Down syndrome (DS) is the commonest chromosomal anomaly among neonates, with a prevalence of 1/700 live births; the non-disjunction type occurs in about 95% of cases. Congenital heart diseases (CHD) in DS undoubtedly affects the progress and survival of children. The worldwide CHD prevalence is estimated to be 6 and up to 13 per 1000 live births. This prevalence is higher in Arab countries due to higher rates of consanguineous marriage, diabetes and obesity. CHDs are the most frequent congenital anomalies in DS cases; they are mainly atrioventricular septal defect (AVSD), patent ductus arteriosus (PDA), atrial septal defect (ASD), ventricular septal defect (VSD), and tetralogy of Fallot (TOF) with AVSD the most common in the Western literature.

The prevalence of CHD in children with DS has been underestimated, but the reported frequency has increased by about 50% in the past three decades. This increase in reported frequency is attributed to improvement in tools of diagnosis and increased awareness of health care providers. The etiology of CHD is multifactorial with important contributions from both environmental and genetic factors. Clinical, epidemiological and embryological...
genetic background of syndromic CHD through knowledge of several signaling transducers and modulators and transcriptional regulators that are important for heart morphogenesis.\textsuperscript{13}

Despite the high prevalence of CHD in children with DS, little progress has been made in identifying associated factors and causes. There are a dearth of studies on CHD in children with DS in Egypt. Therefore, this study aimed to identify the prevalence, types, trend and associated factors of CHD in children with DS in Egypt (Delta region).

**PATIENTS AND METHODS**

This was a hospital record-based retrospective descriptive study carried out in the genetic unit of a tertiary care hospital in Mansoura, Egypt, over 14 years from 2003 to 2016. The institute is a 420-bed, university-affiliated, public teaching hospital that provides primary to tertiary care in the Delta region of Egypt. This region encompasses 10 governorates with 41% of the total Egyptian population.

This study included 1720 karyotype-proven children with DS referred to the unit for genetic evaluation. Data were extracted from the medical archive files of DS patients. These data included age at referral, date of birth, residence, parental consanguinity, parity and maternal age. Also, we collected data about antenatal history including maternal passive smoking, obesity, diabetes, confirmed antenatal infections and folic acid/multivitamin intake in the first trimester of pregnancy. We also considered data on the children, including sex, plurality, maturity and birth weight. Results of chromosomal culture and echocardiography were retrieved for all children with DS.

Data were statistically analyzed using IBM SPSS for Windows program version 16; IBM Corp., Armonk, NY, USA and presented as numbers and percentages. The chi-square test of significance was used for comparison between groups and crude odds ratios (ORs) were computed. The Monte Carlo Exact Test (MCET) was used when the expected frequency less than 5. Factors significantly associated with CHD in bivariate analysis (parental consanguinity, passive maternal smoking, antenatal infections, maternal diabetes, maternal obesity and lack of folic acid/multivitamin supplementation) were entered into a stepwise forward Wald multivariate logistic regression model to find out the independent predictors of CHD. The adjusted OR was presented for significant independent predictors of CHD. Statistical significance was considered if \( P \) values were ≤.05.

The proposal of our research was approved by Institutional Research Board of Medical Faculty of

### Table 1. Prevalence and types of congenital heart diseases in children with Down syndrome.

| Congenital heart diseases | Type of CHD | Number | % of CHD | % of children with Down syndrome |
|---------------------------|-------------|--------|----------|---------------------------------|
| No heart diseases         |             | 1085   |          | 63.1                            |
| Heart diseases            |             | 635    | 100      | 36.9                            |
| Isolated CHD              | Total       | 498    | 78.4     | 29                              |
| VSD                       |             | 253    | 39.8     | 14.7                            |
| AVSD                      |             | 104    | 16.4     | 6.0                             |
| ASD                       |             | 80     | 12.6     | 4.7                             |
| PDA                       |             | 28     | 4.4      | 1.6                             |
| PFO                       |             | 25     | 3.9      | 1.5                             |
| COA                       |             | 3      | 0.5      | 0.2                             |
| PS                        |             | 2      | 0.3      | 0.1                             |
| DORV                      |             | 2      | 0.3      | 0.1                             |
| Dextrocardia              |             | 1      | 0.16     | 0.06                            |
| Multiple CHD              | Total       | 137    | 21.6     | 8                               |
| VSD +PDA                  |             | 26     | 4.1      | 1.5                             |
| VSD +ASD                  |             | 16     | 2.5      | 0.9                             |
| VSD +PFO                  |             | 14     | 2.2      | 0.8                             |
| VSD +AVSD                 |             | 14     | 2.2      | 0.8                             |
| TOF                       |             | 13     | 2        | 0.8                             |
| VSD +ASD +PDA             |             | 9      | 1.4      | 0.5                             |
| VSD + others              |             | 8      | 1.3      | 0.5                             |
| ASD +PFO                  |             | 9      | 1.4      | 0.5                             |
| ASD + VSD +others         |             | 4      | 0.6      | 0.2                             |
| ASD + Others              |             | 11     | 1.7      | 0.6                             |
| PDA + Others              |             | 6      | 0.9      | 0.3                             |
| Other combinations        |             | 7      | 1.1      | 0.4                             |

ASD: atrial septal defect; AVSD: atrioventricular septal defect; CHD: congenital heart diseases; COA: coarctation of aorta; DORV: double outlet right ventricle; PDA: patent ductus arteriosus; PFO: patent foramen ovale; PS: pulmonary stenosis; TOF: tetralogy of Fallot; VSD: ventricular septal defect.
The study was conducted in accordance to the principles of the Helsinki Declaration. Review of patient records was carried out during working hours under the supervision of data managers. No consent forms were obtained from patients as the study was conducted retrospectively.

RESULTS
The age of referral ranged from one month up to 17 years. The prevalence of overall, isolated and multiple CHD in children with DS were 36.9%, 29% and 8%, respectively. Isolated defects accounted for 78.4% of all CHD. VSD, AVSD and ASD were the most frequent isolated defects. VSD + PDA and VSD + ASD were the most frequent multiple defects (Table 1). A downward trend in the prevalence of overall CHD (from 56.2% to 25%) and isolated CHD (from 56.2% to 19.8%) was observed in different birth cohorts (Table 2). The prevalence of CHD was significantly higher in children of mothers with parity 2 and 3 and ≥4 and more in comparison to primipara (Table 3). Parental consanguinity, passive maternal smoking, antenatal infection, maternal diabetes, maternal obesity and lack of folic acid/multivitamin supplementation were associated with an increased CHD risk (crude OR=1.8, 2.1, 1.8, 1.5, 2.5 and 2, respectively). Low birth weight was the only child factor associated with a high risk of CHD (crude OR=1.5). The logistic regression model predicted 65.7% of CHD and revealed that passive maternal smoking, lack of folic acid/multivitamin supplementation and parental consanguinity were the independent predictors of CHD with adjusted ORs of 1.9, 1.8 and 1.9, respectively.

DISCUSSION
In the current study, the prevalence of overall CHD in children with DS was 36.9%. This is lower than previous studies in Egypt. Obviously, our study was the first in Mansoura and Delta region of Egypt including a large number of DS (n=1720) and covering cases born over a long duration (from 1992 to 2016). In Alexandria, Mokhtar and Abdel-Fattah, we studied 514 infants with DS from 1995 to 2000 and found that the prevalence of CHD in DS was 38.5%.

In Cairo, Afifi et al, we studied 90 children with DS prospectively over three years starting in 2006 at the National Research Centre and found that 40% had CHD. Tosson et al studied 116 children with DS and their mothers over one year. The patients were recruited from National Research Centre and Abou-Elreesh Children’s Hospital outpatient clinics, Cairo, Egypt. They reported 43.9% CHD in children with DS.

In other Middle East countries, the rates vary widely. Rates ranging from 40.9% to 61.3% were reported from Saudi Arabia. The recent rates from Libya, Sudan and Iran were 45%, 43.1% and 50%, respectively. Rates from other countries ranged from 43% to 58%.

This variation in the prevalence of CHD in DS can be explained by differing screening programs and diagnostic facilities, and the genetic, socioeconomic and environmental variability of different study populations. Gene-environment interactions and gene-gene interaction may affect certain molecular pathways during embryogenesis. It has been suggested that genetic factors, specific embryological mechanisms and cell characteristics may determine the pattern of heart anomalies.

As observed during this study, isolated CHD accounted for 78.4% of all CHD. This is comparable to previous proportions from Egypt and Saudi Arabia. Lower proportions of isolated CHD were reported in Nigeria, Libya, India and Mexico. However, a much higher proportion of 90.3% of isolated CHD was reported in Pakistan. This difference may be due to variability in age at diagnosis. In other words, patients with more complex CHD die at an earlier stage and before diagnosis.

Regarding the pattern of isolated CHD, the current study showed that VSD, AVSD and ASD were the most frequent isolated CHD. In a recent Egyptian study, VSD, ASD, PDA and AVSD were the most frequent isolated defects. However, in another study AVSD and ASD were the commonest.

Internationally, the pattern of isolated CHD is variable. ASD, AVSD and VSD were the commonest in Libya. In Sudan, Saudi Arabia, India and Western countries AVSD, VSD and ASD were the most frequent. In Iran and Korea, ASD, VSD, PDA and AVSD were the commonest. However, in Pakistan and Mexico, VSD and PDA were the commonest.

Our study confirms the variation in profile and
### Table 3. Bivariate and multivariate logistic regression analysis of factors associated with congenital heart diseases in children with Down syndrome.

|                        | Total | Congenital heart disease | P value | Crude OR (95% CI) | Adjusted OR (95% CI) |
|------------------------|-------|--------------------------|---------|-------------------|---------------------|
| Overall                | 1720  | 635 (36.9)               |         | 34.6-39.2         |                     |
| **Maternal age (y)**   |       |                          |         |                   |                     |
| < 20                   | 90    | 38 (42.2)                |         | Reference         | 0.8 (0.5-1.2)       |
| 20-34                  | 1137  | 405 (35.6)               | .2      | 0.9 (0.6-1.4)     |                     |
| 35 & more              | 493   | 192 (38.9)               | .6      |                   |                     |
| **Family residence**   |       |                          |         |                   |                     |
| Dakahlia               | 1023  | 395 (38.6)               | .008    | 0.67 (0.5-0.9)    |                     |
| Damietta               | 259   | 77 (29.7)                |         | .67 (0.5-0.9)     |                     |
| Kafr Elshakh           | 210   | 74 (35.2)                | .4      | 0.9 (0.6-1.2)     |                     |
| Gharbia                | 155   | 61 (39.4)                | .86     | 1.03 (0.7-1.5)    |                     |
| Other governorates     | 73    | 28 (38.4)                | .97     | 0.98 (0.6-1.6)    |                     |
| **Parity**             |       |                          |         |                   |                     |
| Primipara              | 548   | 162 (29.6)               |         | Reference         | 1.5 (1.2-1.9)       |
| 2nd & 3rd para         | 768   | 298 (38.8)               | ≤.001   | 1.5 (1.2-1.9)     | 1.8 (1.4-2.4)       |
| 4th & more             | 404   | 175 (43.3)               | ≤.001   | 1.8 (1.4-2.4)     | 2.1 (1.7-2.6)       |
| **Parental consanguinity** |       |                          |         | Reference         | 1.8 (1.6-2.3)       |
| No                     | 1320  | 443 (33.6)               |         | Reference         | 1.8 (1.6-2.3)       |
| Yes                    | 400   | 192 (48)                 | ≤.001   | 1.8 (1.6-2.3)     | 1.9 (1.5-2.4)       |
| **Passive smoking during pregnancy** | | | | | | |
| No                     | 936   | 272 (29.1)               |         | Reference         | 1.8 (1.6-2.3)       |
| Yes                    | 784   | 363 (46.3)               | ≤.001   | 1.8 (1.6-2.3)     | 1.9 (1.6-2.4)       |
| **Antenatal infection**|       |                          |         | Reference         | 1.8 (1.4-2.4)       |
| No                     | 1498  | 525 (35)                 |         | Reference         | 1.8 (1.4-2.4)       |
| Yes                    | 222   | 110 (49.5)               | ≤.001   | 1.8 (1.4-2.4)     | 1.8 (1.4-2.4)       |
| **Maternal diabetes**  |       |                          |         | Reference         | 1.8 (1.4-2.4)       |
| No                     | 1531  | 547 (35.7)               |         | Reference         | 1.8 (1.4-2.4)       |
| Yes                    | 189   | 88 (46.6)                | .004    | 1.5 (1.2-2.1)     |                     |
| **Maternal obesity**   |       |                          |         | Reference         | 1.8 (1.4-2.4)       |
| No                     | 1540  | 530 (34.4)               |         | Reference         | 1.8 (1.4-2.4)       |
| Yes                    | 180   | 105 (58.3)               | ≤.001   | 1.8 (1.4-2.4)     | 2.7 (1.9-3.7)       |
| **Folic acid/vitamin supplementation** | | | | | | |
| Yes                    | 717   | 200 (27.9)               |         | Reference         | 2 (1.6-2.4)         |
| No/unsure              | 1003  | 435 (43.4)               | ≤.001   | 2 (1.6-2.4)       | 1.8 (1.5-2.3)       |
type of CHD in DS in the different geographical areas locally and around the world.

Regarding the pattern of multiple CHD, our study showed that VSD + PDA and VSD + ASD were the most frequent anomalies. This agrees with previous studies in Egypt.8,14 The variability in the percent of the different types of multiple CHD between different studies is mostly due to differences in study design, population characteristics (e.g. ethnicity and marital age), time period, availability of prenatal care, and pregnancy termination.29 The exact genetic, epigenetic and environmental causes remain unclear. The wide variations in the frequency and forms of CHD between different studies may suggest that environmental factors have a role in their etiology. Polk et al have unveiled the interaction between trisomy 21 and the Tbx5 gene in the laboratory DS mouse model, suggesting an association between trisomic and Tbx5 genes during cardiac development.30

The current study revealed a downward trend in the prevalence of overall CHD (from 56.2% to 25%) and isolated CHD (from 56.2% to 19.8%). Bergström et al in a recent Swedish community-based study reported that the CHD risk in children with DS decreased over time (reduced by 40% from 1992 to 2012). They attributed this to selective abortion of fetuses with DS or due to improved prenatal diagnosis of complex CHD. However, this explanation is not applicable to Egypt as prenatal screening for CHD is not regularly done and selective abortions are not done except in case of multiple congenital anomalies that may threaten maternal health. It is possible that this decrease coincides with the gradual increase in maternal FA supplementation. Also by 2010, the Egyptian Government applied mandatory folic acid supplementation and iron fortification of the flour used for the bread production to decrease

| Type of CHD | Total | P value | Crude OR (95% CI) | Adjusted OR (95% CI) |
|-------------|-------|---------|-------------------|---------------------|
| VSD + PDA   | 393   | 1.1     | (0.9-1.3)         |                     |
| VSD + ASD   | 242   | .4      | (0.9-1.3)         |                     |

**Table 3 cont.** Bivariate and multivariate logistic regression analysis of factors associated with congenital heart diseases in children with Down syndrome.

| Sex             | Total | Congenital heart disease | P value | Crude OR (95% CI) | Adjusted OR (95% CI) |
|-----------------|-------|--------------------------|---------|-------------------|---------------------|
| Male            | 1086  | 393 (36.2)               |         | Reference         |                     |
| Female          | 634   | 242 (38.2)               | .4      | 1.1 (0.9-1.3)     |                     |
| **Plurality**   |       |                          |         |                   |                     |
| Single          | 1682  | 618 (36.7)               |         | Reference         |                     |
| Twin            | 38    | 17 (44.7)                | .3      | 1.4 (0.7-2.7)     |                     |
| **Maturity**    |       |                          |         |                   |                     |
| Full term       | 1249  | 448 (35.9)               |         | Reference         |                     |
| Preterm         | 436   | 176 (40.4)               | .1      | 1.2 (0.97-1.5)    |                     |
| Postdate        | 35    | 11 (31.4)                | .6      | 0.8 (0.4-1.7)     |                     |
| **Birth weight**|       |                          |         |                   |                     |
| Normal          | 1588  | 575 (36.2)               |         | Reference         |                     |
| Low-birth weight (≤2500 g) | 132 | 60 (45.5) | .034 | 1.5 (1.03-2.1) |                     |
| **Cytogenetic types of Down syndrome** | | | | |
| Non-disjunction | 1558  | 573 (36.8)               |         | Reference         |                     |
| Translocation   | 117   | 49 (41.9)                | .3      | 1.2 (0.8-1.8)     |                     |
| Mosaic          | 45    | 13 (28.9)                | .3      | 0.7 (0.4-1.3)     |                     |

*6 mothers were both active and passive smokers during pregnancy.
AOR: adjusted odds ratio, CHD: congenital heart diseases, CI: confidence interval, COR: crude odds ratio, r: reference category.
Maternal obesity: body mass index ≥30 kg/m2, 38 full term: gestational age 38 – 41 weeks, preterm: gestational age ≤ 37 weeks, postdate: gestational age ≥ 42 weeks. Regression model included all significant variables in bivariate analysis. (Constant= -1.5, Model χ² = 194.5; P = .001, % correctly predicted = 65.7). Variation explained by dependent variable: Cox and Snell R square =0.11; Nagelkerke R square =0.15; -2 log likelihood = 2070.8.
the incidence of both anemia and neural tube defects.31

In our research, the logistic regression model revealed that passive maternal smoking, lack of maternal folic acid/multivitamin supplementation and parental consanguinity were the independent predictors of CHD with adjusted ORs of 1.9, 1.8 and 1.9, respectively. This model was moderately predictive as it predicted only 65.7% of CHD in DS. However, it excluded potential confounders/interacting variables found to be significantly associated with CHD in the bivariate analysis. This indicates the importance of other unstudied risk factors, especially unknown genetic factors.

There were several national and international studies concerning the influence of maternal risk factors on CHD in children with DS. In Alexandria, Mokhtar and Abdel-Fattah found that consanguinity, maternal antibiotics, oral contraceptive use and maternal diabetes were independently associated with increased risk of CHD among DS patients.8 Moreover, first trimester maternal smoking was reported as a modest risk factor for selected CHD phenotype.32 Also a recent Swedish community-based study found that maternal smoking increases the risk of CHD in DS.26

Whether folic acid supplementation is related to CHD is controversial. Several studies have suggested that periconceptional administration of multivitamins (containing folic acid) is associated with reduced incidence of CHD.33-35 Children with DS are at risk for CHD and have been shown to have abnormal folic acid metabolism. Lack of maternal folate supplementation is associated with septal defects in infants with DS.36 Tosson et al concluded that polymorphisms of folate metabolizing genes (MRT A2756 G and MTHFR C677T and A1298C) could not be considered as maternal risk factors for CHD in DS offspring.15 Another study failed to find a preventive role for folic acid on CHD occurrence among infants with DS.37

The association between parental consanguinity and increased CHD risk in the current study is consistent with a previous Egyptian study.8 This suggests that homozygosity at certain loci may be a cause of CHD in DS. However, Iranian and Saudi studies failed to find such an association.2,16

Because of the high prevalence of CHD in DS and difficulty in diagnosis by clinical examination, all children with DS should have an ECG and echocardiogram as early as possible, preferably during fetal life. With advances in management of CHD, early diagnosis and treatment is required to gain best results. National multicenter and community-based studies of CHD in children with DS are now mandatory, and will give the full picture of the situation. There is a need for molecular studies of children with DS with CHD to unravel the genetic role in pathogenesis of CHD in DS. As a retrospective single center study on a selective group of genetically confirmed children with DS, we were unable to study a wide range of associated factors due to limited data.

We conclude that more than one-third of children with DS have CHD with VSD as the most common type. Avoidance of passive maternal smoking and consanguineous marriage together with maternal FA supplementation could contribute to further reduction of CHD in children with DS. Routine prenatal screening using 3/4-dimensional ultrasonography, for at least one time during pregnancy, could be valuable in early prediction of CHD in DS. We advise that other risk factors be assessed, including genetic factors in the future studies. Also, multicenter studies are needed for more globalization and generalization of the data.

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