human	pregnancy complications	pregnancy outcomes	<i>PPAP2B</i> 1.36 -fold significantly up-regulated in placental tissues of preeclamptic mothers	[107]
	PPAP2B		human	embryo viability	female potential fertility	<i>PPAP2B</i> involved in spontaneous abortion due to parthenogenesis	[108]
	PPAP2B		human	embryo implantation	female potential fertility	<i>PPAP2B</i> differential expression effects	[57]
	PPAP2B			female reproductive function	female potential fertility	<i>PPAP2B</i> up-regulated in endometrium	[71]
30	MIA3	Melanoma Inhibitory Activity Family, Member 3	cattle	ovarian functioning	female potential fertility	<i>MIA3</i> 4.6-fold significantly up-regulated	[109]
	MIA3		mouse	placental (dys)function		<i>MIA3</i> expresed in early trophoblast differentiation	[110]
31	IL6R	Interleukin 6 Receptor	pig	endometrium functioning	pregnancy outcomes	<i>IL6R</i> significantly differentially expressed in endometrium	[111]
	IL6R		cattle	endometrium functioning	pregnancy outcomes	<i>IL6R</i> 3.38-fold significantly up-regulated during pregnancy	[112]
	IL6R		human	endometrium functioning in PCOS women	female potential fertility	<i>IL6R</i> significantly up-regulated	[113]
	IL6R		human	pre-term birth SNP variation	pregnancy outcomes	<i>IL6R</i> significantly associated with pre-term birth	[114]
32	HDAC9	Histone Deacetylase 9	human	oocyte function	female potential fertility	HDAC9 expression effects	[115]
	HDAC9		cattle	male fertility	male potential fertility	<i>HDAC9</i> involved in germ cell production	[116]
	HDAC9		pig	birth weight	pregnancy outcomes	HDAC9 expression effects	[117]

	HDAC9		human/	oocyte function	fomalo notontial	HDAC9 expression effects	[118]
			mouse		fertility	-	
	HDAC9		human	birth-related myometrial gene expression	pregnancy outcomes	HDAC9 expression effects	[119]
33	COL4A1	Collagen, Type IV, Alpha 1	pig	neonate survival	pregnancy outcomes	<i>COL4A1</i> expression effects	[120]
	COL4A1		human	testis function	male potential fertility	<i>COL4A1</i> expression effects	[121]
	COL4A1		mouse	folliculogenesis	female potential fertility	<i>COL4A1</i> expression effects	[122]
	COL4A1		human	fetal survival	fetal/offspring mortality	COL4A1 mutation effects	[123]
	COL4A1			fetal/placenta growth and development	pregnancy outcomes	<i>COL4A1</i> expression effects	[124]
34	ABHD2	Abhydrolase Domain Containing 2	_	male fertility	male potential fertility	ABHD2 expression effects	[125]
35	SORT1	Sortilin 1	human	endometrium functioning	pregnancy outcomes	SORT1 significantly expressed during labour	[54]
	SORT1			ovarian functioning	female potential fertility	<i>SORT1</i> significantly up-regulated	[126]
	SORT1		rat	ovarian functioning		SORT1 expression effects	[127]
	SORT1		human	embryo implantation	female potential fertility	SORT1 differential expression effects	[128]
36	SLC22A5	Solute Carrier Family 22 (Organic Cation/Carnitine Transporter), Member 5		male infertility	male potential fertility	<i>SLC22A5</i> mutation related to male infertility	[129]
	SLC22A5		pig	reproductive variation, offspring born alive and total born	reproductive outcomes	<i>SLC22A5</i> genotype effects on reproductive capacity	[130]
	SLC22A5		pig	age at puberty	reproductive outcomes	<i>SLC22A5</i> genotype effects	[131]
37	NOA1	Nitric Oxide Associated 1	human	male fertility, testicular functioning	male potential fertility	<i>NOA1</i> expression effects	[132]
	NOA1		mouse		female potential fertility	NOA1-deficient mouse model	[133]
38	LPL	Lipoprotein Lipase	human	pregnancy complications	pregnancy outcomes	LPL expression effects	[134]
	LPL		human	male infertility	male potential fertility	sperm DNA fragmentation related to <i>LPL</i> expression	[135]
	LPL		human	reproductive timing	reproductive outcomes	LPL expression effects	[7]
	LPL		human	intrauterine growth restriction	pregnancy outcomes	<i>LPL</i> -mediated fetal-placental nutrient transfer	[136]
	LPL		human/ mouse	placental functioning		LPL expression effects	[137]
	LPL			fetal/placental resource transfer, pregnancy	pregnancy outcomes	LPL expression effects	[138]

				complications			
	LPL		human	testis/spermatogene sis	male potential fertility	LPL expression effects	[139]
	LPL		mouse	placental regulation of cholesterol	pregnancy outcomes	<i>LPL</i> involved in maternal- fetal transfer of lipids	[23]
39	COL4A2	Collagen, Type IV, Alpha 2	mouse	fetal viability	fetal/offspring mortality	mouse knockout model for <i>COL4A2</i>	[140]
	COL4A2		human	testis function	male potential fertility	<i>COL4A2</i> expression effects	[121]
	COL4A2		human	offspring viability	fetal/offspring mortality	<i>COL4A2</i> expression effects	[141]
40	ADAMST7	ADAM Metallopeptidase With Thrombospondin Type 1 Motif, 7	mouse	embryogenesis	female potential fertility	<i>COL4A2</i> expression effects	[142]
	ADAMST7		dog	mammary tissue functioning	reproductive outcomes	<i>ADAMST7</i> significantly up- regulated in mammary tissues	[143]
	ADAMST7		human	breastfeeding capacity	reproductive outcomes	ADAMST7 expression effects	[52]

### Table footnotes:

## \*'fitness class' column defined further:

male potential fertility	-	includes processes affecting spermatogenesis, sperm motility, volume or
		function that ultimately affect probability of successful egg fertilization.
female potential fertility	-	includes processes affecting embryogenesis (i.e. oocyte viability, survival),
		functioning of uterus (i.e. implantation receptivity, endometrium functioning),
		placentation (trophoblast cell motility) that ultimately affects initial successful establishment of pregnancy.
pregnancy outcomes	-	includes processes affecting regulation of blood pressure, nutrient and oxygen
		transfer between fetal and placental tissues during pregnancy that ultimately
		influences fetal growth, development and survival.
fetal/offspring mortality	-	includes processes linked to pregnancy defects, resistance to pathogens,
		affecting survival of fetus during pregnancy or perinatal mortality.
reproductive outcomes	-	includes effects on age at maturity, reproductive timing, potential number of
		offspring, breastfeeding capacity.

#### Search criteria:

- For each CAD gene, Google scholar was used to search for studies using the 'Search terms' (below) and the gene name (*BCAS3* is used as an example)
- For each search, only the first page of results was considered. Search results most consistent with all search terms are ranked by page, thus the most relevant results were always on the first page. This approach was also employed to keep this literature search tractable in terms of time (i.e. a search for each of the terms below for one gene usually took ~1 hour).
- We also used the GWAS Catalog (https://www.ebi.ac.uk/gwas/) using the gene name to search for further potential links to fitness related traits

#### Search terms (example using gene BCAS3):

- "BCAS3" and "reproduction" and gene and -"noncommercial use, distribution, and reproduction in any"
- "BCAS3" and "fitness" and gene
- "BCAS3" and "fertility" and gene
- "BCAS3" and "menarche" and gene
- "BCAS3" and "menopause" and gene
- "BCAS3" and "birth" or "birth weight"
- "BCAS3" and "pregnancy" and gene
- "BCAS3" and "placenta" and gene

- "BCAS3" and "implantation" and gene
- "BCAS3" and "oocyte" and gene
- "BCAS3" and "sperm" and gene
- "BCAS3" and "testis"

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