Preliminary Examination of Racial Disparities in Cerebral Palsy:

Using gene expression and clinical data

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Racial Disparities in CP

- In a review of literature published since 1993, reports on CP prevalence show Black children have a higher prevalence that White children.
  - % Difference in prevalence ranged from 15-29%
- Most recently Maenner et al (2012) reported the CP prevalence for Black children to 3.9 per 1000 children.
  - Whites: 2.7/1000 children;

Racial Disparities in CP

- There is a striking lack of research focused on understanding the cause(s) of racial disparities in CP.

- Searching US-based studies published 1993, we found only 1 study which attempted to explain racial disparities in CP by investigating basic socio-demographic factors along with the onset of prenatal care, birthweight, and gestational age.

Low Birthweight and Preterm Birth

- Low birthweight and preterm birth are powerful predictors of CP.
- Hypothesized that Black-White difference in prevalence of low birthweight and preterm birth are the cause of the Black-White disparities in CP.
- However, Black-White disparities in CP prevalence have been found even among term and normal birthweight infants.

- Are there any other pathways that may lead to disparities?

Infection/Inflammation

- Research suggests that maternal infections during pregnancy increase the risk of having an infant being diagnosed with CP.
- Many maternal infections including chorioamnionitis disproportionately affect black women.
- Inflammatory responses to maternal infection mediated by cytokines and chemokines may not be the same for every racial or ethnic group.

Birth Asphyxia

- Black children have a higher risk of birth asphyxia than White children.
  - California study: Wu et al (2004) found Blacks were 28% more likely than Whites to be diagnosed with birth asphyxia.
  - National study: Mohamed et al (2014) found Black were 23% more likely than Whites to have a diagnosis of birth asphyxia.

Objective

- Describe socio-demographic, clinical, and biological factors occurring during pregnancy and in the immediate perinatal period that may lead to racial disparities in CP using gene expression and clinical data.

METHODS

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Data Source

- Data stem from the Origins, Wellness & Life-history in CP (OWL) Study
  - 2009-2012 matched case-control study
  - Children with and without CP
  - Born in Michigan
  - Age 2-15 years at time of recruitment
  - Specialty and Primary Care Clinics
    - Ann Arbor, Lansing, and Grand Rapids Michigan

Data Source

- Multiple sources of data in the OWL Study
  - Birth Certificate
  - Maternal & Child Hospital Discharge Abstracts
  - Maternal Interview
  - mRNA isolated from Archived Newborn Bloodspots

Prelim Racial Disparities Study

Participants restricted to:

- CP diagnosis
- Race: Black or White
  - child's race was defined by maternal race.
- Birth Certificate and Microarray Data available
- White children had to have:
  - birth year ± 1 year of a Black child with CP
  - gestational age group similar to that of a Black child with CP
    - <28 wks, 28-32 weeks, >37 weeks

Overall Sample Characteristics (N=89)

Characteristics	% (n)
Race	
White	84.5 (75)
Black	15.7 (14)
Birth Year	
Mean (SD), Range	2003 (4), 1994-2009
Male	57.3 (51)
Gestational Age	
Mean (SD), Range	35.6 (5.8), 23-42
<37 weeks	31.5 (28)

Statistical Analysis: Clinical Data

In all clinical data analyses:

- Predictor variable: race
- Outcome: maternal or child characteristic of focus
- Categorical Characteristics
  - Used Logistic Regression with robust error estimation
  - Used Exact Logistic Regression when maximum likelihood estimation did not converge.
- Continuous Characteristics
  - Linear regression with robust error estimation

Statistical Analysis: Clinical Data

- Unadjusted and adjusted regression models
  - adjusted for child's birth year, sex, and gestational age for all outcomes.
  - When examining disparities in functional limitations, regression models where further adjusted for CP type.
    - child's birth year, sex, gestational age, and CP type
- Used a relaxed p-value of 0.10 to denote statistical significance.

Clinical Data Outcomes

- Socio-demographic (at time of child's birth)
  - Maternal Age
  - Maternal Education
  - Medicaid Coverage
- Pregnancy & Birth Characteristics
  - Birthweight
  - Fetal Growth (Small- and Large-for-gestational age)
  - 5 minute Apgar Score
  - Labor & Delivery Complications
  - Signs of Neonatal Encephalopathy
  - Maternal Infection
- Cerebral Palsy
  - CP Type (hemiplegic, diplegic, quadraplegic)
  - Functional Limitations (gross motor, manual ability, and communication)

Statistical Analytic: Microarray Data

- 7 gene sets (3 empirical; 4 canonical) representing four physiological pathways hypothesized to contribute to the development of cerebral palsy.
  - Inflammatory*
  - Hypoxic*
  - Thyroidal
  - Coagulative

Statistical Analytic: Microarray Data

- Used Gene Sets Net Correlations Analysis (GSNCA) to assess differences in intergene correlations in gene sets between Black and White children with CP.
  - Differences between groups in the structure of genes' cross-correlations for a given gene set.
  - Adjusted for birth year, sex, and gestational age.

RESULTS

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RESULTS: CLINICAL DATA

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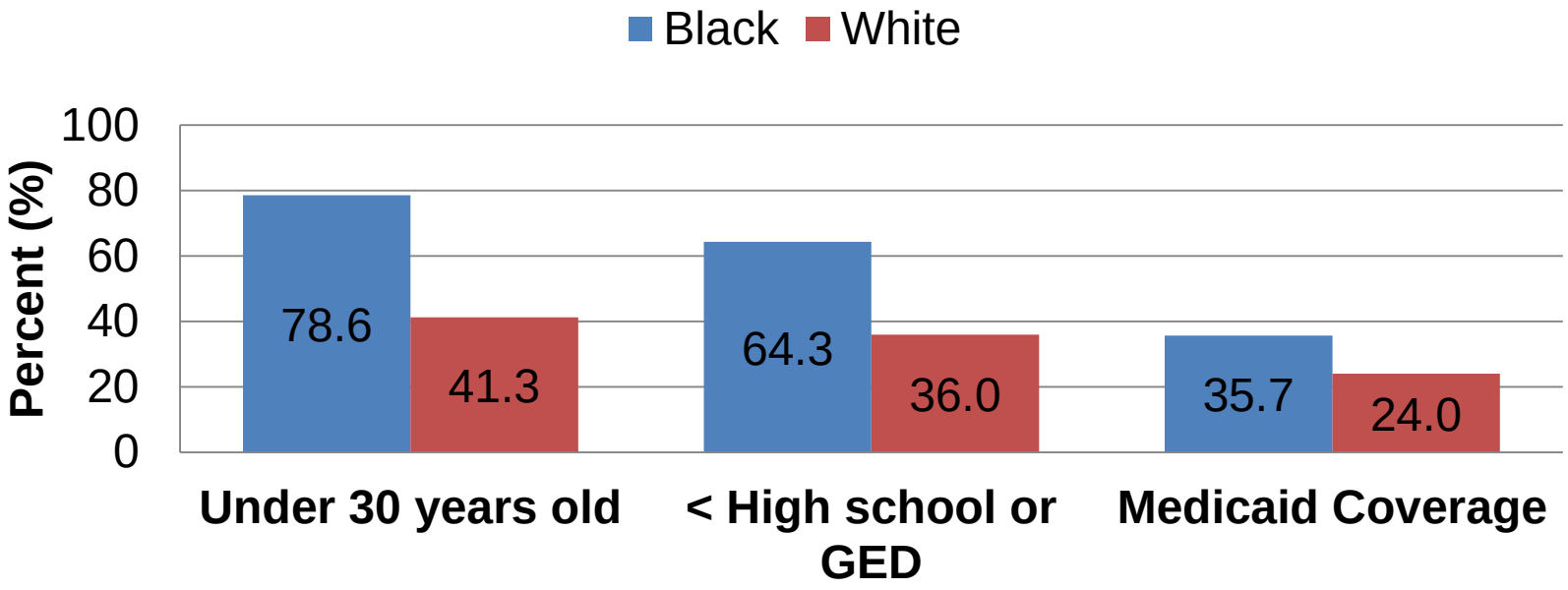
Maternal Characteristics[a,b]

†Adjusted for birth year, sex, gestational age.

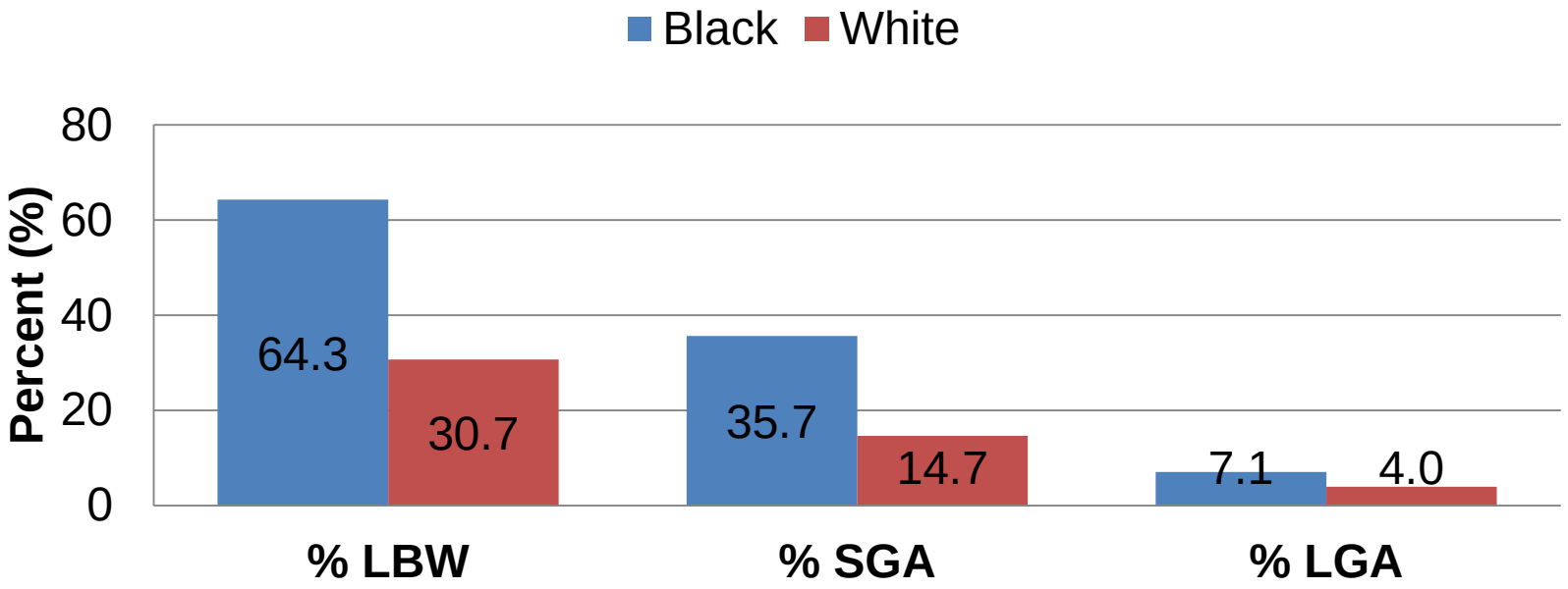


	Unadjusted p-value	Adjusted† p-value
% <30 years old	**0.011**	**0.022**
% ≤High school/GED	**0.074**	**0.059**
% Medicaid Coverage	0.343	0.101

a. At time of child's birth.
b. N= 89 children (14 Black; 75 White)

Birth Characteristics[a]

† Adjusted for birth year, sex, gestational age.

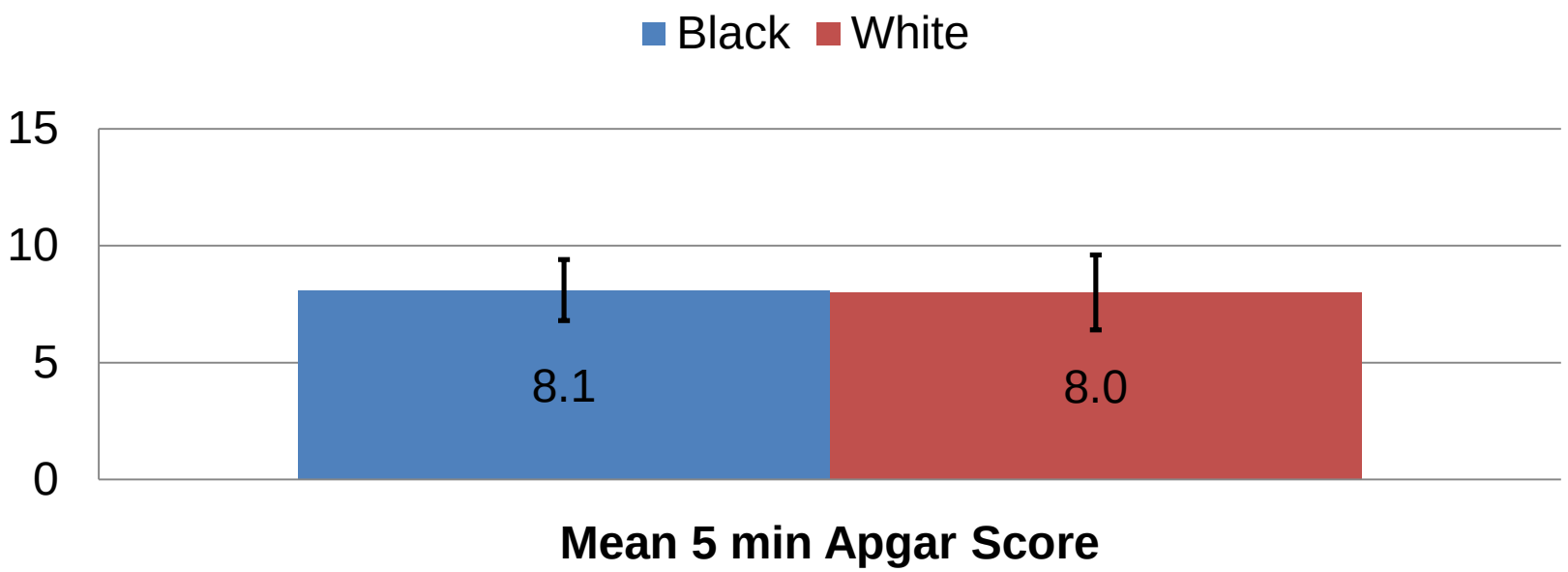


	Unadjusted p-value	Adjusted† p-value
% LBW	**0.031**	**0.052**
% SGA	0.121	**0.044**
% LGA	0.502	0.879

a. N= 89 children (14 Black; 75 White)

Birth Characteristics[a]

† Adjusted for birth year, sex, gestational age.

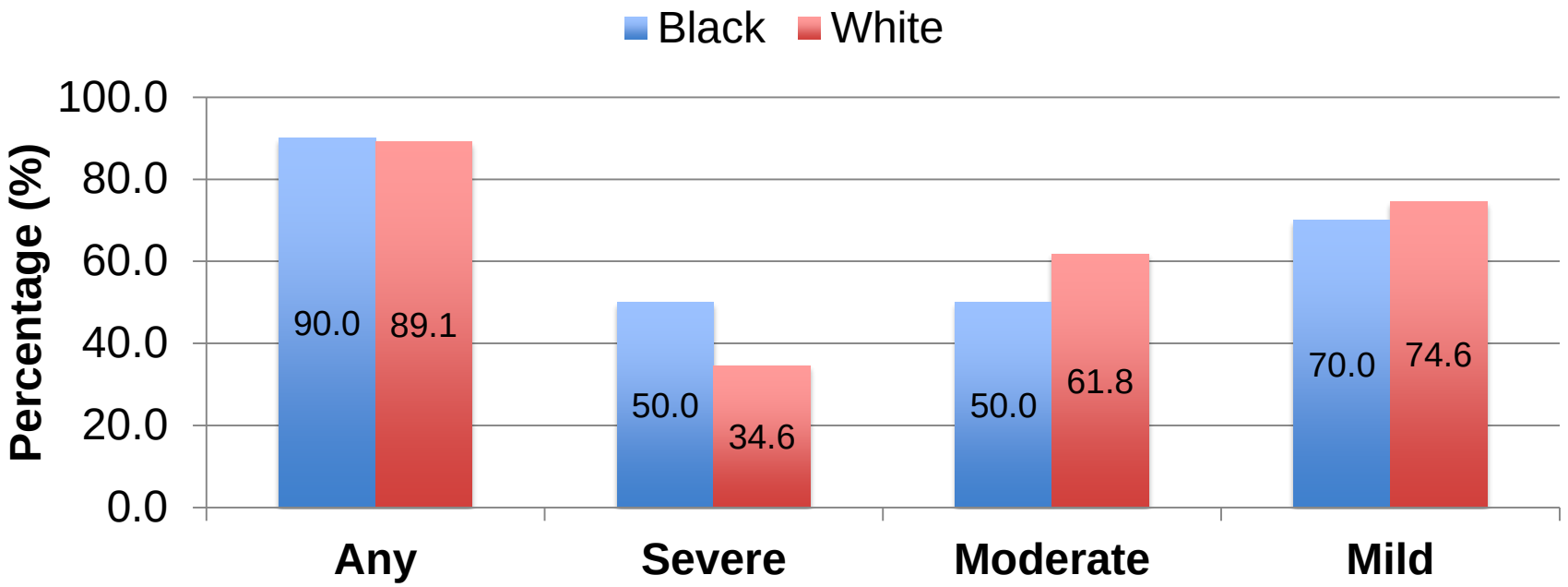


	Unadjusted p-value	Adjusted† p-value
Mean 5 min Apgar	0.644	0.509

a. N= 89 children (14 Black; 75 White)

Labor & Delivery Complications[a]

† Adjusted for birth year, sex, gestational age.

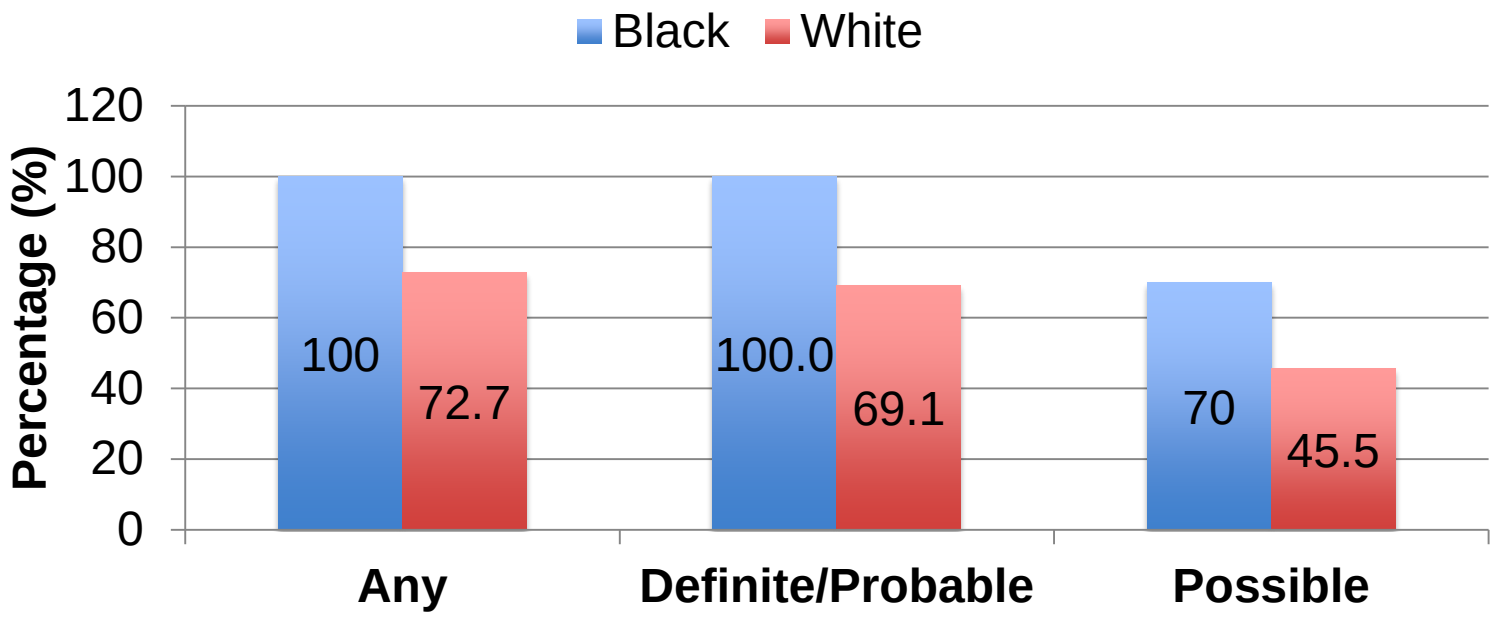


	Unadjusted p-value	Adjusted† p-value
Any	1.0	0.950
Severe	0.497	0.382
Moderate	0.504	0.760
Mild	0.713	0.894

a. 24 kid missing at least 1 source of clinical data. N= 65 (55 White and 10 Black)

Signs of Neonatal Encephalopathy[a]

† Adjusted for birth year, sex, gestational age.

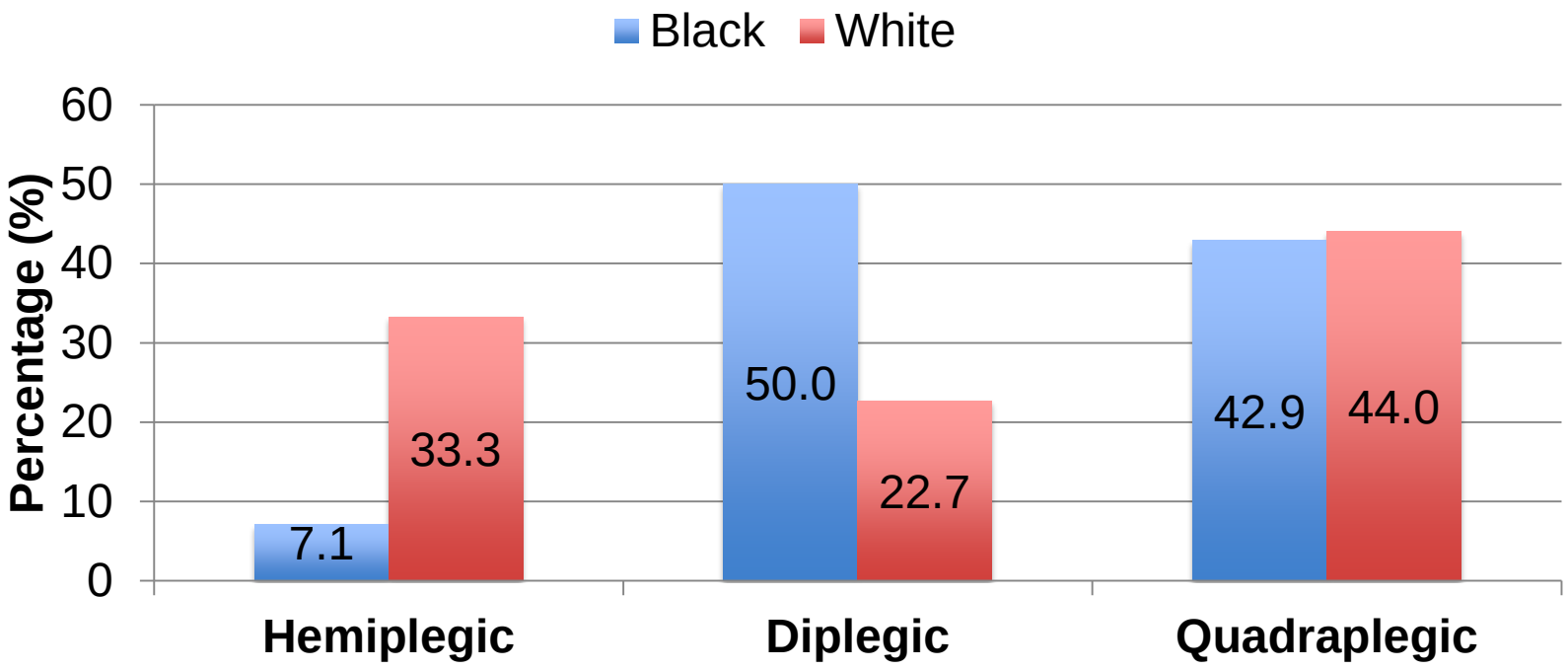


	Unadjusted p-value	Adjusted† p-value
Any	0.100	0.394
Definite/Probable	**0.052**	0.230
Possible	0.185	0.920

a. 24 kid missing at least 1 source of clinical data. N= 65 (55 White and 10 Black)

CP Type[a]

† Adjusted for birth year, sex, gestational age.

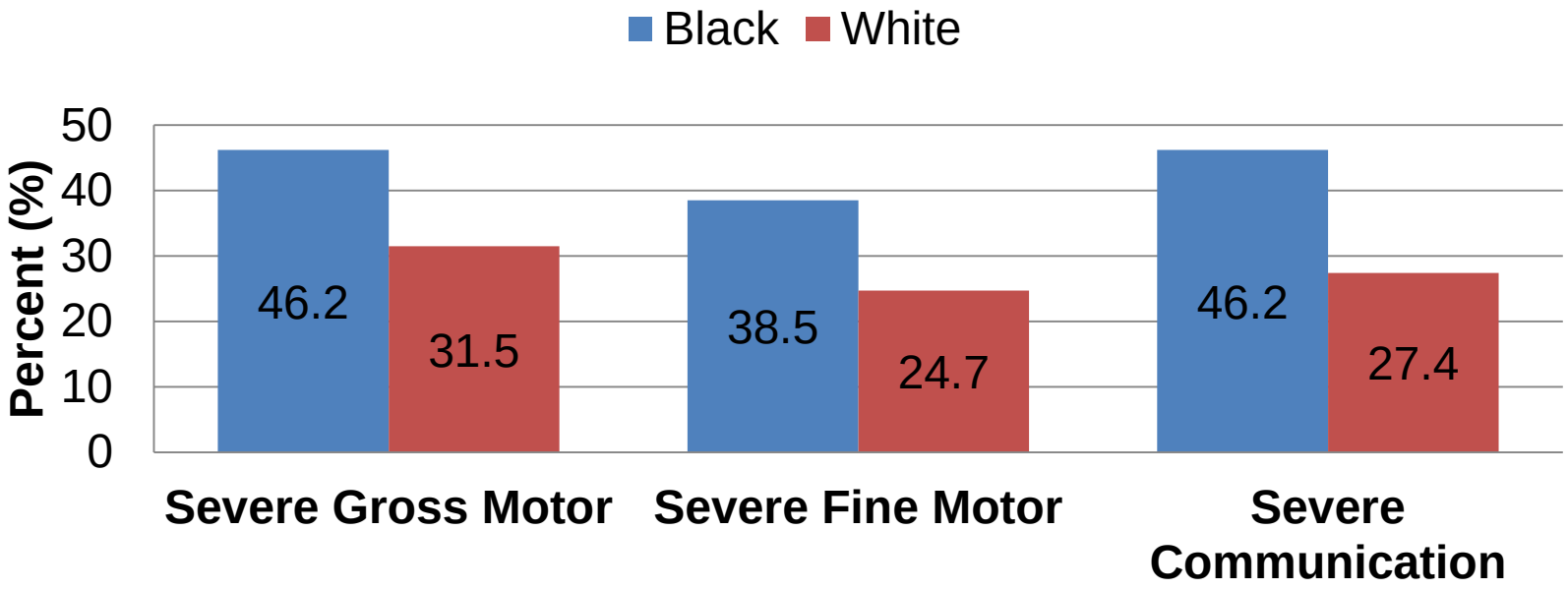


	Unadjusted p-value	Adjusted† p-value
Hemiplegic	**0.058**	0.120
Diplegic	**0.049**	**0.066**
Quadraplegic	1.0	0.860

a. 1 child missing information on CP type (n=88).

Severe Functional Limitations[a]

‡ Adjusted for birth year, sex, gestational age, and CP type.



	Unadjusted p-value	Adjusted‡ p-value
Severe Gross Motor[b]	0.348	**0.023**
Severe Manual Ability[c]	0.320	0.230
Severe Communication[d]	0.102	**0.095**

a. 3 children missing information on functional scales (1 Black; 2 White). N=86
b. GMFCS LEVEL ≥ 4.
c. MACS LEVEL ≥ 4.
d. CFCS LEVEL ≥ 4.

RESULTS: MICROARRAY DATA

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Hypothesized Pathways Leading to Cerebral Palsy

Pathway	Gene Sets, n=number of genes	GSNCA p-value
Coagulative	Canonical GO:0007596, (n=93)	0.1149
Inflammatory	Canonical GO:0050727, (n=31)	0.4305
	Empirical FIRS, (n=36)	**0.0399**
Hypoxic/Asphyxial	Canonical ASPHYXIAL, (n=36)	**0.0420**
	Empirical HYPOXIA.1, (n=31)	0.5184
Thyroidal	Canonical V$T3R_Q6, (n=199)	0.2797
	Empirical T3.UP, (n=139)	0.0869

Discussion

- Preliminary results suggest low birthweight and fetal growth restriction may be one pathway through which racial disparities in CP manifest, but…

there may be more to the story.

Discussion

- In analysis of clinical data, we found no significant differences between Whites and Blacks in labor complications, signs of neonatal encephalopathy, maternal infection.
- However, significant differences in gene expression suggest asphyxia and inflammation may be physiological pathways through which racial disparities operate.
- Our preliminary results also a hormonal physiological pathways might also lead to racial disparities in CP.

Discussion

- Like Maenner et al (2012), we found Black children with CP were more likely to have severe gross motor function limitations than White children with CP.
- We also found Black children with CP had greater communication functional limitations communication than White children with CP.
- Additional research is needed to better understand what factors that drive these disparities in CP.

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